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Two male patients aged 55 and 77 years, respectively, presented to the casualty department with fever, chills and right abdominal upper quadrant tenderness. They also had hyperbilirubinaemia. Based on CT scan findings and blood cultures yielding Bacteroides fragilis, a diagnosis of pylephlebitis (septic thrombophlebitis of the mesenteric veins and/or the portal vein) was made. This is a condition with a mortality rate of 10-70%. Primary sources such as diverticulitis are often seen in patients with pylephlebitis, in which bacteria are drained by the mesenteric veins and cause a thrombus in the portal system. In the two patients no primary focus was detected. They were treated with intravenous antibiotic therapy followed by oral antibiotics, and were discharged in good health. Pylephlebitis can be complicated by liver abscesses. Treatment consists of broad-spectrum antibiotics which are adjusted based on the blood cultures results. The duration of treatment is between two and six weeks, depending on the presence of liver abscesses. In patients with abscesses that cannot be drained, longer treatment may be indicated.
2. LABORATORY METHODS AND TECHNIQUES


A simple, selective, precise and stability-indicating high-perform-
ance thin-layer chromatographic method of analysis of tizanidine hydrochloride both as a bulk drug and in formulations was devel-
oped and validated. The method employed TLC aluminium plates pretreated with silica gel 60F-254 as the stationary phase. The sol-
vent system consisted of toluene-acetone-ammonia (5:5:0.1, v/v/v). This system was found to give compact spots for tizanidine hydro-
chloride (Rf value of 0.32±0.01). Tizanidine hydrochloride was subjected to acid and alkali hydrolysis, oxidation and photodegra-
dation. Also, the degraded product was well separated from the pure drug. Densitometric analysis of tizanidine hydrochloride was carried out in the absorbance mode at 315 nm. The linear regression analysis data for the calibration plots showed good linear relation-
ship with r²=0.9922 in the concentration range 300-1000 ng per
spot. The mean value of correlation coefficient, slope and intercept, were 0.9922±0.002, 0.064±0.001 and 38.09±1.71, respectively. The method was validated for precision, recovery and robustness. The limits of detection and quantification were 88 and 265 ng per spot, respectively. The drug does not undergo degradation under acidic and basic conditions. The samples degraded with hydrogen peroxide showed additional peak at Rf value of 0.12. This indicates that the drug is susceptible to oxidation. Statistical analysis proves that the method is repeatable and selective for the estimation of said drug. As the method could effectively separate the drug from its degradation product, it can be employed as a stability-indicating one. © 2003 Elsevier B.V. All rights reserved.

377. Flow-injection chemiluminescence detection for studying protein binding of terbutaline sulfate on on-line microdialysis sampling - Wang Z., Zhang Z., Fu Z. et al. [Z. Zhang, Department of Chemistry, Institute of Analytical Science, Southwest China Nor-
mal University, Beibei, Chongqing, 400715, China] - J. PHARM. BIOMED. ANAL. 2003 33/4 (765-773) - sum in ENGL

The binding of terbutaline sulfate to bovine serum albumin was studied in vitro using the technique of microdialysis sampling com-
bined with flow-injection chemiluminescence analysis (FLA-CL). In the presence of formaldehyde, terbutaline sulfate can be oxidized by KMnO₄ to produce high chemiluminescence emission in sulfate acid media. The concentration of terbutaline sulfate is proportional with the CL intensity in the range of 1×10⁻⁷-2×10⁻⁵ mol l⁻¹ with a detection limit of 3×10⁻⁹ mol l⁻¹. The drug and protein were mixed in different molar ratios in 0.067 mol l⁻¹ phosphate buffer, pH 7.4, and incubated at 37°C in a water bath. The microdialysis probe was utilized to sample the mixed solution at a perfusion rate of 0.5 µl min⁻¹ and the dialytic efficiency of terbutaline sulfate un-
der the experimental conditions was 26.3%. The data obtained by proposed microdialysis flow-injection chemiluminescence method was analyzed with Scratthard analysis and Klotz plot. The estimated association constant (K) and the number of the binding site (n) on one molecule of BSA by Scratthard analysis were 4.11×10⁻⁴ mol⁻¹ and 1.06, respectively. The proposed system proved that FLA-CL coupled with on-line microdialysis sampling is a simple and reliable technique for the study of drug-protein interaction. © 2003 Elsevier B.V. All rights reserved.


Hydroxamic acids, the naturally occurring and synthetic products, generally have low toxicities and are of interest for many therapeutic applications. The present investigation describes the measurement of hydrogen bond donor (HBD) strength of ten hydroxamic acids by measuring theirlog(GOW) values. Hydroxamic acid functional group contains two oxygen and one nitrogen atom as the acceptor sites. Thus, HBA strength of these reagents is also computed. A knowledge of these parameters is valuable in the field of toxicology, pharmacology and environmental sciences. © 2003 Published by Elsevier B.V.

379. Determination of imipramine in presence of iminodibenzyl and in pharmaceutical dosage form - El Zeyne B.A., Mostafa A.A. and Farid N.F. [N.F. Farid, Department of Analytical Chem-
istry, Faculty of Pharmacy, Cairo University, 23 El-ahar St., Cairo, Egypt] - J. PHARM. BIOMED. ANAL. 2003 33/4 (775-782) - sum in ENGL

Two spectrophotometric methods for the determination of impi-
ramine in presence of iminodibenzyl as an impurity are described. The first method is a ratio-spectra first derivative spectrophotometry, the signals were measured at 240.2 nm for imipramine. Calibration graph was found linear in the range 5-30 µg ml⁻¹. The second method is based on the reaction of imipramine base, being an elec-
tron donor, with p-chloranilic acid, being γ acceptor, to form a purple colored charge transfer complex. The absorbance was mea-
sured at 520.5 nm without interference with iminodibenzyl. Both methods are rapid, simple and do not require any preliminary sep-
aration or treatment of the samples. Furthermore, the two methods were applied to pharmaceutical dosage form. © 2003 Elsevier B.V. All rights reserved.

See also: 381, 389, 392, 395, 492, 540, 584, 592, 593, 612, 675, 679, 700, 707, 713, 732, 733.

3. PHARMACOKINETICS

380. A review of the effects of chronic exercise and physical fitness level on resting pharmacokinetics - Persky A.M., Ed-
ington N.D. and Derendorf H. [Dr. A.M. Persky, Div. of Drug Delivery/Disposition, School of Pharmacy, Univ. of N. Carolina at Chapel Hill, C.B. No. 7360 Beard Hall, Chapel Hill, NC 27599-
7360, United States] - INT. J. CLIN. PHARMACOL. THER. 2003 41/11 (504-516) - sum in ENGL

Pharmacological intervention in cooperation with physical ac-
tivity is currently being used in the prevention and treatment of diseases like cardiovascular disease and obesity. Physical activity, both acute and chronic, can cause changes in physiology that can alter the observed pharmacokinetics of drugs. Objective: The pur-
pose of this paper is to focus on how chronic exercise can change pharmacokinetics. Results: Chronic exercise can affect drug ab-
sorption by the increase in collateral blood flow and absorption may also be affected by changes in gastrointestinal transit times. Chronic exercise may affect volume of distribution of drugs by the increases in lean body mass, decreased fat mass, increased plasma protein and increased plasma volume that occurs with physical condition-
ing. Changes in hepatic clearance of drugs may explain the differences in systemic clearance seen when comparing physically trained subjects to sedentary ones. Some studies have shown that hepatic enzymes are increased with training but other studies have found no change or lower activities. Finally, renal elimination of drugs may be altered by changes in protein binding but there is little evidence that renal elimination of drugs changes with long-
term exercise. Conclusion: Therefore, changes in pharmacokinetics associated with chronic exercise can differ from those during acute

381. Center specificity in the limited sampling model (LSM): Can the LSM developed from healthy subjects be extended to disease states? - Mahmood I. [Dr. I. Mahmood, Office of Thera-

Background and objectives: Area under the curve (AUC) can be related to the therapeutic or toxic effect of a drug. In order to accurately measure AUC, multiple blood samples are required.
but in a clinical setting, frequent blood sampling from the patients is time-consuming and expensive. The limited sampling model (LSM) is one of the approaches that is gaining popularity due to its simplicity for the estimation of AUC using 1-3 samples. Despite its simplicity, the LSM has some shortcomings. One of the major drawbacks of the LSM is that the LSM developed under a given condition may not be extended to other conditions. For example, the LSM developed from healthy subjects may not be extended to disease states such as renal or hepatic impairment or vice versa. This characteristic of the LSM can be referred to as “center-specific”. In this investigation, the LSM developed from the healthy subjects was used to predict AUC in patients with renal or hepatic impairment. Methods: Two sets of simulated plasma concentration versus time data for 2 antihypertensive drugs and measured plasma concentration versus time data for 2 representative drugs (A and B) were used in the analysis. Results and conclusion: The results of the study indicate that the LSM developed from healthy subjects is inadequate to predict AUC in patients with hepatic or renal impairment, indicating center specificity of the LSM.

382. Increase in tacrolimus trough levels after steroid withdrawal - Van Duijnphoven E.M., Boots J.M.M., Christiaans M.H.L. et al. [E.M. Van Duijnphoven, Department of Internal Medicine, University Hospital of Maastricht, PO. Box 5800, 6202 AZ Maastricht, Netherlands] - TRANSPANT INT. 2003 16/10 (721-725) - sumin in ENGL. Although there are experimental reports of cytochrome P450 3A4 iso-enzyme (CYP3A4) induction by glucocorticoids, there are no clinical reports about an interaction between tacrolimus and steroids. Therefore, tacrolimus trough level and dose were compared after dose-normalization before and after withdrawal of prednisolone. After withdrawal of 5 mg prednisolone, the median tacrolimus dose-normalized level increased by 14% in the retrospective (n = 54), and by 11% in the prospective (n = 8) part of the study. After withdrawal of 10 mg, this increase was 33% (n = 30) and 36% (n = 14), respectively. An additional pharmacokinetic part of the study (n = 8) revealed an 18% increase in AUC (P = 0.05) after withdrawal of 5 mg prednisolone, which is compatible with a reduced metabolism after steroid withdrawal. The significant increase in tacrolimus exposure after steroid withdrawal may on the one hand counteract the reduction in immunosuppression intended by steroid withdrawal, and, on the other hand, may result in an increase of serum creatinine which could be misinterpreted as rejection.

383. Considerations in Analyzing Single-Trough Concentrations Using Mixed-Effects Modeling - Booth B.P. and Gobburu J.W.S. [Dr. B.P. Booth, Ctr. for Drug Eval. and Research, Off. Clin. Pharmacol./Biopharmaceut., Div. of Pharmaceutical Evaluation I, 5600 Fishers Lane, Rockville, MD 20857, United States] - J. CLIN. PHARMACOL. 2003 43/12 (1307-1315) - sumin in ENGL. The purpose of this study was to assess the effect of trial design and data analysis choices on the bias and precision of pharmacokinetic (PK) parameter estimation. NONMEM was used to simulate and analyze plasma concentrations collected according to a dense (five samples) or sparse (single-trough samples) sampling scheme for a one-compartment open model with intravenous administration. The results indicated that the bias on estimates of CL with only single-trough data was 17% compared to less than 1% for only dense data. The estimates of CL were improved by fixing all other parameters and estimating only mean and variance of CL (-11% to 1.4%, depending on the estimation method). Adding dense data led to further improvements (+2.3% to 0.3%, depending on further improvements). In these cases, first-order conditional estimation (FOCE) methods resulted in better estimates of CL than first-order (FO) methods. These steps also improved the Bayesian estimates of CL. These studies support the following recommendations: (1) avoid collecting single-trough concentrations unless there is reasonable knowledge about the PK of the drug; (2) if collecting single-trough concentrations is inevitable, avoid estimating all parameters when modeling single-trough concentration data; (3) use prior information by modeling the single-trough concentration data along with dense data from other studies; and (4) use Bayes estimates if the PK model and its parameters are known with reasonable certainty.

384. Improvement of physicochemical and biopharmaceutical properties of theophylline by poly(ethylene glycol) conjugates - Zacchigna M., Di Luca G., Catani F. et al. [M. Zacchigna, Dip.to di Scienze Farmaceutiche, piazzale Europa 1, 34127 Trieste, Italy] - FARMACO 2003 38/12 (1307-1312) - sumin in ENGL. In vitro permeation studies of theophylline esters with poly(ethylene glycol) (PEG) and methoxy poly (ethylene glycol) (mPEG) were prepared. Quantitative yields of the pure products were obtained. Unlike the parent drug, the drug-polymer conjugates are freely water-soluble at room temperature. In vitro release experiments in aqueous buffer demonstrate that both conjugates are stable in buffer of pH 7.4 and 1.2. In vivo release studies after oral administration of theophylline conjugates demonstrate a good result of continuous absorption. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

385. Determination of the Dermal Penetration of Esterom Component Using Microdialysis Sampling - McDonald S. and Lunte C. [C. Lunte, Department of Chemistry, University of Kansas, Lawrence, KS 66045, United States] - PHARM. RES. 2003 20/11 (1827-1834) - sumin in ENGL. Purpose. Esterom® Solution, an investigational pharmaceutical product, is derived from the esterification of benzoylmethylecgonine (cocaine) in 1.2 propanediol. The resulting solution contains a mixture of components. Esterom Solution is intended to be a topical analgesic to relieve pain and increase the range of motion in patients suffering from acute inflammation of the shoulder or back. Although the components of Esterom are known, the components that are responsible for analgesia have only recently been identified. The purpose of this research is to evaluate which components have the ability to penetrate the skin, how much actually penetrates, and if and/or how each component is metabolized and distributed locally. Methods. Linear microdialysis probes were implanted into rat dermis. The individual components present in the Esterom Solution were applied separately to the dermis directly over a probe. Dermal dialysis samples were collected to evaluate the dermal penetration of each compound following topical application. Results. Following a 10 mg/50 μL application, 1.8 ± 0.6 μg/mg of benzoylmethylecgonine was detected at the plateau after approximately 220 min. Following hydroxypropyl benzoate application, complete hydrolysis to benzoic acid was observed with a plateau concentration of 13.7 ± 19 μM (150 min plateau). When applied separately, hydroxypropyl benzoylmethylecgonine and ecgonine penetrate the skin with plateau concentrations of 32 ± 9 μM (15 h plateau) and 36 ± 5 μM (150 min plateau) respectively. Benzoylcgonine, the hydrolytic product of HP-BE, was also detected with a plateau concentration of 3.9 ± 0.1 μM (16 h plateau) Applied topically, ecgonidine, methylecgonidine, benzoylgonine, and hydroxypropyl ecgonidine were not detected. Conclusions. Of the components with analgesic activity, the only compound that penetrates the skin is hydroxypropyl benzoylmethylecgonine. Dermal microdialysis was shown to be an effective technique to monitor the skin penetration of topically applied compounds.

386. High Bioavailability of α-Tocopherol Loaded into Poly(DL-Lactyl-Co-Glycolic Acid) Microspheres in Apolipoprotein B Knockout Mice - Yokogawa K., Shima Y., Hashimoto T. et al. [K.-I. Miyamoto, Department of Hospital Pharmacy, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan] - PHARM. RES. 2003 20/11 (1846-1850) - sumin in ENGL. Purpose. To assess the potential clinical value of α-tocopherol-loaded poly (DL-lactyl-co-glycolic acid) (PLGA) microspheres, we examined the disposition kinetics of α-tocopherol after administration of the microspheres to apolipoprotein B (apo B) knockout mice as a model of abetalipoproteinemia. Methods. PLGA microspheres containing α-tocopherol were prepared by a solvent-evaporation method. The concentration of α-tocopherol was measured by gas chromatography-mass spectrometry. Results. The mean value of particle size of α-tocopherol-loaded PLGA microspheres was 108 μm. The loading and the trapping efficiency of α-tocopherol in PLGA microspheres was 20.8% and 86.6%, respectively. When α-tocopherol solution (25 mg/kg) was subcutaneously administered to apoB(-/-) and apoB (+/+) mice, the plasma concentrations of α-tocopherol reached a peak at 6 h and decreased to the endogenous
level within 4 days in both types of mice. However, the area un- der the plasma concentration-time curve (AUC) of apob (+/+ ) mice was significantly smaller than that in the case of apob (−/−) mice. When α-tocopherol-loaded PLGA microspheres (100 mg/kg) were subcutaneously administered, the plasma concentrations of α-tocopherol increased slowly and remained about 2-fold higher than the endogenous level at 5 to 10 days after administration in both types of mice, and there was no significant difference between the AUC values. The PLGA microsphere preparation of α-tocopherol is expected to be a very useful drug delivery system in vitamin E supplementation therapy for abetalipoproteinemia.

387. Solubilization of Cationic Drugs in Lung Surfactant - Liao X. and Wiedmann T.S. (T.S. Wiedmann, University of Minnesota, Department of Pharmacuetics, 308 Harvard St. SE, Minneapolis, MN 55455, United States) - PHARM. RES. 2003 20(11) (1858-1863) - sum in ENG.

Purpose. The association of Hydrophobic, cationic drugs with lung surfactant was determined to assess the pharmacokinetic implications on drug disposition and retention in the lung. Methods. The distribution coefficients, K, were determined at 25 and 37°C in an aqueous solution to the lung surfactant. The pKa of quinacrine was 7.43 / 330, 4,490 / °C. In a series of structurally related, cationic drugs. Drugs were dispersed into lung surfactant, equilibrated, and then centrifuged to separate the aqueous phase from the surfactant pellet. Drug concentrations in the supernatant and pellet were determined following dilution using spectrophotometric assays. In addition, the apparent dissociation constant of quinacrine in the presence and absence of surfactant was determined by measuring the pH-dependent absorption spectra. The effect of stereochromy on the distribution of drugs into surfactant was examined with (R)- and (S)-propranolol. Results. The mole fraction distribution coefficients 1 for amitriptyline, promethazine, promazine, ethopropazine, imipramine, R-propranolol, and S-propranolol at 25°C were 6.566 ± 0.500, 28.400 ± 1.500, 121.080 ± 160, 54.800 ± 330, 4.490 ± 250, 8.680 ± 280, 8.190 ± 350, respectively. At 37°C, the distribution coefficients were generally smaller indicating a significant exothermic heat of transfer for these solutes from aqueous solution to the lung surfactant. The pKa of quinacrine was 7.33 ± 0.04 in aqueous solution and was shifted to 7.62 ± 0.06 in the presence of lung surfactant. From this shift, the double layer potential for quinacrine-lung surfactant was estimated to be -0.012 V assuming a dielectric constant equivalent to that of water. Conclusions. Cationic drugs have more favorable distributions from an aqueous phase to the lipid phase of lung surfactant. The transfer process generally has both a large entropic and enthalpic contribution. The latter thermodynamic aspect may be related to the charge interaction between the solute and the negatively charged surfactant. Finally, no significant effect of stereochromy was evident with the distribution of (R)- and (S)-propranolol.

388. Biotransformation of tamoxifen in a human endometrial explant culture model - Sharma M., Shuibert D.E., Sharma M. et al. (J.R. Olson, Dept. of Pharmacology and Toxicology, State Univ. of New York at Buffalo, 102 Farber Hall, Buffalo, NY 14214, United States) - CHEM. BIOL. INTERACT 2003 146(3) (237-249) - sum in ENG.

Although long-term tamoxifen therapy is associated with increased risk of endometrial cancer, little is known about the ability of endometrial tissue to biotransform tamoxifen to potentially reactive intermediates, capable of forming DNA adducts. The present study examined whether explant cultures of human endometrium provide a suitable in vitro model to investigate the tissue-specific biotransformation of tamoxifen. Fresh human endometrial tissue, microscopically uninvolved in disease, was cut into 1-2 mm uniform explants and incubated with media containing either 25 or 100 nM tamoxifen in a 24-well plate. Metabolites were analyzed by reversed-phase HPLC using postcolumn, online, photochemical activation and fluorescence detection. Three metabolites, namely, α-hydroxytamoxifen, 4-hydroxytamoxifen, and N-desmethyltamoxifen were identified in culture medium and tissue lysates. N-desmethyltamoxifen was found to be the major metabolite in both tissue and media extracts of tamoxifen-exposed explants. Incubations of tamoxifen with recombinant human cytochrome P450 enzymes (CYP1A1 and CYP2D6) produced all three of the above tamoxifen metabolites, while CYP1A1 and CYP3A4 catalyzed the formation of α-hydroxytamoxifen and N-desmethyltamoxifen, and CYP1A2 and CYP1B1 only formed the α-hydroxy metabolite. CYP2D6 exhibited the greatest activity for the formation of all three tamoxifen metabolites. Western immunoblots of microsomes from human endometrium detected the cytochrome P450 presence of CYP2C9, 3A, 1A1 and 1B1 in fresh endometrium, while CYP2D6 and 1A2 were not detected. Immunohistochemical (IHC) analysis also confirmed the presence of CYPs 2C9, 3A and 1B1 in fresh human endometrium and in viable tissue cultured for 24 h with or without tamoxifen. Together, the results support the use of explant cultures of human endometrium as a suitable in vitro model to investigate the biotransformation of tamoxifen in this target tissue. In addition, the results support the role of CYPs 2C9, 3A, 1A1 and 1B1 in the biotransformation of tamoxifen, including the formation of the DNA reactive α-hydroxytamoxifen metabolite, in human endometrium. © 2003 Elsevier Ireland Ltd. All rights reserved.


Objectives. To investigate, in an elderly population: (1) the effects of oral B-vitamin therapy on P-tHcy, S-MMA and Hb/MCV, (2) the appropriate decision limit for 'high' metabolite concentrations and (3) the estimated prevalence of vitamin B12/folate deficiency on the basis of different decision limits. Design. Double-blind placebo-controlled intervention study. Setting: Outpatient clinic. Subjects: A total of 209 community-dwelling subjects, mean age 76 years (range 70-93) y. Intervention: Four months of oral daily supplementation with 0.5 mg cyanocobalamin, 0.8 mg folic acid and 3 mg vitamin B6. Results: High P-tHcy; was found in 64% of men and 45% of women, high S-MMA in 11% of both. Vitamin B12 deficiency was observed in 7.2% and folate deficiency in 11% of all subjects. Health-related upper reference limits for the metabolites at the start were higher than the laboratory's upper reference limits. The latter were, however, similar to those of the vitamin replete group. There was a significant decrease in P-tHcy (P< 0.001) and S-MMA (P = 0.009) after 4 months of vitamin treatment. In a multivariate analysis, the P-tHcy change correlated positively with baseline P-tHcy and inversely with baseline P-folate and transferrin saturation (Fe/TIBC ratio). The S-MMA change correlated with baseline S-MMA and inversely with baseline vitamin B12 and age. Conclusions: Suboptimal vitamin status is an important cause of elevated P-tHcy's and S-MMA in apparently healthy elderly subjects. Oral B-vitamin therapy is an effective and convenient way to normalise P-tHcy's and S-MMA.


From an actinomycete strain, Streptomyces sp. K99-5041, lanopylins A1, B1, and B2 were isolated as new natural products that inhibited the reaction of recombinant human lanosterol synthase. The crude extract from the whole broth of this strain inhibited the reaction of recombinant human lanosterol synthase. The crude extract from the whole broth of this strain was fractionated by silica gel column chromatography to afford an active fraction that showed a single spot on TLC. Detailed analyses of this fraction with liquid chromatography-mass spectrometry revealed that it contained lanopylins A1, B1, and B2, novel lanosterol synthase inhibitors. The structure and biological activities of these compounds are described in detail.
contained 20 homologous compounds with differing side chain lengths. The fraction was separated by preparative HPLC to afford four of these homologues, lanoplysin A1, B1, A2, and B2. Detailed spectroscopic analyses of these isolated compounds led to the identification of their structures. Lanoplysin A1 and B1 were (3E)-isohexadecylmethylidene-2-methyl-1-pyrroline and (3E)-hexadecylmethylidene-2-methyl-1-pyrroline, respectively, and lanoplysin A2 and B2 were homologues with the insertion of one cis-ethyleneylidene in the side chain of lanoplysin A1 and B1, respectively. These compounds inhibited recombinant human lanosterol synthase with IC50 values of 15, 18, 33, and 41 μM, respectively.

391. SMTP-4D, -5D, -7D and -8D, a new series of the non-lysine-analog plasmogen modulators with a D-amino acid moiety - Hu W., Kitano Y. and Hasumi K. [K. Hasumi, Dept. of Applied Biological Science, Tokyo Noko University, 3-5-8 Sawaiicho, Fuchu, Tokyo 183-8509, Japan] - J. ANTIBIOT. 2003 56/10 (832-837) - sum in ENGL

Stapabin and SMTPs, tripleyn phenol metabolites of the fungus Stachybotrys microspera, are a family of non-lysine-analog plasminogen modulators that enhance both activation and fibrin binding of urokinase type plasminogen. The introduction of a D-amino acid moiety modulating plasminogen conformation. These compounds, including SMTP-4D, -5D, -7D and -8D have an amino acid or an amino alcohol moiety in their structure, and precursor amino acids feeding greatly increases the biosynthesis of a metabolite of interest. In the present study, we have isolated five novel SMTPs (designated SMTP-4D, -5D, -6D, -7D and -8D) from precursor D-amino acid-fed cultures. Physico-chemical properties as well as chromatographic behavior were distinct from those of the corresponding L-amino acid analogs, which are selectively accumulated in L-amino acid-fed cultures and share common properties with corresponding natural products. The D-series SMTPs enhanced uroki nose-catalyzed plasminogen activation by 10-fold at 80-180 μM.


The potencies of mammalian cell-derived recombinant human erythropoietin pharmaceutical preparations, from a total of five manufacturers, were assessed by in vivo bioassay using standardized protocols. Eight-week-old normochromic mice received a single subcutaneous injection followed by blood sampling 96 h later or multiple daily injections with blood sampling 24 h after the last injection. Reticulocyte counting by microscopic examination was employed as the endpoint using the brilliant cresyl blue or selective hemolysis methods, together with automated flow cytometry. Different injection schedules were investigated and dose-response curves for the European Pharmacopoeia Biological Reference Preparation of erythropoietin were compared. Manual and automated methods of reticulocyte counting were correlated with respect to assay validity and precision. Using 8 mice per treatment group, intra-assay precision determined for all of the assays in the study showed coefficients of variation of 12.1-28.4% for the brilliant cresyl blue method, 14.1-30.8% for the selective hemolysis method and 8.5-19.7% for the flow cytometry method. Applying the single injection protocol, a combination of at least two independent assays was required to achieve the precision and confidence limits indicated by the manufacturers, while the multiple daily injection protocol yielded the same acceptable results within a single assay. Although the latter protocol using flow cytometry for reticulocyte counting gave more precise and reproducible results (intra-assay coefficients of variation: 5.9-14.2%), the well-characterized manual methods provide equally valid alternatives for the quality control of recombinant human erythropoietin therapeutic products.


Tipranavir (TPV) is a non-peptidic protease inhibitor belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrones, which exhibits potent and specific activity against HIV type 1 (HIV-1) and 2 (HIV-2). Clinical and therapeutic plasma levels of TPV are achieved by concomitant administration of ritonavir (RTV). Therefore, TPV has been coformulated with RTV in clinical trials. TPV has demonstrated antiviral activity against HIV-1 isolates that are resistant to reverse-transcriptase and selected peptidase protease inhibitors. Therefore, TPV is emerging as one of the newer drugs in the armamentarium against HIV-1 in patients demonstrating multi-drug resistance. TPV administered orally to humans exhibits linear pharmacokinetics at doses of 100 - 2000 mg. Steady-state plasma levels are attained within 7 days of initiating multiple dosing. The half-life of the drug is ~6 h at steady-state. The plasma concentration is lower with repeated dosing than predicted from single-dose studies due to induction of the cytochrome P450 3A4 isomorph of the liver microsomal enzyme system. Phase II clinical trials have shown that the administration of TPV and RTV in combination is safe and generally well-tolerated in HIV-1-infected adults. Phase III trials are underway to compare the efficacy of this drug versus other antiretroviral regimens. Gastrointestinal toxicity has been described with TPV, the most frequent side effect being diarrhea. Nausea, vomiting and abdominal pain is rare. There is no known evidence of teratogenicity or effect on fertility. TPV dosed twice-daily, in the range of 500 - 1250 mg and combined with 100 - 200 mg of RTV has been shown to substantially and durably reduce viral load in HIV-1-infected drug-naive and experienced patients.

394. Molecular mechanisms underlying midbrain dopamine neuron development and function - Smidt M.P., Smits S.M. and Burbach J.P.H. [M.P. Smidt, Dept. of Pharmacology and Anatomy, Rudolf Magnus Inst. of Neuroscience, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, Netherlands] - EUR. J. PHARMACOL. 2003 480/1-3 (75-88) - sum in ENGL

The mesencephalic dopaminergic system is involved in the control of multiple brain functions including movement control and emotion and is of clinical importance because it is implicated in several psychiatric disorders, of which many are considered to have a neurodevelopmental origin. Studies into the developmental pathways of these neurons have led to the identification of the transcription factors En1, Ptf1a, Nurr1 and Lmx1b, all shown to be important for the development of the mesencephalic dopaminergic system. In this paper, we discuss the consequences of genetic ablation of essential developmental genes. Furthermore, we discuss the consequences of changes in dopamine homeostasis for the function of the mesencephalic dopaminergic system. Finally, we analyse the potential of the mesencephalic dopaminergic system to adapt to gene dysfunction. © 2003 Elsevier B.V. All rights reserved.

395. HPLC-UV method development and validation for 16-dehydroprogrenolone, a novel oral hypolipidaemic agent, in rat biological matrices for application to pharmacokinetic studies - Singh S.K., Mehrotra N., Sabarinath S. and Gupta R.C. [R.C. Gupta, Institute, Chattar Manzil Palace, P.O. Box No. 173, Lucknow 226001, India] - J. PHARM. BIOMED. ANAL. 2003 33A (755-764) - sum in ENGL

An accurate and precise HPLC assay has been developed and validated for determination of dehydroprogrenolone (DHP) in rat plasma, bile, urine and feces. Separation was achieved using a C18 reversed phase column with a mobile phase comprising of acetonitrile and deionized water (55:45% v/v) using a UV detector, set at a wavelength of 248 nm. The method, applicable to 200-μl plasma, bile and urine, involved double extraction of the samples with n-hexane. The sample clean up for feces involved single extraction of 50 mg of sample with 3 ml of acetonitrile. The method was sensitive with a limit of quantitation of 20 ng/ml in all the matrices and absolute recovery -92%. Precision and accuracy were within the acceptable limits, as indicated by relative standard deviation varying from 4.7 to 11.2% and bias values ranging from 1.8 to 8.8%. Moreover, DHP was stable in plasma, bile and urine up to 90 days of storage at -60°C and after being subjected to freeze-thaw cycles. The method was applied to generate the pharmacokinetics
of DHP in rats after oral and intravenous administration. © 2003 Elsevier B.V. All rights reserved.

396. Health benefits and potential risks related to consumption of fish or fish oil - Sidhu K.S. [K.S. Sidhu, Inst. for Environmental Toxicology, Michigan State University, C321 Holden Hall, East Lansing, MI 48824, United States] - REGUL. TOXICOL. PHARMACOL. 2003 38/3 (336-344) - summ in ENGL

The nutritional benefits of fish consumption relate to the utilization of proteins of high biological value, as well as certain minerals and vitamins that fish provide. Fish or fish oil contains omega-3 polyunsaturated fatty acids (PUFAs) that appear to play several useful roles for human health. Conversely, some carcinogenic contaminants are also stored in the adipose tissue of fish. The objective of this paper is to evaluate the potential health benefits and risks related to the consumption of fish or fish oil. Health benefits related to the consumption of fish or omega-3 PUFAs were obtained by an extensive literature search. Potential health risks related to carcinogenic contaminants (e.g., dioxin, PCB, etc.) in fish were estimated using the U.S. EPA-approved cancer risk assessment guidelines. Potential health risk estimates were evaluated by comparing them with the acceptable excess risk level of 10⁻⁶⁻¹⁰⁻⁴. Scientific data indicate that the consumption of fish or fish oil containing omega-3 PUFAs reduces the risk of coronary heart disease, decreases mild hypertension, and prevents certain cardiac arrhythmias and sudden death. Risk estimates in humans for carcinogenic environmental contaminants in fish ranged from an excess risk level of 3·10⁻⁶⁻¹·0·10⁻⁴. These risk estimates appear to meet the acceptable excess risk level criteria. Therefore, consumption of fish in accordance with the State of Michigan Fish Advisory Guidelines is safe and should be encouraged. The top 11 fish species [e.g., sardines, mackerel, herring (Atlantic and Pacific), lake trout, salmon (Chinook, Atlantic, and Sockeye), anchovy (European), sablefish, and bluefish] provide an adequate amount of omega-3 PUFAs (2·7-7.5g/meal) and should be encouraged. The top 11 fish species [e.g., sardines, mackerel, herring (Atlantic and Pacific), lake trout, salmon (Chinook, Atlantic, and Sockeye), anchovy (European), sablefish, and bluefish] provide an adequate amount of omega-3 PUFAs (2·7-7.5g/meal) and should be encouraged.

397. Diving emergencies - DeGorordo A., Vallejo-Manzur F., Chann K. and Varon J. [J. Varon, Baylor College of Medicine, University of Texas, Health Science Center-Houston, 2219 Dorrington St., Houston, TX 77030, United States] - RESUSCITATION 2003 59/2 (171-180) - summ in ENGL, PORT, SPAN

Self-Contained Underwater Breathing Apparatus (SCUBA) diving popularity is increasing tremendously, reaching a total of 9 million people in the US during 2001, and 50,000 in the UK in 1985. Over the past 10 years, new advances, equipment improvements, and improved diver education have made SCUBA diving safer and more enjoyable. Most diving injuries are related to the behaviour of the gases and pressure changes during descent and ascent. The four main pathways in diving medicine include: barotrauma (sinus, otor, and pulmonary); decompression illness (DCI); pulmonary edema and pharmacological, and toxic effects of increased partial pressures of gases. The clinical manifestations of a diving injury may be seen during a dive or up to 24 h after it. Physicians living far away from diving places are not excluded from the possibility of encountering diver-injured patients and therefore need to be aware of these injuries. This article reviews some of the principles of diving and pathophysiology of diving injuries as well as the acute treatment, and further management of these patients. © 2003 Elsevier Ireland Ltd. All rights reserved.


The integrity of lipid microdomains is disrupted after cell treatment with cholesterol-depleting reagents, such as methylβ-cyclodextrin (MCD). We investigated the roles of lipid microdomains in the regulation of intracellular signaling events and functional responses in isolated human neutrophils with MCD caused inhibition of intracellular calcium increase evoked by interleukin-8 (IL-8) or low concentrations of formyl-Met-Leu-Phe (fMLP). No significant decrease of the initial peak of the calcium response was measured when neutrophils were stimulated with 100 nM or higher concentrations of fMLP. MCD inhibited the phosphorylation of extracellular signal-regulated kinase (Erk)-induced by IL-8 or lower concentrations of fMLP. However, Erk phosphorylation evoked by higher concentrations of fMLP was only slightly affected. MCD treatment increased phosphorylation of p38 MAP kinase and caused strong up-regulation of both CD11b and CD66b in resting neutrophils. Cholesterol depletion greatly inhibited IL-8-induced elastase release but had little effect of fMLP-induced degranulation. Our study brings evidence suggesting that lipid microdomains are critically required for the signaling events triggered by IL-8. Calcium mobilization and elastase release induced by WKYVMV, a selective agonist for formyl peptide receptor-like 1 (FPR1), were significantly inhibited by MCD, suggesting that the resistance of fMLP-mediated responses to MCD is not related to the partition of receptor subtypes to lipid microdomains. It is more probable that cholesterol depletion interferes with the ability of different G proteins to couple to their corresponding receptors and this might account for the differential effects of MCD treatment on chemoattractant-induced effects in human neutrophils. © 2003 Elsevier B.V. All rights reserved.


This review addresses the use of high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) as affinity separation methods to characterise drugs or potential drugs-bio polymer interactions. Targets for the development of new drugs such as enzymes (IMERs), receptors, and membrane proteins were immobilized on solid supports. After the insertion in the HPLC system, these immobilized bio-polymers were used for the determination of binding constants of specific ligands, substrates and inhibitors of pharmaceutical interest, by frontal analyses and zonal elution methods. The most used bio-polymer immobilization techniques and methods for assessing the amount of active immobilized protein are reported. Example of increased stability of immobilized enzymes with reduced amount of used protein were shown and the advantages in terms of recovery for reuse, reproducibility and on-line high-throughput screening for potential ligands are evidenced. Dealing with the acquisition of relevant pharmacokinetic data, examples concerning human serum albumin binding studies are reviewed. In particular, papers are reported in which the serum carrier has been studied to monitor the entanisoselective binding of chiral drugs and the mutual interaction between co-administered drugs by CE and HPLC. Finally CE, as merging techniques with very promising and interesting application of microscale analysis of drugs' binding parameters to immobilized bio-polymers is examined. © 2003 Elsevier B.V. All rights reserved.


Compared with traditional sampling methods, microdialysis is a technique for protein unbound drug sampling without withdrawal of biological fluids and involving minimal disturbance of physiological function. Conventional total drug sample consists of unbound drugs and protein bound drugs, which are loosely bound to plasma proteins such as albumin and alpha-1 acid glycoprotein, forming an equilibrium ratio between bound and unbound drugs. However, only the unbound fraction of drug is available for absorption, distribution, metabolism and elimination, and delivery to the target sites for pharmacodynamic actions. Although several techniques have been used to determine protein unbound drugs from biological fluids, including ultrafiltration, equilibrium dialysis and microdialysis, only microdialysis allows simultaneous sampling of protein unbound chemicals from plasma, tissues and body fluids such as the bile juice.
and cerebral spinal fluid for pharmacokinetic and pharmacodynamic studies. This review article describes the technique of microdialysis and its application in pharmacokinetic studies. Furthermore, the advantages and limitations of microdialysis are discussed, including the detailed surgical techniques in animal experiments from rat blood, brain, liver, bile duct and in vitro cell culture for inhibiting gene transfer by cationic lipids and polymers. © 2003 Elsevier B.V. All rights reserved.

401. Separation methods applicable to the evaluation of enzyme-inhibitor and enzyme-substrate interactions - Burns K.L. and May S.W. [S.W. May, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, United States] - J. CHROMATOGR. B ANAL. TECHNOL. BIOMED. LIFE SCI. 2003 797/1-2 (175-190) - summ in ENGL

Enzymes catalyze a rich variety of metabolic transformations, and do so with very high catalytic rates under mild conditions, and with high reaction regiospecificity and stereospecificity. These characteristics make biocatalysis highly attractive from the perspectives of biotechnology, analytical chemistry, and organic synthesis. This review, containing 128 references, focuses on the use of separation techniques in the elucidation of enzyme-inhibitor and enzyme-substrate interactions. While coverage of the literature is selective, a broad perspective is maintained. Topics considered include chromatographic methods with soluble or immobilized enzymes, capillary electrophoresis, biomolecular interaction analysis tandem mass spectrometry (BIA-MS), phage and ribosomal display, and immunoisolated enzyme reactors (IMERs). Examples were selected to demonstrate the relevance and applicability of these methods for determining enzyme kinetic parameters, ranking of enzyme inhibitors, and stereospecific synthesis and separation of chiral entities. © 2003 Elsevier B.V. All rights reserved.

402. Capillary electrophoresis-based immunoassay - Yeung W.S.B., Luo G.A., Wang Q.G. and Ou J.P. [W.S.B. Yeung, Dept. of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, Hong Kong] - J. CHROMATOGR. B ANAL. TECHNOL. BIOMED. LIFE SCI. 2003 797/1-2 (217-228) - summ in ENGL

Capillary electrophoresis-based immunoassay (CEIA) is a developing analytical technique with a number of advantages over conventional immunoassay, such as reduced sample consumption, simpler procedure, easy simultaneous determination of multiple analytes, and short analysis time. However, there are still a number of technical issues that researchers on CEIA have to solve before the assay can be more widely used. These issues include method to improve the concentration sensitivity of the assay, requirement for robust separation strategy for different analytes, and method to increase the throughput of the assay. The approaches to solve these issues are reviewed. Several studies have been devoted to develop general separation strategies for CEIA, and to enhance the sensitivity of detection. The recent development of microchip-based CEIA is encouraging and is likely to address more drawbacks of CEIA, particularly on the throughput issue. © 2003 Elsevier B.V. All rights reserved.

403. Extracellular and intracellular barriers in non-viral gene delivery - Ruppen M., Honkakoski P., Riikko S. et al. [A. Urtti, Department of Pharmaceutics, University of Kuopio, Harjulantie 1 A, 70211 Kuopio, Finland] - J. CONTROL. RELEASE 2003 93/2 (213-217) - summ in ENGL

Complexes of DNA with cationic lipids and cationic polymers are frequently used for gene transfer. Extracellular interactions of the complexes with anionic glycosaminoglycans (GAGs) may interfere with gene transfer. Interactions of GAGs with carrier DNA complexes have been studied using tests for DNA relaxation (ethidium bromide intercalation), DNA release (eluted bromohydrin), capillary electrophoresis, biomolecular interaction analysis tandem mass spectrometry (BIA-MS), phage and ribosomal display, and immunoisolated enzyme reactors (IMERs). Examples were selected to demonstrate the relevance and applicability of these methods for determining enzyme kinetic parameters, ranking of enzyme inhibitors, and stereospecific synthesis and separation of chiral entities. © 2003 Elsevier B.V. All rights reserved.

404. Serotonin receptors in platelets of bipolar and schizoaffective patients: Effect of lithium treatment - Pandey G.N., Pandey S.C., Ren X. et al. [G.N. Pandey, Psychiatric Institute, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor Street, Chicago, IL 60612, United States] - PSYCHOPHARMACOLOGY 2003 170/2 (115-123) - summ in ENGL

Rationale: Abnormalities of serotonin (5HT) function have been implicated in mood disorders, and lithium treatment may produce its beneficial effects by modifying serotonergic mechanisms. It has also been observed that 5HT3A receptors are upregulated both in the postmortem brain and platelets of patients with depression and suicidal behavior. However, the role of 5HT3A receptors in bipolar disorders and in the mechanism of action of lithium is unclear. Objective: The major objective of this study was to examine if abnormalities of 5HT3A receptors are associated with bipolar disorder in patients with bipolar disorders and in the mechanism of action of lithium is unclear. It is also not clear whether the increase in 5HT3A receptors in bipolar or schizoaffective patients, or in suicidal bipolar or schizoaffective patients, is a trait or state marker.

405. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses - Melkerson K.I. and Dahl M.-L. [K.I. Melkerson, Department of Molecular Medicine, Sollentuna Psychiatric Polyclinic, Karolinska Institute, Stockholm, Sweden] - J. CONTROL. RELEASE 2003 93/2 (157-166) - summ in ENGL

Rationale: Recent results suggest that treatment with the atypical antipsychotics clozapine and olanzapine is associated with increased insulin and lipid levels. Objective: The aim of this study was to investigate potential relationships between insulin or other hormones related to glucose-insulin homeostasis and lipid or steady-state serum concentrations of clozapine or olanzapine in patients on therapeutic doses. Methods: Thirty-four patients, diagnosed with schizophrenia or related psychoses accounted for 30-60% of the patients, hyperglycemia in 10-30%, hyperlipidemia in 40-60% and hyperleptinemia in 10-20%. Moreover, levels of insulin, C-peptide and triglycerides correlated positively to the clozapine serum concentration and to the ratio of olanzapine to N-desmethylolanzapine concentrations. In contrast, levels of C-peptide, leptin GAGs (heparan sulfate, chondroitin sulfates B and C) completely blocked transcription, except in the case of liposomes with DOPE. Sulfated GAGs relaxed and released DNA from some complexes, but these events were not prerequisites for the inhibition of transcription. Furthermore, preliminary results suggest that cell surface GAGs are implicated in the inhibition gene transfer by cationic lipids and polymers. © 2003 Elsevier B.V. All rights reserved.
and blood glucose were inversely correlated to the serum concentration of the metabolic N-desmethylolanzapine. Conclusions: Metabolic abnormalities (i.e. hyperinsulinemia, hyperlipidemia and hyperleptinemia) and insulin resistance were associated with both clozapine and olanzapine treatments. Levels of insulin and triglycerides increased by increasing clozapine serum concentration and by increasing ratio of olanzapine to N-desmethylolanzapine; the last due to the metabolite N-desmethylolanzapine probably having an inverse effect to the main compound olanzapine. Thus, the metabolic abnormalities induced by these two drugs are clozapine-concentration dependent in clozapine-treated patients, and ratio of olanzapine to N-desmethylolanzapine- concentration dependent in olanzapine-treated patients.

406. Importance of P-glycoprotein for drug disposition in humans - Fromm M.F. [Dr. M.F. Fromm, Dr. Margarete Fischer-Bosch-Institut, Auerbachstr. 112, 70376 Stuttgart, Germany] - EUR. J. CLIN. INVEST. SUPPL. 2003 332 (6-9) - sum in ENGL

The ATP-binding cassette transporter P-glycoprotein is now recognized as an important determinant for disposition of multiple drugs. The use of P-glycoprotein-expressing cell lines, the generation of P-glycoprotein knockout mice as well as studies in animals and humans contributed to a better understanding on the role of active transport in drug disposition. P-glycoprotein is located in tissues with excretory function such as intestine, liver and kidney. Moreover, due to its expression in important blood-tissue barriers (blood-brain and blood-testis barriers), in lymphocytes and in placenta it limits tissue penetration of its substrates. Induction and inhibition of P-glycoprotein have now been identified as important underlying mechanisms of drug interactions in humans. Using selected examples, this review summarizes currently available data on the impact of P-glycoprotein for bioavailability of drugs, drug interactions and drug effects.


Osteoporosis is a skeletal disorder characterised by compromised bone predisposing a person to an increased risk of fracture. Osteoporosis develops through an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts resulting in increased bone loss. Numerous agents used for the prevention and treatment of osteoporosis slow bone loss by decreasing both bone resorption and formation. These include bisphosphonates, hormone replacement therapy, selective oestrogen receptor modulators and calcitonins. All reduce vertebral fracture risk and some reduce non-vertebral fracture risk, but none routinely increases bone mass and strength or restores lost bone architecture. In many respects, antiresorptive therapies halt or reverse bone loss but not for patients who have osteoporosis, particularly those who have sustained their first fracture and are at high risk for subsequent fractures, there is a need to develop agents that stimulate bone formation and, thus, reverse osteoporosis. Teriparatide is the recombinant human 1-34 amino acid sequence of parathyroid hormone recently approved in the US for the treatment of men and postmenopausal women at high risk for osteoporotic fracture and in Europe for the treatment of postmenopausal women with osteoporosis. When given by once-daily injection, teriparatide increases bone mass by stimulating formation of new bone, resulting in the restoration of bone architecture.

408. Polymorphisms and the Pocketbook: The Cost-Effectiveness of CYP2C19 homozygous extensive metabolizers (EMs), heterozygous EMs and poor metabolizers (PMs), altering the antihypertensive regimen in the genotyped cohort only. The authors took the perspective of a third-party payer, and the denominator was ulcer episode prevented. In the reference case, the use of CYP2C19 genotyping prior to initiating antihypertensive therapy was dominant (costs were saved with each ulcer episode prevented) in all geographic regions of the United States. The subsequent break-even analysis showed a range of $89.20 to $118.96 from Hawaii to the Midwest, respectively required to eliminate the cost-savings from each genotype test performed. Using probabilities most unfavorable to genotyping, the variation of peoples with Pacific Rim origins from 0% to 100% altered the cost-effectiveness from $495 to $2125 per ulcer event prevented, respectively. The results suggest that treatment decisions for H. pylori infection that are based on a patient's CYP2C19 genotype decreases expenses for health plans implementing testing. This analysis provides an economic basis to support recent calls to expand this technology into routine clinical care to prevent toxicity of narrow therapeutic index drugs.

409. Pharmacokinetics and Pharmacodynamics of Mesna-Mediated Plasma Cysteine Depletion - Smith P.F., Booker B.M., Creaven P. et al. [P.F. Smith, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States] - J. CLIN. PHARMACOL. 2003 43/12 (1324-1328) - sum in ENGL

Cellular glutathione (GSH) levels are related to the resistance of tumor cells to platinum and alkylating agents, and depletion of GSH may enhance the activity of these drugs. The pharmacodynamic effects of mesna on depleting plasma cysteine, a GSH precursor, were evaluated in 22 patients as part of a Phase I study. Escalating doses of ifosfamide and mesna were administered; carboplatin was administered to achieve an AUC of 4 mg-min/mL. Plasma samples were collected and assayed by reverse-phase high-performance liquid chromatography (HPLC) for total mesna and total cysteine concentrations at 0, 1, 3, 6, 24, 25, 28, and 48 hours. A one-compartment pharmacokinetic model was fit to the mesna plasma concentrations, using M.A.P Bayesian estimation (ADAPT II). Pharmacodynamics were evaluated by fitting an inhibitory Emax model to the cysteine concentration data. Both the pharmacokinetic (median R² = 0.95; range = 0.85-0.98) and pharmacodynamic (median R² = 0.96; range = 0.74-1.0) models fit the data well. Mean (coefficient of variation (CV%)) mesna pharmacokinetic parameter estimates were as follows: Vₘ = 15.5 (29) L/m², CL of 4.6 (29) L/h/m², and half-life of 2.2 (37) hours. Mean (CV%) pharmacodynamic parameter estimates were as follows: Eₘ = 31.7 (19) µg/mL and EC₅₀ of 10.3 (52) µg/mL. Mesna produced a rapid, concentration-dependent reduction in plasma cysteine concentrations that could be adequately characterized by an inhibitory Emax model. The depletion of plasma cysteine was facilitated by ifosfamide, suggesting a pharmacodynamic interaction between these two agents. Further increases in mesna doses beyond those administered in this study would be unlikely to provide additional benefit.


Meropenem, a carbapenem broad-spectrum antibiotic, is regularly used in patients undergoing continuous venovenous hemodiafiltration (CVVHDF). Its disposition was studied over one dosage interval in 15 patients under CVVHDF on a steady regimen of 500 or 1000 mg every 8 to 12 hours. Meropenem levels were measured in plasma and filtrate-dialysate by high-performance liquid chromatography (HPLC) with UV detection. The mean CVVHDF flow rates were 7.1 ± 0.9 L/h for blood (mean ± SD), 0.5 ± 0.3 L/h for predilution solution, 1.2 ± 0.3 L/h for countercurrent dialysate, and 1.8 ± 0.5 L/h for the total filtrate-dialysate. The pharmacokinetic analysis was based both on a noncompartmental approach and on a four-compartment modeling. The mean (coefficient of variation (CV)) total body clearance, volume of distribution at steady state
state, and mean residence time were, respectively, 5.0 L/h (46%), 14.3 L (29%), and 4.8 h (36%). The hemodialfiltration clearances calculated from plasma data alone and plasma with filtrate-dialy- sate data were 1.2 L/h (26%) and 1.6 L/h (39%), respectively. The compartmental model was used to optimize the therapeutic schedule of meropenem, considering reference minimal inhibitory concen- tration (MIC) of sensitive strains (4.4 mL/L). The results indicate that two different therapeutic schedules of meropenem are equally applicable to patients receiving CVVHD: either 750 mg tid or 1500 mg bid.


HMR1031 is an inhaled drug being developed for the treatment of asthma using an Ultrahaler® dry-powder inhalation device. A pharmacokinetic study of HMR1031 suggests that two different therapeutic schedules of meropenem are equally applicable to patients receiving CVVHD: either 750 mg tid or 1500 mg bid.

413. Antiparasitic activity of highly conjugated pyrimidine-2,4-dione derivatives - Azas N., Rathelot F., Djkoe S. et al. [N. Azas, Laboratoire de Parasitologie, EA 864, Faculté de Pharmacie, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 5, France] - FARMACO 2003 58/12 (1263-1270) - sum in ENGL.

The inhibitory activity of highly conjugated pyrimidine-2,4-dione derivatives, against several drug-resistant Plasmodium falciparum, Trichomonas vaginalis and Leishmania infantum compared to their toxicity versus human cells. © 2003 Published by Éditions scientifiques et médicales Elsevier SAS.

414. Synthesis of aniline-type analogues of farnesyl diphasphate and their biological assays for prenyl protein transfor- mable activity - Minutilo F., Bertini S., Betta L. et al. [M. Macchia, Dpto. di Scienze Farmaceutiche, Università di Pisa, Via Bonannò 6, 56126 Pisa, Italy] - J. CLIN. PHARMACOL. 2003 58/12 (1277-1281) - sum in ENGL.

Stable analogues of farnesyl diphasphate, possessing an aniline-type FPP in the prenyl-mimetic moiety and phosphono- acetamido(ox) groups in the place of the metabolically unstable diphasphate unit, were synthesized and submitted to biological assays. The enzyme inhibition tests performed on FTase and GGTase I show that the newly synthesised compounds based on a combination of the aniline-containing portions with (phosphonoacetamido)oxy groups do not afford potent inhibitors. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.


The expression of cyclooxygenase-2 (COX-2) is a characteris- tic response to inflammation and can be inhibited with sodium salicylate. TNF-α plus IFN-γ can induce extracellular sig- nal-regulated kinase (ERK), IKK, IκB degradation and NF-κB activation. The inhibition of the ERK pathway with selective in- hibitor, PD98059, blocked cytokine-induced COX-2 expression and PGE2 release. Salicylate treatment inhibited COX-2 expression induced by TNF-α/IFN-γ and regulated the activation of ERK, IKK and IκB degradation and subsequent NF-κB activation in MC3T3E1 osteoblasts. Furthermore, antioxidants such as cata- lase, N-acetyl-cysteine or reduced glutathione attenuated COX-2 expression in combined cytokines-treated cells, and also inhibited the activation of ERK, IKK and NF-κB in MC3T3E1 osteoblasts. In addition, TNF-α/IFN-γ stimulated ROS release in the osteo- blasts. However, salicylate had no obvious effect on ROS release in DCFDA assay. The results showed that salicylate inhibited the activation of ERK and IKK, IκB degradation and subsequent NF-κB activation independent of ROS release and suggested that salicylate exerts its anti-inflammatory action in part through inhibition of ERK, IKK, IκB, NF-κB and resultant COX-2 expression way.

417. Metabolites of orally administered Magnolia officinalis ex- tract in rats and man and its antidepressant-like effects in mice

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421. Unique actinomycin D binding to self-complementary d(CXYGGCCY'G) sequences: Duplex disruption and binding to a nominally base-paired hairpin - Chen F.-M., Sha F., Chin K.-H. and Chou S.-H. [F.-M. Chen, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37209-1561, United States] - NUCLEIC ACIDS RES. 2003 31/14 (4238-4246) - summ in ENGL

422. Therapeutic modulation of endogenous gene function by agents with designated DNA-sequence specificities - Uil T.G., Haismn H.J. and Rots M.G. [M.G. Rots, Department of Therapeutic Gene Modulation, University Center for Pharmacy, PO Box 196, 9700 AD Groningen, Netherlands] - NUCLEIC ACIDS RES. 2003 31/21 (6064-6078) - summ in ENGL
Designer molecules that can specifically target pre-determined DNA sequences provide a means to modulate endogenous gene function. Different classes of sequence-specific DNA-binding agents have been developed, including triplex-forming molecules, synthetic polynucleotides and designer zinc finger proteins. These different types of designer molecules use different principles of engineered sequence specificity are reviewed in this paper. Furthermore, we explore and discuss the potential of these molecules as therapeutic modulators of endogenous gene function, focusing on modulation by stable gene modification and by regulation of gene transcription.

423. Energetics of echinomycin binding to DNA - Leng F., Chaires J.B. and Waring M.J. [M.J. Waring, Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge CB2 1PD, United Kingdom] - NUCL. ACIDS RES. 2003 31/21 (6191-6197) - sum in ENGL

Differential scanning calorimetry and UV thermal denaturation have been used to determine a complete thermodynamic profile for the bis-intercalative interaction of the peptide antibiotic echinomycin with DNA. The new calorimetric data are consistent with all previously published binding data, and afford the most rigorous and direct determination of the binding enthalpy possible. For the association of echinomycin with DNA, we found $\Delta G = -7.6 \text{ kcal mol}^{-1}$, $\Delta H = +3.8 \text{ kcal mol}^{-1}$ and $\Delta S = +38.9 \text{ cal mol}^{-1} \text{ K}^{-1}$ at 200$^\circ$C. The binding reaction is clearly entropically driven, a hallmark of a process that is predominantly stabilized by hydrophobic interactions, though a deeper analysis of the free energy contributions suggests that direct molecular recognition between echinomycin and DNA, mediated by hydrogen bonding and van der Waals contacts, also plays an important role in stabilizing the complex.


Decreased production of endothelium-derived nitric oxide (NO) has been implicated in the pathogenesis of cardiovascular diseases. Metabolic end products of nitric oxide (NOx) are often used as markers for endothelial NO production in humans. Decreased endothelium-derived NO has been suggested to mediate some of the deleterious effects of conventional cardiovascular risk factors such as hypercholesterolemia, smoking, and physical inactivity because they induce a decrease in plasma NOx. A substantial number of patients with cardiovascular diseases suffer from comorbid major depressive disorder, which is a predictor of a poorer cardiovascular outcome. Paroxetine is a first-line antidepressant and has been reported to decrease plasma NOx, theoretically suggesting a potential deleterious effect on the cardiovascular system. We assessed the hypothesis that paroxetine would induce a decrease in plasma NOx in healthy volunteers. Plasma NOx levels were measured by chemiluminescence at baseline, after 8 weeks of paroxetine administration, and at postdiscontinuation. Contrary to our hypothesis, we found that paroxetine administration induced a significant increase in plasma NOx that normalized after paroxetine discontinuation. It remains to be demonstrated that the paroxetine-induced increase in plasma NOx is associated with a modification of the cardiovascular risk in patients with major depressive disorder.


Purpose. To evaluate the uptake of chitosan molecules (fCS) and nanoparticles (fNP), and their ability to mediate insulin transport in Caco-2 cell monolayers. Methods. Cell-associated fCS and fNP were evaluated by fluorometry, trypan blue quenching, and confocal microscopy using FITC-labeled chitosan. Chitosan-mediated transport of FITC-labeled insulin was studied in Caco-2 cell monolayers cultured on permeable inserts. Results. Caco-2 cells showed twofold higher association with fNP than fCS after 2-h incubation with 1 mg/ml samples. fNP uptake was a saturable ($K_m = 1.04 \text{ mg/ml}$; $V_{\text{max}} = 74.15 \text{ mg/h)}$ concentration- and temperature-dependent process that was inhibited by coadministered chlorpromazine. fCS uptake was temperature dependent, but was less sensitive to concentration and was inhibited by filipin. Postuptake quenching with 100 $\mu$g/ml of trypan blue suggests a significant amount of intracellular fNP, although the bulk of fCS was extracellular. Internalized fNP were located by confocal microscopy at 15 $\mu$m from the apical membrane, but there was no apparent breach of the basal membrane. This might explain the failure of the nanoparticles to mediate significant insulin transport across the Caco-2 cell monolayer. Conclusions. Formulation of chitosan into nanoparticles transforms its extracellular interactions with the Caco-2 cells to one of cellular internalization via cluthrin-mediated endocytosis.


Purpose. The validity of using drug amount-depth profiles in stratum corneum to predict uptake of clobetasol propionate into stratum corneum and its transport into deeper skin layers was investigated. Methods. The technique of layering was found to be compatible with a two-layer skin model. Results. The concentration-depth profile of clobetasol propionate in stratum corneum for the diffusion experiment is biphasic. A logarithmic decline of the drug concentration over the first four to five tape strips flattens to a relatively constant low concentration level in deeper layers. The drug concentration-depth profile for the equilibrium experiments displays a similar shape. Conclusions. The shape of the concentration-depth profile of clobetasol propionate is mainly because of the variable partitioning coefficient in different stratum corneum layers.

427. Poly-L-Arginine Enhances Paracellular Permeability via Serine/Threonine Phosphorylation of ZO-1 and Tyrosine Dephosphorylation of Occludin in Rabbit Nasal Epithelium - Ohtake K., Maeno T., Ueda H. et al. [H. Natsume, Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan] - PHARM. RES. 2003 20/11 (1838-1845) - sum in ENGL

Purpose. The purpose of the present study is to explore whether a polycationic drug, poly-L-Arg (Poly-L-Arg), is capable of changing the TJ permeability of fluorescein isothiocyanate-labeled dextran (MW 4.4 kDa, FD-4) and associated with the Ca$^{2+}$-dependent signaling pathways. Methods. In vitro, the protein kinases (PKC) and serine/threonine protein kinases (Ca$^{2+}$/CaM-dependent) in TJ permeability of FD-4 induced by 0.2 mg/ml poly-L-Arg was not altered by treatment with inhibitors of possible Ca$^{2+}$ mobilization pathways followed by exposure of poly-L-Arg, suggesting that the promoting effect of poly-L-Arg is independent of Ca$^{2+}$-related signaling pathways. On the other hand, the protein kinase C inhibitor (staurosporine) and Ca$^{2+}$/CaM-dependent kinase (calmodulin) in TJ permeability of FD-4 induced by poly-L-Arg, indicating that serine/threonine phosphorylation by Ca$^{2+}$-independent PKC and tyrosine dephosphorylation of junction proteins may have occurred. Furthermore, immunofluorescent microscopy of ZO-1, a TJ associated protein, and occludin, an integral membrane protein localizing at TJ, after preincubation with PKC and tyrosine phosphorylation inhibitors followed by poly-L-Arg treatment has shown that ZO-1 and occludin occurred by way of serine/threonine phosphorylation by...
null
human urine and bovine serum. We determined the effect of indirubin in MCF-7 breast cancer cells on induction of the activities of cytochromes P450 (CYP1A1 and 1B1, as measured by estradiol and ethynylestradiol metabolism, and on induction of the CYP1A1 and CYP1B1 mRNAs. With 4-hr exposure, the effects of indirubin and TCDD at 10nM on CYP activity were comparable, but the effects of indirubin, unlike those of TCDD, were transitory. Indirubin-induced ethynylestradiol-0-deethylase activity was maximal by 6-9hr post-exposure and had disappeared by 24hr, whereas TCDD-induced activities remained elevated for at least 72hr. The effects of indirubin on CYP mRNA induction were maximal at 3hr. Indirubin was metabolized by microsomes containing cDNA-expressed human CYP1A1 or CYP1B1. The potency of indirubin was comparable to that of TCDD in a CYP1B1-promoter-driven luciferase assay, when MCF-7 cells were co-exposed to the AhR ligands together with the CYP inhibitor, elliphticine. Thus, if indirubin is an endogenous AhR ligand, then AhR-mediated signaling by indirubin is likely to be transient and tightly controlled by the ability of indirubin to induce CYP1A1 and CYP1B1, and hence its own metabolism. © 2003 Elsevier Inc. All rights reserved.


The inhibition of arterial tone produced by two nitric oxide (NO)-derivatives of biological relevance, dinitrosyl-iron complexes with cysteine (DNIC-CYS) or with glutathione (DNIC-GSH), was compared. Both compounds induced vasorelaxation within the same range of concentration (3-300nM) in endothelium-denuded rat aortic rings. Consistent with a faster rate of NO release from DNIC-CYS than from DNIC-GSH, the relaxant effect of DNIC-CYS was rapid in onset and tended to recover with time, whereas the one from DNIC-GSH tended to recover with time, whereas the one from DNIC-GSH was comparable to that of TCDD in a CYP1B1-promoter-driven luciferase assay, when MCF-7 cells were co-exposed to the AhR ligands together with the CYP inhibitor, elliphticine. Thus, if indirubin is an endogenous AhR ligand, then AhR-mediated signaling by indirubin is likely to be transient and tightly controlled by the ability of indirubin to induce CYP1A1 and CYP1B1, and hence its own metabolism. © 2003 Elsevier Inc. All rights reserved.


Glycyrrhetinic acid, a hydrolys product of one of the main constituents of licorice, the triterpenic glycoside of glycyrrhetic acid, when added to rat liver mitochondria at micromolar concentrations induces swelling, loss of membrane potential, pyridine nucleotide oxidation, and release of cytochrome c and apoptosis inducing factor. These changes are Ca2+ dependent and are prevented by cyclosporin A, bongkrekic acid, and N-ethylmaleimide. All these observations indicate that glycyrrhetic acid is a potent inducer of mitochondrial permeability transition and can trigger the pro-apoptotic pathway. © 2003 Elsevier Inc. All rights reserved.

436. Naturally occurring 2'-hydroxy-substituted flavonoids as high-affinity benzodiazepine site ligands - Huen M.S.Y., Leung J.W.C. et al. [H. Xue, Department of Biochemistry, Hong Kong Univ. of Sci/Technology, Clear Water Bay, Kowloon, Hong Kong] - BIOCHEM. PHARMACOL. 2003 66/12 (2397-2407) - summa in ENGL

Screening of traditional medicines has proven invaluable to drug development and discovery. Utilizing activity-guided purification, we previously reported the isolation of a list of flavonoids from the medicinal herb Scutellaria baicalensis Georgie, one of which manifested an affinity for the benzodiazepine receptor (BDZR) comparable to that of the synthetic anxiolytic diazepam (Kd=6.4nM).

In the present study, this high-affinity, naturally occurring flavono-"{}id derivative, 5,7,2'-trihydroxy-6,8-dimethoxyflavone (K36), was chosen for further functional and behavioral characterization. K36 inhibited [(3H)lumitrazepam binding to native BDZR with a Kd value of 6.05nM. In electrophysiological experiments K36 potentiated currents mediated by rat recombinant α1β2γ3 GABAA receptors expressed in Xenopus oocytes. This potentiation was characterized by a threshold (1nM) and half-maximal stimulation (24nM) similar to diazepam. This enhancement was demonstrated to act via the BDZR, since co-application of 1μM of the BDZR antagonist Ro15-1788 reversed the potentiation. Oral administration of K36 produced significant BDZ-mediated anxiolysis in the mice elevated plus-maze, which was abolished upon co-administration of Ro15-1788. Sedation, myorelaxation and motor incoordination were not observed in the chosen dosage regimen.

Structure-activity relationships utilizing synthetic flavonoids with different substitutions on the flavone backbone supported that 2'-hydroxy-substitution is a critical moiety on flavonoids with regard to BDZR affinities. These results further underlined the potential of flavonoids as therapeutics for the treatment of BDZR-associated syndromes. © 2003 Elsevier Inc. All rights reserved.

437. Inhibition of plasmalemmal Na+/Ca2+ exchange by mitochondrial Na+/Ca2+ exchange inhibitor 7-chloro-5,1,5 dihydro-4,1-benzo-azepin-2(3H)-one (CGP-37157) in cerebellar granule cells - Cyra A. and Kieforderwska L. [L. Kieforderwska, Department of Psychiatry, Psychiatric Institute, University of Illinois at Chicago, 1601 W. Taylor St., Chicago, IL 60612, United States] - BIOCHEM. PHARMACOL. 2003 66/12 (2409-2411) - summa in ENGL

In the heart, 7-chloro-5-(2-chlorophenyl)-1,5 dihydro-4,1-benzo-azepin-2(3H)-one (CGP-37157) inhibits mitochondrial but not sarcoplasmal Na+ /Ca2+ exchange. Therefore, CGP-37157 is often used as an experimental tool to study the role of mitochondrial Na+/Ca2+ exchange in Ca2+ homeostasis in various cells, including neurons. However, neurons express several K+-dependent (NCKX) and K+-independent (NCX) isoforms of plasmalemmal Na+/Ca2+ exchange not expressed in the sarcolemma. Because it has never been determined whether CGP-37157 inhibits plasmalemmal NCKX and/or NCX isoforms in neurons, we investigated the inhibition of 7-chloro-5-(2-chlorophenyl)-1,5 dihydro-4,1-benzo-azepin-2(3H)-one (CGP-37157) in cerebellar granule cells.

In primary cultures of cerebellar granule cells, CGP-37157 with IC50 of 13nM inhibits plasmalemmal Na+ /Ca2+ exchange not expressed in the sarcolemma. Because it has never been determined whether CGP-37157 inhibits plasmalemmal NCKX and/or NCX isoforms in neurons, we investigated the inhibition of 7-chloro-5-(2-chlorophenyl)-1,5 dihydro-4,1-benzo-azepin-2(3H)-one (CGP-37157) in cerebellar granule cells.
domains of the human (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxo-
propionic acid (AMPA) and kainate-selective ionotropic glutamate receptors (GlurRs): GlurK-1 and KA1-2. Based on the analysis of the known X-ray structures of GlurK2 in complex with glutamate, kainate, and AMPA, we have constructed binding motifs (relative positioning of a ligand in the binding site and the physico-chemical interactions that take place) for selected agonist ligands and found explanations for ligand-binding selectivity to homomeric receptors among the different GlurRs. Even a single sequence difference can explain significant differences in ligand-
binding affinities between two receptors. In total, there are seven residues surrounding the binding cavity that affect agonist selectivity: in GlurK2, these residues are Pro478, Thr480, Leu650, Ser654, Thr686, Tyr702, and Met708. Each of these seven positions has been shown, or is predicted, to influence the presence of one or more water molecules that, when present, may form bridging hydrogen bonds between particular ligands and receptors. By using this knowledge it should be possible to design new selective agonist ligands with high affinity for any AMPA/kainate receptor. © 2003 Elsevier Inc. All rights reserved.

43.9. Agonist-induced desensitization and endocytosis of hetero-

The purpose of the present study was to examine the effects of calyco
din on dendrite outgrowth from human melanocytes was examined by Western blotting, while the release of tumor necrosis factor-α in human keratinocytes was ex-
plained by enzyme-linked immunosorbent assay. The effects of AGI-1140 and UVB on phosphorylation of p53 serine 15 in human keratinocytes was ex-
amed by Western blotting, while the release of tumor necrosis factor-α (TNF-α) and prostatoligand E2 (PGE2) was determined by enzyme-linked immunosorbent assay. The effects of AGI-1140 and UVB on cell cycle arrest of human melanocytes, keratinocytes, fibroblasts, and endothelial cells were compared using fluorescence-
activated cell sorting. Results: Similar to UVB, AGI-1140 induced both melanogenesis and NO in melanoma cells. AGI-1140 also

44.1. Antimigraine dotarizine blocks P/Q Ca2+ channels and exocytosis in a voltage-dependent manner in chromaffin cells - Ruiz-Noorte A., Mayorgas I., Hernández-Guijo J.M. et al. [L. Gandía, Depto. de Farmacia. y Terap., Facultad de Medicina, Univ. Autónoma de Madrid, c/ Arzobispo Morcillo, 4, 28029 Mad-
rid, Spain] - EUR. J. PHARMACOL. 2003 481/1 (41-50) - sum in ENGL.

The mechanism of blockade of P/Q Ca2+ channels by antimig-
aine, dotarizine, was studied in voltage-clamped bovine adrenal chromaffin cells. Inward currents through P/Q channels were phar-
macologically isolated by superfusing the cells with α-conotoxin GVIA (1 µM) plus nifedipine (3 µM). Dotarizine (10-30 µM) blocked the P/Q fraction of I Na, and promoted current inactivation. Thus, dotarizine caused a greater blockade of the late I Na, com-
pared with blockade of the early peak I Na. This effect was more
prominent, the longer was the duration of the depolarising pulse. The blockade of I Na was also greater at more depolarising holding potentials (i.e. -60 mV), than was the blockade produced at more hyperpolarising holding potentials (i.e. -80 or -110 mV). Caltechol-
amine secretory responses to brief pulses (2 s) of a Krebs-HEPES solution containing 100 mM K+ and 2 mM Ca2+ was blocked by 3 µM dotarizine. Blockade was faster and greater when dotarizine was applied on cells that were previously depolarised with Krebs-
HEPES deprived of Ca2+ and containing increasing concentrations of K+. This voltage-dependent blockade of P/Q channels and exocy-
tosis might be the underlying mechanism explaining the dotarizine prophylaxis of migraine attacks. © 2003 Elsevier B.V. All rights reserved.


Flushing is one of the most common vasodilation-related adverse effects associated with Ca2+ channel antagonist treatment. This symptom is known to occur more frequently in women than men. The present study aimed at investigating the effect of ovariectomy on nifedipine-induced flushing in mice. Ovariectomy markedly increased the tail skin temperature, a parameter of skin flushing, induced by nifedipine at a dose showing no influence on blood pres-
sure. This event was blocked by estradiol replacement. Estrogen withdrawal is, therefore, included in the risk factors for nifedipine-induced flushing and this risk is lessened by estrogen replacement. © 2003 Elsevier B.V. All rights reserved.

44.3. Effects of a melanogenic bicyclic monoterpenep diol on cell cycle, p53, TNF-α, and PGE2 are distinct from those of UVB - Kraus E., Galvin J.W., Bounakis S. et al. [D.A. Brown, AGI Der-
matics, 205 Buffalo Avenue, Freeport, NY 11520, United States] - PHOTODERMATOL. PHOTOMED. 2003 19/6 (295-302) - sum in ENGL.

Purpose: Bicyclic monoterpenep (BMT) diols are small-molecule compounds that mimic ultraviolet radiation (UVR) by inducing melanogenesis. The objective of this study was to compare the effects of 2,2-dimethyl-3-propionaldehyde-norbornane (AGI-1140), a novel BMT diol, and ultraviolet B (UVB) on UVB on melanogenesis and nitric oxide (NO). The effect of AGI-1140 on dendrite outgrowth from human melanocytes was examined by quantitative microscopy. The effect of AGI-1140 and UVB on phosphorylation of p53 serine 15 in human keratinocytes was ex-
amed by Western blotting, while the release of tumor necrosis factor-α (TNF-α) and prostaglandin E2 (PGE2) was determined by enzyme-linked immunosorbent assay. The effects of AGI-1140 and UVB on cell cycle arrest of human melanocytes, keratinocytes, fibroblasts, and endothelial cells were compared using fluorescence-
activated cell sorting. Results: Similar to UVB, AGI-1140 induced both melanogenesis and NO in melanoma cells. AGI-1140 also

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induced dendrite outgrowth from melanocytes, indicative of differentiation. However, whereas UVB induced G2 cell cycle arrest with phosphorylation of p53 at serine 15, AGI-1140 induced G1 cell cycle arrest without this phosphorylation. Additionally, unlike UVB, AGI-1140 did not increase the secretion of TNF-α or PGE2, mediators of UVB-induced immunosuppressive and inflammatory responses in the skin that may contribute to carcinogenesis. Conclusion: This study shows that melanogenesis can be induced by AGI-1140 without many of the deleterious effects associated with UVB.

444. Enhancement of photodynamic effect in normal rat keratinocytes by treatment with 1,25 dihydroxy vitamin D3 - Matsuyama A., Nakano H., Harada K. et al. [Dr. K. Hanada, Department of Dermatology, Hiroaki Univ. School of Medicine, Hirosaki 036-8562, Japan] - PHOTODERMATOL. PHOTOIMMUNOL. PHOTOMED. 2003 19/6 (303-308) - summ in ENGL

Background: To better understand the pathogenesis of photodynamic therapy (PDT)-induced apoptosis cytotoxic calcium (Ca2+) was measured using cultured fetal rat keratinocytes (FRSKs). Moreover, the influence of 1,25 dihydroxy vitamin D3 (1,25(OH)2D3) with the action of increasing [Ca2+] on the PDT effect was studied. Methods: FRSKs were treated with a medium containing the photosensitizer, aluminum phthalocyanine tetrasulfonate (AlPcTs), and were then exposed to selective visible light derived from a halogen lamp. Electrophoresis of DNA extracted from the PDT-treated cells revealed DNA fragmentation, a sign of apoptosis in cultured FRSKs under the condition with or without 1,25(OH)2D3. Results: PDT-treated FRSKs exhibited increased levels of [Ca2+]; these levels were significantly elevated further by the treatment of cells with 1,25(OH)2D3. However, cells treated with ethylene glycol bis (b-aminoethyl)-ether-NN,N,N',N'-tetracetic acid (EGTA), a chelator of extracellular calcium, prior to PDT did not show any DNA fragmentation either in the presence or absence of 1,25(OH)2D3. Conclusion: PDT-induced apoptosis in FRSKs may be caused by the influx of extracellular calcium. Addition of 1,25(OH)2D3 clearly enhanced the DNA fragmentation in the cultured FRSKs, indicating the effect of increased [Ca2+]. The combination therapy of AlPcTs-PDT with the administration of 1,25(OH)2D3 may contribute to the enhancement of the AlPcTs-PDT effect.

445. Thiamine protects against paraquat-induced damage: Scavenging activity of reactive oxygen species - Jung LL and Kim I.G. [J.G. Kim, Department of Radiation Biology, Environment Radiation Research Group, Korea Atominenergie Forschung, PO. Box 105, Yusong, Taejon 305-600, South Korea] - ENVIRON. TOXICOLOG. PHARMACOL. 2003 15/1 (19-26) - summ in ENGL

To demonstrate the superoxide anion (O2-) scavenging activity of thiamine, we comparatively investigated the inhibition of cell growth reduction and repression of the oxidative stress-inducible gene expression (sodS, sodA, zwf and soi-19::lacZ) triggered by paraquat, intracellular O2- generator, using an Escherichia coli highly resistant to paraquat toxicity, an in vitro experiment of nitroblue tetrazolium (NBT) reduction was performed. The NBT reduction by O2- generated in the xanthine/xypxanthine system was inhibited by the thiamine supplement in a dose-dependent manner. Moreover, it competed with the 2-deoxy-D-ribose in absorbing the hydroxyl radical (·OH) generated by ··-irradiation (800 Gy) and thus inhibited the formation of malondialdehyde in vitro. In conclusion, this evidence suggests that thiamine may partly act as an antioxidant to scavenge ·OH directly and then affect the cellular response to oxidative stress induced by reactive oxygen species. © 2003 Elsevier B.V. All rights reserved.

446. Increase in number of annexin V-positive living cells of rat thymocytes by intracutural Pb2+ - Nishizaki Y., Nakao H., Umebayashi C. et al. [Y. Oyama, Department of Life Sciences, Fac. of Integrated Arts and Sciences, University of Tokushima, Minami-Joyo-shi 3-11, Tokushima 770-8502, Japan] - ENVRNOM CLIN. TOXICOL. PHARMACOL. 2003 15/1 (45-51) - summ in ENGL

Lead is ubiquitous in our environment and lead poisoning is a major public health problem worldwide. In this study, to see if intracutural Pb2+ induces the exposure of phosphatidylserine in rat thymocyte membranes, we have examined the effect of PbCl2 on rat thymocytes treated with A23187 using a flow cytometer with appropriate fluorescent indicators under nominally Ca2+-free condition. PbCl2 at 1-30 μM dose-dependently induced the exposure of phosphatidylserine on outer membranes, associated with increasing the concentration of intracellular Pb2+. The potency of intracutural Pb2+ to induce the apoptotic change in thymocyte membranes seems to be greater than those of intracellular Ca2+ and Cd2+. Results suggest that intracutural Pb2+ triggers apoptosis of rat thymocytes. This action of Pb2+ may be one of mechanisms for the lead-induced changes in immunity. © 2003 Elsevier B.V. All rights reserved.

447. Captopril enhanced insulin-stimulated glucose synthesis in skeletal muscle but not fatty acid synthesis - F. Kojima, J. Umezawa, Y. Iino, A. Sato, K. Hanada, T. Nishizaki, S. Fujiwara, T. Hayashi, and K. Hanada [Department of Dermatology, Hiroaki Univ. school of Medicine, Hirosaki 036-8562, Japan] - PHOTODERMATOLOGY. PHOTOIMMUNOLOGY. PHOTOMEDICINE. 2003 19/6 (303-308) - summ in ENGL

In addition to the hypothetic apoptosis, angiotensin-converting enzyme (ACE) inhibitors exert a beneficial effect on glucoregulation. In the present study, the effect of ACE inhibition by captopril on glucose utilization in peripheral tissues was investigated in non-obese rats with hereditary hyperglycemia (HHTg) associated with hyperinsulinemia and insulin resistance. Normoglycemic Wistar rats served as controls (C). Rats of both groups received a high-sucrose diet, and a half of each group also captopril in drinking water (10 mg/kg body weight) for 2 weeks. Captopril administration reduced fasting glycemia and postprandial triglyceridemia in HHTg rats, while the fasting levels of nonesterified fatty acids (NEFA), glyceroa, and lactate were decreased in both groups. The sensitivity of skeletal muscle to insulin action evaluated as in vitro 4C-glucose incorporation into glycogen was significantly increased by captopril treatment both in HHTg (3.5 ± 0.48 v2.0 ± 0.12 μmol glucose/g wet weight [ww]) and C (3.3 ± 0.21 v 2.48 ± 0.09 μmol glucose/g ww). In isolated adipose tissue, the insulin-stimulated 4C-glucose incorporation into neutral lipids was increased, after captopril administration, by 137% in C and by 35% only in HHTg. After captopril treatment, insulin-stimulated de novo fatty acid synthesis rose significantly in C while remaining low in HHTg. The inhibitory stress-inducible gene expression was comparable in both C and HHTg rats treated with captopril and with captopril-treated controls (C). Separate experiments were designed to assess the possible involvement of bradykinin in mediating captopril action. Both C and HHTg rats fed a high-sucrose diet for 2 weeks were treated with captopril intraperitoneal (IP) 1 hour before captopril administration. In C, captopril administration enhanced the insulin-stimulated de novo glucose incorporation into lipids in adipose tissue by 25%, and into glycogen in the musculus soleus by 45%; this effect was eliminated by HOE-140 (100 μg/kg intraperitoneally [IP]) 1 hour before captopril administration. In C, captopril administration increased the insulin sensitivity of peripheral tissue in both C and HHTg rats, but with different efficacy. While the insulin-sensitizing action of captopril on skeletal muscle was comparable in HHTg and C rats, there were differences in the effect of captopril on adipose tissue. The difference became particularly manifest in the de novo fatty acid synthesis. © 2003 Elsevier Inc. All rights reserved.

5. EFFECTS ON ORGANS AND SYSTEMS


Periprosthetic bone loss is an important factor that limits implant survival after total hip arthroplasty (THA). In a randomized trial we previously reported that pamidronate therapy prevented periprosthetic bone loss and decreased urinary excretion of N-telopeptide collagen cross-links over the first 6 months after THA, but had no apparent effect on free deoxypyridinoline excretion (J Bone Miner Res 2001; 16:556-564). In this study we investigated this discrepant observation that pamidronate reduced conjugated cross-link excretion but had no effect on free-cross links. Free and total deoxypyridinoline (DPD) were assayed by reverse-phase high-performance liquid chromatography (HPLC) and by immunosorbent assay (ELISA) at preoperative baseline and at week 6 after surgery in 46 subjects who had taken part in the trial. Randomly selected, 22 subjects received a single 90 mg intravenous infusion of pamidronate and 24 received placebo. Acute rises in free and total DPD occurred in both study groups at week 6 (P < 0.05). Total DPD excretion was lower in the pamidronate group than in the placebo group when measured by both HPLC and ELISA (P < 0.05). No difference in free DPD was found between groups. A rise in the ratio of free to total DPD occurred in the pamidronate group at week 6 (P = 0.03), but not in the placebo group. Pamidronate treatment suppresses excretion of total DPD. This is consistent with the effect of pamidronate on other bone turnover markers and periprosthetic bone loss after THA. Urinary-free DPD is a poor marker of response to treatment as the ratio of free-to-total cross-links is affected by amino-bisphosphonate therapy.


It is still not completely clear whether or not carbamazepine (CBZ) causes alterations in vitamin D status and in bone metabolism. The objective of this study was therefore to investigate prospectively in healthy adults the effects of CBZ on serum levels of 25-hydroxyvitamin D (25(OH)D) and on biomarkers of bone formation and resorption. Twenty-one free-living male adults were taking 800 mg/day CBZ for 10 weeks. The study was performed from December 1997 until September 1998 at a geographic latitude of 51°N. Blood samples were collected before treatment (t1), 33 days after starting treatment (t2), and 70 days (SE 3.6) after starting treatment (t3). In 13 out of the 21 subjects blood samples were also drawn 64 days (SE 9.0) after treatment had been terminated (t4). Serum 25(OH)D levels remained constant during study periods t1-t3. 25(OH)D levels were, however, significantly higher at t4 compared to t1-t3. Serum concentrations of intact osteocalcin, a bone formation marker, and C-telopeptide, a bone resorption marker, were similar during all examinations. Moreover, serum levels of parathyroid hormone, calcium, and inorganic phosphate did not change. Data indicate that CBZ per se does not alter bone metabolism and does not lead to decreased circulating 25(OH)D levels in young males without epilepsy. Variations in 25(OH)D levels are in line with the seasonal fluctuations in vitamin D status.


The objective of the this study was to examine the effects of fondaparinux, a synthetic anticoagulant substance similar to heparin, on osteochoasts compared with previously used heparins. Its effects have been shown in clinical trials to be highly effective in thromboembolism prophylaxis. Unfractionated heparin (UHF), dalteparin, enoxaparin and fondaparinux were added to osteochoast cultures in the therapeutic range and two decimal powers above and below it in each case. The results showed that the mitochondrial activity and protein synthesis of osteochoasts treated with fondaparinux were significantly higher than in the other groups. Similar effects could be demonstrated for the matrix collagen type II content and calcification. In contrast enoxaparin, dalteparin and UHF lead to a significant decrease of matrix collagen type II content and calcification in concentrations equal or higher than the therapeutic one. No inhibitory in-vitro effects of fondaparinux on osteochoast survival were demonstrated could be demonstrated within the concentration range investigated (0.01 - 100 µg/ml). We conclude that fondaparinux can be used to avoid the heparin-related negative influence on osteochoast-depenent fracture healing and endoprosthetic implant integration.

See also: 548, 552, 565, 626, 738.

5.1. Central nervous system and sense organs


Verteporfin (Visudyne®) therapy (phodynamic therapy with intravenous liposomal verteporfin) is the first treatment to effectively prevent the loss of visual acuity in patients with subfoveal choroidal neovascularisation (CNV) secondary to age-related macular degeneration (AMD), pathological myopia or presumed ocular histoplasmosis syndrome (POHS). In adult patients with classic subfoveal CNV or occult with no classic subfoveal CNV secondary, or subfoveal CNV secondary to pathological myopia or POHS, verteporfin therapy slows or prevents loss of visual acuity. In well designed clinical trials, verteporfin therapy was superior to placebo in patients with subfoveal classic-containing CNV and occult with no classic CNV secondary to AMD at 12 and/or 24 months (Treatment of Age-related macular degeneration with Photodynamic therapy [TAP] Investigation and Verteportin In Photodynamic therapy [VIP-AMD] trial) and in patients with pathological myopia at 12 months (Verteporfin In Photodynamic therapy [VIP-PM] trial). Limited data suggest that verteporfin therapy also prevents loss of visual acuity in patients with subfoveal CNV secondary to POHS. Verteportin therapy was generally well tolerated in clinical trials; most adverse events were mild to moderate in intensity and transient. The most frequently reported verteporfin therapy-related adverse events (incidence >2%) were visual disturbance, injection-site reactions, photosensitivity reactions and infusion-related back pain. Approximately 5% of patients with occult with no classic subfoveal CNV secondary to AMD reported severe vision decrease within 7 days of treatment in clinical trials; 2 years later, several patients had recovered some of this loss. Conclusion: Photodynamic therapy with verteporfin, the first photosensitiser approved for the treatment of subfoveal CNV, is a well tolerated treatment that stabilises or slows visual acuity loss in adult patients with predominantly classic or occult with no classic subfoveal CNV secondary to AMD, and subfoveal CNV secondary to pathological myopia or POHS. Thus, verteporfin therapy provides a valuable option for the management of these patients for whom treatment options are few, and should
be considered as a first-line therapy in these difficult-to-manage conditions.

452. Carboxy anhdyrase inhibitors: Topically acting antiglau-
coma sulfonamides incorporating esters and amides of 3- and 4-
carboxybenzocyclohexanone with -Casini A., Scozzafava A., Mincione F.
e Biomorgane, Via della Lastruccia 3, 50019 Sesto Fiorentino, Florence, Italy] - BIOORG.MED. CHEM. LETT; 2003 13/17 (2867-
2873) - sum in ENGL

453. Dopamine agonists in Parkinson’s disease - Tintner R.
and Jankovic J. [R. Tintner, Parkinson’s Disease Center, Department
of Neurology, Baylor College of Medicine, 6550 Fannin, Houston,
TX 77030, United States] - EXPERT OPIN. INVEST. DRUGS 2003
12/11 (1903-1820) - sum in ENGL

- Levodopa (LD), the immediate precursor of dopamine, is the
most effective agent in the treatment of Parkinson’s disease (PD).
While quite successful in treating the primary motor deficits of
PD, most patients eventually develop LD-related motor fluctuation,
dyskinesias and other adverse effects associated with chronic LD
therapy. There is also concern that LD is neurotoxic, although this
has not been demonstrated in any in vivo studies. Dopamine
agonists (DAs) have been shown to be about as effective as LD in
symptomatic treatment of mild-to-moderate PD. In addition, there
is a lower tendency to develop motor fluctuations and dyskinesias
with DA treatment than after initiation of therapy with LD. Fur-
thermore, there is preclinical and clinical data to suggest a slowing
of neurodegeneration with DAs. The adverse effects of DAs are
similar to those experienced with LD, except that the ergot agents
are associated with a small risk of tissue fibrosis not noted with
the non-ergot DAs.

454. Dopamine Receptor Ligands. Part VII (1): Novel 3-Substi-
tuted 5-Phenyl-1,2,3,4,5,6-hexahydro-azepino-[4,5-b]indoles as
Ligands for the Dopamine Receptors - Becker M. and Le-
Friedrich-Schiller-Universitat Jena, Philosophenweg 14, D-07743
Jena, Germany] - ARCH. PHARM. 2003 336/10 (466-476) - sum
in ENGL

A number of 5-phenyl-1,2,3,4,5,6-hexahydro-azepino-[4,5-b]in-
doels 3 were synthesized with different substituents at the azepine-N
position (methyl, allyl, 2-phenyl-ethyl, cyclopropylmethyl- and
unsubstituted). Furthermore, the indole-N-methylated compound
was synthesized and by using norephedrine and norpseudoephedrine
as a chiral pool, 4-methyl-5-phenyl-1,2,3,4,5,6-hexahydro-azepino-
[4,5-b]indole were prepared which contained racemisation at the
reacting C-atom. These compounds, as well as the ring-open amino-
alkohols, were screened for their af
ction on hD1, hD2L,
hD5- and D2 receptors (please check sentence). They had micromolar
affinities for the receptors and showed the highest af
ction to the
e subtype family. The cyclic compounds possessed the highest
af
ction, with the cyclo-propylmethyl-(3 c) and methyl-substituents
(3 e) being the most active of the tested compounds. Based on
an intracellular CAMP-assay, the unsubstituted compound (at the
azepine-N position) turned out to be an agonist for the D1
 and
e subtype family, whereas the substituted compounds showed
(partial) agonistic, or even inverse agonistic af
ction.

455. Anatomical and functional brain variables associated with
clozapine response in treatment-resistant schizophrenia - Mo-
lima V., Rezg S., Sarranueva P. et al. [V. Molina, Department of
Psychiatry, Hospital Doce de Octubre, Edificio de Medicina
Comunitaria, Avda de Córdoba, km 5.4, 28041, Madrid, Spain]-
- PSYCHIATRY RES. NEUROIMAGING 2003 124/3 (153-161) - sum
in ENGL

Clozapine alleviates the symptoms of a significant proportion of
treatment-resistant schizophrenia patients. Previous studies suggest
that the reactivity of stathmin is associated with prefrontal and
temporal anatomy as well as with prefrontal, basal ganglia and
thalamic metabolism. A sample of 25 treatment-resistant
(TRI) schizophrenic patients underwent magnetic resonance imag-
ing (MRI) and 18F-deoxyglucose positron emission tomography
(PET) before and after treatment with clozapine. We investigated
the association between changes in positive, disorganized, and
negative schizophrenic syndromes with clozapine treatment and
a set of cerebral variables that included total intracranial volume
(ICV); hippocampal, dorsolateral prefrontal (DLPF) and temporal
grey-matter volume and metabolism; and metabolic activity of
the thalamus, pallidum/putamen, and caudate head. Improvement
in positive symptoms with clozapine was directly related to tempo-
rally gray-matter volume, whereas improvement of disorganization
symptoms was inversely related to ICV and hippocampal volume.
Patients with high baseline DLPF cortical volume and metabolic ac-
tivity were more likely to experience improvement in their negative
symptoms. We conclude that clinical improvement with clozapine
can be related with the anatomy and metabolism of prefrontal and
temporal brain areas, with the structural integrity of the DLPF and
temporal regions showing the maximum predictive capacity. © 2003 Elsevier
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456. Hypothalamic melanocortin neurons integrate signals of
energy state - Cowley M.A., [M.A. Cowley, Division of Neurosci-
ence, OR National Primate Research Center, OR Heath and Science
University, 505 NW 185th Avenue, Beaverton, OR 97006, United States] - EUR. J. PHARMACOL. 2003 480/1-3 (5-11) - sum
in ENGL

Neurons of the arcuate nucleus of the hypothalamus appear to
be sites of convergence of central and peripheral signals of en-
ergy stores, and profoundly modulate activity of the melanocortin
circuits, providing strong rationale for pursuing these circuits as
therapeutic targets for disorders of energy homeostasis. Recent
studies in our lab and those of our collaborators have shown that
leptin modulates different populations of hypothalamic cells in dif-
f erent ways. In this report, we outline an integrated model of leptin’s
action in the arcuate nucleus, derived from our electrophysiological
studies of brain slice preparations taken from transgenic mice bred
to express a variety of fluorescent proteins in specific cell types.
We also discuss the recently withdrawn obesity drug fenfluramine,
which appears to act on proopiomelanocortin neurons via serotonin
2c receptors. Finally, we review current inquiries into the ability of
the hormone ghrelin to stimulate appetite by its activation of neuro-
peptide Y neurons and inhibition of proopiomelanocortin neurons.
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457. Anorexia nervosa: Towards a neurobiologically based ther-
apy - Moller C., Bergh C. and Ammar A. [P. Sodersten, Sect. of
Applied Neuroendocrinology, Center for Eating Disorders, Karo-
linska Institutet, Novum, S-141 57 Huddinge, Sweden] - EUR. J.
PHARMACOL. 2003 480/1-3 (67-74) - sum in ENGL

Eating disorders, i.e. anorexia and bulimia nervosa, are disorders
of eating behavior and body weight regulation. Most likely be-
cause there are few, if any, effective treatments, eating disorders
are considered to be chronic disorders interrupted only by intermittent
periods of short-lived remission. The neurobiology of eating, most
of which explores hypothalamic mechanisms, has had no influence
on the treatment of eating disorders, with the exception of psy-
chopharmacology. However, while most patients are currently
being treated with psychoactive drugs, there is no evidence that these
are effective. This may be because pharmacological attempts so far have targeted
the wrong symptoms. We review the symptomatology of anorexia
nervosa and bulimia and the outcome of presently used interventions. Ev-
erybody agrees that outcome must improve and to attack this clinical
problem, we suggest a neurobiologically plausible framework for
how the disorders develop and how they are maintained and outline a
method of treatment and its results. © 2003 Elsevier B.V. All
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Brain-derived neurotrophic factor (BDNF) belongs to a family of proteins related to nerve growth factor, which are responsible for neuron proliferation, survival and differentiation. A more diverse role for BDNF as a neuronal extracellular transmitter has, nevertheless, been proposed. Here we show that BDNF synthesized by dopamine neurons is responsible for the appearance of the dopamine D3 receptor during development and maintains its expression in adults. Moreover, BDNF triggers behavioral sensitization to levodopa in hemiparkinsonian rats. In monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which develop levodopa-induced dyskinesia, we show an overexpression of this receptor. Administration of a dopamine D3 receptor-selective partial agonist strongly attenuated levodopa-induced dyskinesia, while leaving unaffected the therapeutic effect of levodopa. These results suggest that the dopamine D3 receptor participates in both dyskinesia and the therapeutic action of levodopa and that partial agonists may normalize dopamine D3 receptor function and correct side-effects of levodopa therapy in PD patients. © 2003 Elsevier B.V. All rights reserved.


Pharmacological manipulation of the 5-hydroxytryptamine (5-HT) system has long been associated with a regulation of feeding behaviour, however, the initial part of this article reviews evidence that central 5-HT systems similarly modulate reward-related behaviours, particularly drug reward. The second part of this article considers what we believe to be strong emerging pharmacological and genetic evidence that many of these effects are mediated through 5-HT2C receptor signalling mechanisms. Finally, we consider the potential for selective 5-HT2C agonists as therapies for substance abuse disorders and the medical implications for different 5-HT2C receptor isoforms generated by RNA editing. © 2003 Elsevier B.V. All rights reserved.


The aim of the present study was to find out whether (+)-8-hydroxy-2-di-n-propylaminotetralin (8-OH-DPAT), a prototypical 5-HT1A agonist, and (+)-2-[2-(4-fluorophenyl)-3-pyridylmethyl]-thiobenzamidomethyl]-chromane HCl (EMD 128130), a compound with serotonin 5-HT1A-agonist and dopamine D2-like antagonist properties, are able to attenuate the haloperidol-induced (1 mg/kg) muscle rigidity in rats. Muscle tone was examined using a combined mechanano- and electromyographic (EMG) method that simultaneously measured the mechanical muscle resistance (MMG) of the rat's hind foot to passive movements in the ankle joint, and the EMG activity of two antagonist muscles. Both 8-OH-DPAT (0.125-0.5 mg/kg i.p.) and EMD 128130 (1-10 mg/kg i.p.) dose-dependently decreased the haloperidol-enhanced MMG to passive movements, as well as the tonic and the long-latency reflex EMG activities. Provided these results can be extrapolated to humans, the efficacy of EMD 128130 in relieving the haloperidol-induced muscle rigidity supports the concept that novel antipsychotics with 5-HT1A agonist and dopamine D2 antagonist activities should have a favourable extrapyramidal side-effect profile. © 2003 Elsevier Ltd. All rights reserved.


This study examines the effects of serotonin (5-HT)1A receptor ligands on the in vivo release of 5-HT and dopamine (DA) in the prefrontal cortex of mice. Oral MKC-242 and 8-OH-DPAT, selective 5-HT1A receptor agonists, decreased cortical 5-HT release at low and high doses, while the receptor agonists increased cortical DA release only at a high dose. Local application of the selective 5-HT1A receptor agonist, WAY100635, via a dialysis probe, antagonized oral MKC-242-induced increase in cortical DA release, but did not affect the decrease in cortical 5-HT release. Local application of 8-OH-DPAT at 100 and 300 nM via a dialysis probe increased cortical DA release, but did not affect cortical 5-HT release. The effects of oral MKC-242 and 8-OH-DPAT on 5-HT release were blocked by low and high doses of WAY100635, while blocking the agonist-induced increase in DA release required a high dose of WAY100635. These results suggest that 5-HT release and DA release in the frontal cortex of mice are regulated by pre- and postsynaptic 5-HT1A receptors, respectively, and that the presynaptic 5-HT1A receptor-mediated response is more potent inhibition by WAY100635 than the postsynaptic 5-HT1A receptor-mediated response in mice. © 2003 Elsevier Ltd. All rights reserved.


The aim of the present study was to find out whether (+)-8-hydroxy-2-di-n-propylaminotetralin (8-OH-DPAT), a prototypical 5-HT1A agonist, and (R)-(+)-2-[2-(4-fluorophenyl)-3-pyridylmethyl]-thiobenzamidomethyl]-chromane HCl (EMD 128130), a compound with serotonin 5-HT1A-agonist and dopamine D2-like antagonist properties, are able to attenuate the haloperidol-induced (1 mg/kg) muscle rigidity in rats. Muscle tone was examined using a combined mechanano- and electromyographic (EMG) method that simultaneously measured the mechanical muscle resistance (MMG) of the rat's hind foot to passive movements in the ankle joint, and the EMG activity of two antagonist muscles. Both 8-OH-DPAT (0.125-0.5 mg/kg i.p.) and EMD 128130 (1-10 mg/kg i.p.) dose-dependently decreased the haloperidol-enhanced MMG to passive movements, as well as the tonic and the long-latency reflex EMG activities. Provided these results can be extrapolated to humans, the efficacy of EMD 128130 in relieving the haloperidol-induced muscle rigidity supports the concept that novel antipsychotics with 5-HT1A agonist and dopamine D2 antagonist activities should have a favourable extrapyramidal side-effect profile. © 2003 Elsevier Ltd. All rights reserved.


In the rat subthalamic nucleus, which plays a critical role in the control of motor behaviour, specific binding of [3H]-prazosin was detected by radioligand binding to homogenates and by autoradiography in slices. [3H]-Prazosin binding to homogenates [Bmax 71±5 fmol/mg protein, Kd 0.27±0.05 nM] was competed for by the α1A-antagonist prazosin (1 μM). Extracellular single-unit recordings in slices showed that in a subpopulation (61 out of 94 cells) of rat subthalamic neurons with regular, single-spike firing pattern, noradrenaline induced a concentration-dependent increase in the firing rate (EC50 2.5±0.2 μM, maximum effect 272±33% of basal). The action of noradrenaline...
was mimicked by the selective \(\alpha_1\)-agonist phentolamine but not by selective \(\alpha_2\)-or \(\beta\)-agonists, and was blocked by the \(\alpha_1\)-antagonist prazosin but not by \(\alpha_2\)-or \(\beta\)-antagonists. The excitatory effect of noradrenaline was not prevented by perfusion with low \(\left[Ca^{2+}\right]_o\)/high \(\left[Mg^{2+}\right]_o\) solution. In four out of 11 neurones perfusion with 3 \(\mu M\) noradrenaline resulted in a shift from bursting to regular firing. Taken together, our results indicate that rat subthalamic neurones express \(\alpha_1\)-adrenoceptors responsible for noradrenaline-induced stimulation of the firing rate of a subpopulation of neurones. By modulating the spontaneous activity of STN neurones, noradrenergic pathways might have a significant role in regulating basal ganglia function and thus motor activity. © 2003 Elsevier Ltd. All rights reserved.

464. MK-801 and 7-Ni attenuate the activation of brain NF-\(\kappa B\) induced by LPS - Glezer I., Manhoz C.D., Kawamoto E.M. et al. [C. Scavone, Department of Pharmacology, Inst. of Biomedical Science-ICB-1, University of São Paulo, Ave. Professor Lineu Prestes, 1524, São Paulo 05508-900, Brazil] - NEUROPHARMACOLOGY 2003 45/8 (1120-1129) - sumn in ENG.

The activation of nuclear factor-\(\kappa B\) (NF-\(\kappa B\)) leads to an increase in the expression of genes involved in important events in the central nervous system (CNS), such as development, plasticity and inflammation. It has been shown that inflammatory stimuli in the brain increases excitatory glutamatergic transmission, especially at the excitatory synapse of the ventral tegmental area (VTA). Olanzapine, an atypical antipsychotic, may exert specific ceramide to block apoptosis. The excitatory effect of the leptin nerve growth factor (NGF) deprivation. Here, we report for the first time that ceramide generated "de novo" is also anti-apoptotic. Moreover, \(C_6\)-ceramide is converted to long-chain ceramides in a process inhibited by fumonisin B1. The anti-apoptotic effect of \(C_6\)-ceramide is due to the rapid decrease in p75NTR expression that occurs upon NF-\(\kappa B\) activation. © 2003 Elsevier B.V. All rights reserved.

465. Inhibition of rat sympathetic neuron apoptosis by ceramide. Role of \(p75^{STR}\) in ceramide generation - Song M.-S. and Posse De Chaves E.I. [E.I. Posse De Chaves, Department of Pharmacology, Faculty of Medicine, University of Alberta, Edmonton, Alta. T6G 2Z2, Canada] - NEUROPHARMACOLOGY 2003 45/8 (1130-1150) - sumn in ENG.

\(C_6\)-ceramide protects sympathetic neurones from apoptosis caused by nerve growth factor (NGF) deprivation. Here, we report for the first time that ceramide generated "de novo" is also anti-apoptotic. Moreover, \(C_6\)-ceramide is converted to long-chain ceramides in a process inhibited by fumonisin B1. The anti-apoptotic effect of \(C_6\)-ceramide is due to the rapid decrease in p75NTR expression that occurs upon NF-\(\kappa B\) activation. These results suggest that a considerable part of NF-\(\kappa B\) activation by LPS is linked to the NMDA/NO pathway in CNS. © 2003 Elsevier Ltd. All rights reserved.


The mesolimbic dopaminergic system, of which the cell bodies are located in the ventral tegmental area, has been implicated in the physiology of reward and the related pathophysiology of drug abuse. This area has been a site of significant interest to study the effects of drugs of abuse and neurotransmitter systems implicated in the rewarding effects of these compounds. One important aspect of synaptic transmission is the ability of synapses to strengthen or weaken their connection as a consequence of synaptic activity. Recently, it has been apparent that this phenomenon is also present in the ventral tegmental area and that this may bear important functional consequences for the ways in which drugs of abuse assert their effect. Here, we will review the effects of neurotransmitter systems and drugs of abuse on cellular activity and synaptic transmission in the ventral tegmental area. © 2003 Elsevier B.V. All rights reserved.

467. Augmented responses to morphine and cocaine in mice with a 12-lipoxygenase gene disruption - Walters C.L., Wang B.-C., Godfrey M. et al. [J.A. Bleney, Department of Pharmacology, 125 John Morgan Building, Univ. of PA School of Medicine, 3620 Hamilton Walk, Philadelphia, PA 19104-6084, United States] - PSYCHOPHARMACOLOGY 2003 170/2 (124-131) - sumn in ENG.

Rationale: Recent studies have shown that pharmacological inhibition of the 12-lipoxygenase pathway selectively blocks opioid inhibition of GABAergic synaptic currents. A similar mechanism has been shown for the regulation of glutamate release in the ventral tegmental area (VTA) during acute withdrawal from morphine, although the functional significance of these effects in vivo are not known. Objectives: We have utilized mice with a disruption of the "leukocyte-type" 12-lipoxygenase gene (12-LO\(^{-}\)/ mice) to examine a variety of general behavioral responses as well as several specific responses to morphine and cocaine. Methods: Behavioral responses to morphine include sensitivity to thermal stimuli and withdrawal from chronic morphine treatment. Responses to cocaine were measured through locomotor activity. Results: General behavioral responses in 12-LO\(^{-}\)/ mice are not different from their wild-type controls. However, these mutant mice showed enhanced morphine-induced analgesia. However, this effect is eliminated following chronic morphine treatment. In addition, 12-LO\(^{-}\)/ mice demonstrated enhanced somatic signs of opiate withdrawal relative to littermate controls. Lastly, cocaine-mediated increases in locomotor activity was augmented acutely but not chronically in 12-LO\(^{-}\)/ mice. Conclusions: Together, these results suggest a role for metabolites of arachidonic acid metabolism in morphine- and cocaine-induced behavioral responses and may reflect a utilization of this pathway following acute but not chronic drug administration.

468. Effects of olanzapine infusions to the ventral tegmental area on lordosis and midbrain 3\(\times\),5\(\times\)-THP concentrations in rats - Frye C. and Seliga A. [C. Frye, Department of Psychology, University at Albany-SUNY, 1400 Washington Avenue, Albany, NY 12222, United States] - PSYCHOPHARMACOLOGY 2003 170/2 (132-139) - sumn in ENG.

Rationale: The progesterone metabolite and neurosteroid 5\(\times\)-pregnan-3\(\alpha\)-ol-20-one (3\(\times\),5\(\times\)-THP) facilitates sexual behavior of estradiol-primed rodents through its actions in the ventral tegmental area (VTA). Olanzapine, an atypical antipsychotic, may exert some of its actions by increasing 3\(\times\),5\(\times\)-THP levels. Objective: If olanzapine has effects by increasing 3\(\times\),5\(\times\)-THP levels, then olanzapine administration to the VTA should facilitate female sexual behavior of estradiol-primed rodents concomitant with increasing midbrain levels of 3\(\times\),5\(\times\)-THP. Methods: In experiment 1, estradiol-primed ovariectomized rats infused with olanzapine at 0 \(\mu g\) or vehicle at 47 \(\mu g\), and tested for sexual behavior at 47.5 \(\mu g\). In experiment 2, estradiol-primed ovariectomized rats infused with olanzapine (10 \(\mu g\)) or vehicle, tested for sexual behavior, then tissues were
collected for measurement of midbrain progesterone and 3α,5α-THP, and plasma corticosterone, progesterone, and 3α,5α-THP. In experiment 3, estradiol-primed, ovariectomized rats were administered progesterone (500 µg, SC), tested for sexual behavior, then tissues were collected for midbrain and plasma progesterone and 3α,5α-THP levels. Results: Injections of 10 or 20 µg olanzapine to the VTA significantly increased the incidence and intensity of lordosis, and the occurrence of preceptive and aggressive behaviors. Rats infused with olanzapine to the VTA had significantly greater levels of midbrain 3α,5α-THP than did vehicle-administered rats. Olanzapine did not increase progesterone or corticosterone levels. Conclusions: Olanzapine increases lordosis and midbrain 3α,5α-THP when infused to the VTA which suggests that olanzapine’s behavioral effects may result, in part, through actions of 3α,5α-THP, independent of progesterone or corticosterone.

469. Motor effects of GABA<sub>A</sub> antagonist in globus pallidus: Studies of locomotion and tremulous jaw movements in rats - Wisniewski A., Corea M., Arizzi M.N. et al. [J.D. Salamonie, Department of Psychology, University of Connecticut, Storrs, CT 06269-1020, United States] - PSYCHOPHARMACOLOGY 2003 170/2 (140-149) - sum in ENGL

Rationale: Although most rodent studies related to parkinsonian syndromes identifying a putative role of a CRF-modulated axoneme or also have been used as a rodent model of tremor for investigating the circuitry of the basal ganglia. Objective: There are multiple pathways involved in the generation of parkinsonian symptoms. The globus pallidus is a basal ganglia relay nucleus, and the present study was conducted to investigate the effect of pallidal GABA antagonist locomotion and tremulous jaw movements. Methods: Suppression of locomotion and induction of tremulous jaw movements were produced by repeated (i.e., 14 day) systemic administration of the dopamine D2 antagonist haloperidol, and by acute systemic injection of the muscarinic agonist pilocarpine. The GABA<sub>A</sub> antagonist bicuculline was injected into the globus pallidus, and its effects on locomotion in haloperidol- and pilocarpine-treated rats were assessed in the first group of experiments. In the second group of experiments, the effects of intrapallidal infusions of bicuculline on haloperidol- and pilocarpine-induced jaw movements were observed. Results: Pallidal GABA antagonist stimulation locomotion when no other treatment was present, and also when animals were co-administered haloperidol or pilocarpine. Bicuculline suppressed haloperidol-induced jaw movements in a dose-related manner, and had no effect on pilocarpine-induced jaw movements. Conclusions: These results support the notion that there are distinct pathways conveying basal ganglia outflow and demonstrate the striatopallidal pathway is involved in the generation of the haloperidol-induced tremulous jaw movements. These findings are consistent with some features of current models of basal ganglia function and may lead to an understanding of the mechanisms that generate parkinsonian symptoms.

470. Role of corticotropin releasing factor (CRF) receptors 1 and 2 in CRF-potentiated acoustic startle in mice - Risborough V.B., Hauger R.L., Pelleymounter M.A. and Geyer M.A. [M.A. and 2 in CRF-potentiated acoustic startle in mice and determine the respective roles of CRF<sub>1</sub> and CRF<sub>2</sub> receptors probability prevents achieving sufficient concentrations of the lower affinity compounds at NMDA receptors to produce PCP-like discriminative stimulus effects.

472. Acetyl-L-carnitine permeability across the blood-brain barrier and involvement of carnitine transporter OCTN2 - Inano A., Sai Y., Nikaido H. et al. [T. Tani, Dept. of Molecular Biopharmaceutics, Faculty of Pharmaceutical Sciences, Tokyo University of Science, 12 Ichigaya-Funagawara-machi, Shinjuku, Tokyo 162-0826, Japan] - BIOPHARM. DRUG DISPOS. 2003 24/8 (357-365) - sum in ENGL

OCTN2 (SLC22A5), an organic cation / carnitine transporter, is widely distributed throughout the body, including the brain. In the present study, the involvement of OCTN2 in acetyl-L-carnitine (ALCAR) permeation across the blood-brain barrier was examined using a microdialysis method in mouse. OCTN2 function was examined by comparison of wild-type mice with jvs mice, which express defective OCTN2 and are considered a model for primary systemic carnitine deficiency. Zero-net-flux method analysis indicated higher in vivo recovery of ALCAR and lower physiological ALCAR concentration in thalamus extracellular fluid (ECF) in jvs mice compared with wild-type mice. Externally added ALCAR showed significantly slower initial uptake across the BBB in jvs mice. These results indicated that OCTN2 is functionally involved
in ALCAR transfer across the BBB. Total radioactivity in ECF after i.v. administration of radiolabelled ALCAR remained constant for the rest of the experimental period. Accordingly, our results indicate that ALCAR is transported from blood to brain ECF by OCTN2 at least in part, and its concentration in brain ECF is regulated by other events such as protein binding and anabolic reactions in the brain, as well as by transport across the BBB. Copyright © 2003 John Wiley & Sons, Ltd.


Due to its interface function between the body and the environment, the skin is chronically exposed to both endogenous and exogenous reactive oxygen species. Skin antioxidant network protects the skin against oxidative injury and prevents the production of oxidation products, such as 4-hydroxy-2-nonenal or malonaldehyde, which are able to induce protein damage, apoptosis or release of pro-inflammatory mediators, such as cytokines. When oxidative stress overwhelms the skin antioxidant capacity the subsequent modification of cellular redox apparatus leads to an alteration of cell homeostasis and a generation of degenerative processes. Topical application or oral administration of antioxidants has been recently suggested as preventive therapy for skin pigmentation and UV-induced cancer. The recognition that ROS can act as second messengers in the induction of several biological responses, such as the activation of NF-kB or AP-1, the generation of cytokines, the modulation of signaling pathways, etc., has led many researchers to focus on the possible effects of antioxidants in many pathological processes. The recent demonstration that the peroxisome proliferators-activated receptors, whose natural ligands are polyunsaturated fatty acids and their oxidation products, have a central role in the induction of some skin diseases, such as psoriasis or acne, has indicated new links between free radicals and skin inflammation. Based on these findings, the review summarises the possible correlations between antioxidant imbalance, lipid oxidative breakage and skin diseases, from both a pathological and therapeutic points of view.


The tolerability, pharmacodynamics, and pharmacokinetics of BIA 3-202 (50 mg, 100 mg, and 200 mg twice-daily) and a novel catechol-O-methyltransferase (COMT)-inhibitor, were investigated in healthy volunteers. BIA 3-202 was administered to four sequential groups of 8 healthy male subjects under a double-blind, randomized, placebo-controlled design. Within each group, 2 subjects were randomized to treatment with placebo. Treatment duration was 9 days: single dose on the first and last days and twice or thrice daily on days 3 to 8. BIA 3-202 was well tolerated at all dose regimens tested. Median maximum plasma BIA 3-202 concentrations were attained at 0.5 to 2.5 hours postdose. Thereafter, concentrations declined with a t1/2 of approximately 2 hours. The increase in the extent of systemic exposure, as measured by AUC(0-c), was approximately proportional to the administered dose. Steady state of plasma BIA 3-202 concentrations occurred by day 4 in all dose groups. Less than 1% of the total dose administered was excreted in urine up to 48 hours postdose. BIA 3-202 markedly reduced soluble COMT (S-COMT) activity in erythrocytes, with maximum inhibition occurring at 1 to 2 hours postdose; enzyme activity returned to baseline levels by approximately 8 hours. Inhibition of S-COMT activity appeared to increase with increasing doses of BIA 3-202 on both day 1 and day 9. In conclusion, BIA 3-202 was well tolerated in all the oral multiple-dose regimens tested. BIA 3-202 was shown to inhibit S-COMT activity in erythrocytes, and its pharmacokinetics appeared to be linear (i.e., dose independent and time invariant).

475. Levetiracetam: Relative Bioavailability and Bioequivalence of a 10% Oral Solution (750 mg) and 750-mg Tablets - Coupez R., Straetemans R., Sehgal G. et al. [Dr. Z. Lu, UCB Pharma, Inc., 1950 Lake Park Drive, Smyrna, GA 30080, United States] - J. CLIN. PHARMACOL. 2003 43/12 (1370-1376) - sum in ENGL

Levetiracetam, an antiepileptic drug, is used worldwide as an adjunctive treatment for partial-onset seizures. The availability of a new oral solution formulation would provide an additional treatment option for patients who have difficulty swallowing tablets. A phase I single-center, randomized, open-label, two-way crossover, single-dose study was conducted to confirm that a 10% oral solution of levetiracetam was bioequivalent to the 750-mg oral tablet and to characterize its pharmacokinetics. Each of 24 healthy subjects received a single oral 750-mg dose of the randomized levetiracetam formulation (7.5 mL of 10% solution or 750-mg tablet) on day 1 and a single oral dose of the alternate formulation on day 8. Serial blood samples were collected from 0 to 36 hours after each dose administration for determination of plasma levetiracetam concentrations. Pharmacokinetic parameters were calculated, and bioequivalence of the two formulations was evaluated. The mean levetiracetam plasma concentration-time curves and pharmacokinetic parameters essentially were identical for the oral 10% solution and tablet and consistent with previously reported levetiracetam pharmacokinetics. The 90% confidence limits of the geometric mean ratio of the two formulations for area under the plasma concentration-time curve from time 0 to infinity, area under the plasma concentration-time curve from time 0 to last measurable time point, and maximum plasma concentration were within the 80% to 125% range, demonstrating bioequivalence of the two formulations. Both levetiracetam formulations were well tolerated. The levetiracetam 10% oral solution is a bioequivalent, well-tolerated alternative to the tablet formulation in patients who have difficulty swallowing.


A series of N-[4-(arylpiperazin-1-yl)-methyl] derivatives of 3-arylpyrrolidine-2,5-dione and 2-aza-spiro[4.4]nonane-1,3-dione were synthesized and tested for anticonvulsant activity in the maximum electroshock seizure (MES) and metrazol seizure testing. The IC50 values of the compounds in the series were N-[4-(3-chlorophenyl)-piperazin-1-yl]-methyl-3-(2-chlorophenyl)-pyrrolidine-2,5-dione (ED50=14.18 mg/kg) and N-[4-(2-methoxyphenyl)-piperazin-1-yl]-methyl-3-(3-bromo-phenyl)-pyrrolidine-2,5-dione (ED50=33.64 mg/kg). Structures of the novel compounds were confirmed by elemental and spectral analyses. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.


Here, we summarize recent data pertaining to the effects of GABA4 receptor modulators on the receptor gene expression in order to elucidate the molecular mechanisms behind tolerance and dependence induced by these drugs. Drug selectivity and intrinsic activity seems to be important to evidence at the molecular level the GABA4 receptor tolerance. On the contrary, we suggested that all drug tested are equally potentially prone to induce dependence. Our results demonstrate that long-lasting exposure of GABA4 receptors to endogenous steroids, benzodiazepines and ethanol, as well as their withdrawal, induce marked effects on receptor structure and...
function. These results suggest the possible synergic action between endogenous steroids and these drugs in modulating the functional activity of specific neuronal populations. We report here that endogenous steroids may play a crucial role in the action of ethanol on dopaminergic neurons. © 2003 Elsevier B.V./ECNP. All rights reserved.

478. Neuroadaptative mechanisms of addiction: Studies on the extended amygdala - Koob G.F. [G.F. Koob, Division of Psychopharmacology, Department of Neuropharmacology, Scripps Research Institute, 10550 North Torrey Pines Road, San Diego, CA 92037, United States] - EUR. NEUROPSYCHOPHARMACOL. 2003 13/6 (442-452) - sumin ENGL

A conceptual structure for drug addiction focused on allostatic changes in reward function that lead to excessive drug intake provides a heuristic framework with which to identify the neurobiologic neuropeptide mechanisms involved in the development of drug addiction. The brain reward system implicated in the development of addiction is comprised of key elements of a basal forebrain macrostructure termed the extended amygdala and its connections. Neuropharmacologic studies in animal models of addiction have provided evidence for the dysregulation of specific neurochemical mechanisms not only in specific brain reward circuits (opiod peptides), but also in other brain systems that may contribute to higher positive reinforcing effects. This study indicates that both a large and relapse in addiction. © 2003 Elsevier B.V./ECNP. All rights reserved.

479. Dopamine mediation of positive reinforcing effects of amphetamine in stimulant-naive healthy volunteers: Results from a large cohort - Abi-Dargham A., Kegeles L.S., Martinez D. et al. [M. Laruelle, Division of Functional Brain Mapping, Columbia Univ. Coll. of Phys./Surgs., New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, United States] - EUR. NEUROPSYCHOPHARMACOL. 2003 13/6 (459-468) - sumin ENGL

A positive experience during a first encounter with a drug of abuse is predictive of subsequent use and might represent a vulnerability factor to develop addiction. This paper presents a meta-analysis of data collected in 60 healthy volunteers who underwent a low-dose amphetamine challenge (0.3 mg/kg, i.v.) during imaging of dopaminergic (D2/D3) receptor availability. Amphetamine-stimulated DA release induced a small, significant and highly variable decrease in striatal D2/D3 receptor availability (-8.3 ± 6.7%). The magnitude of the decrease in D2/D3 receptor availability was significantly correlated with positive reinforcing effects of the drug reported by the subject (r=0.14, p<0.003). Age was associated with decreased potency of dopamine to elicit positive reinforcing reinforcing effects. This study indicates that both a large dopamine response and young age during a first encounter with a drug of abuse potential contribute to higher positive reinforcing effects. © 2003 Elsevier B.V./ECNP. All rights reserved.


This paper provides an evidence-based risk-benefit assessment of acamprosate and naltrexone in the treatment of alcohol dependence. A risk-benefit assessment is based on the premise that the choice of treatment depends on a number of factors, notably the adverse event profile and efficacy. An evidence-based approach attempts to operationalize how such risk-benefit assessments are made to inform physician choices. This approach involves a systematic assessment of all published double-blind, placebo-controlled trials. Based on this review, we conclude that acamprosate and naltrexone are both useful in the treatment of alcohol dependence. However, the two drugs act in different ways in the brain, and their clinical profiles are different. Treatment effects seem to be more reliable for acamprosate, and this drug is better tolerated. The safety of the two drugs in combination has been supported by two independent double-blind studies, and combination treatment may offer an advantage for some patients. © 2003 Elsevier B.V./ECNP. All rights reserved.

481. Effects of Sertraline on Sleep Architecture in Patients with Depression - Jindal R.D., Friedman E.S., Berman S.R. et al. [Dr. R.D. Jindal, W. Psychiatric Institute and Clinic, 3811 O’Hara Street, Pittsburgh, PA 15213, United States] - J. CLIN. PSYCHOPHARMACOL. 2003 23/6 (549-552) - sumin ENGL

Sertraline, an SSRI, has been supported by two independent double-blind studies, and drug is better tolerated. The safety of the two drugs in combination has been supported by two independent double-blind studies, and combination treatment may offer an advantage for some patients. © 2003 Elsevier B.V./ECNP. All rights reserved.


Treatment of depression is often accompanied by weight changes. Previous studies indicate that leptoins plays no role in this change despite showing a strong correlation with body mass index (BMI) in healthy people. The aim of this study was to evaluate the effect of imipramine and fluoxetine on BMI and its correlation with leptin. Eighteen depressed female patients randomly received either drug for 3 months. BMI was calculated and fasting blood samples were assayed for glucose, leptin, insulin, free fatty acids (FFA), and lipids. The difference between the changes in BMI (imipramine +1.0 kg/m², fluoxetine -0.5 kg/m²) was statistically significant (P <0.05, t = 2.06). There was a significant positive correlation between overall BMI and leptin (r = 0.784, P < 0.001) but not between BMI and insulin or FFA. However, fasting insulin levels and calculated insulin resistance levels dropped substantially in the imipramine group. We conclude that the use of tricyclic antidepressants (TCAs) in depressed patients at risk for developing type 2 diabetes remains unresolved at this stage.

483. Sertraline and Cognitive Behavioral Therapy for Depressed Alcoholics: Results of a Placebo-Controlled Trial - Moak D.H., Anton R.F., Latham P.K. et al. [Dr. D.H. Moak, Department of Psychiatry, Medical University of South Carolina, 67 President Street, Charleston, SC 29425, United States] - J. CLIN. PSYCHOPHARMACOL. 2003 23/6 (553-562) - sumin ENGL

Alcoholism and depression are common disorders that frequently coccur in the same individual. Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of depression and also had decreased drinking in some studies of heavy drinkers and alcoholics. The reported effect of serotonergic medications on alcohol intake in depressed alcoholics has not been consistent. Most previous studies have not investigated the use of an SSRI in the
context of cognitive behavioral therapy (CBT), a known efficacious treatment of both alcoholism and depression. The study presented here was a randomized placebo-controlled 12-week trial of sertraline combined with individual CBT focused on both alcoholism relapse prevention and depressive symptoms. Subjects were 82 currently depressed, actively drinking alcohol-dependent individuals. Subjects had either primary (independent) major depression (70 subjects) or substance-induced mood disorder and at least 1 first-degree relative (parent, sibling, or child) with an affective disorder (12 subjects). Depression and alcohol consumption outcomes were measured weekly over 12 weeks. Sertraline was well tolerated and all subjects had decreases in both depression and alcohol use during the study compared with baseline. Subjects who received sertraline had fewer drinks per drinking day than subjects who received placebo, but other drinking outcomes were not different between the 2 treatment groups. Treatment with sertraline was associated with less depression at the end of treatment in female subjects compared with female subjects who received placebo. Less drinking during the study was associated with improved depression outcome. The findings in this study suggest that sertraline, compared with placebo, may provide some modest benefit in terms of drinking outcome and also may lead to improved depression in female alcohol-dependent subjects. Additionally, alcohol relapse prevention CBT, delivered according to manual guidelines with modifications that provide specific attention to depression, appeared to be of benefit to subjects, although this interpretation is limited by the design of the study.

484. Sertraline in Panic Disorder: Initial Treatment Versus Switch Strategy - Mavissakalian M.R. [Dr. M.R. Mavissakalian, Anxiety Disorders Program, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106, United States] - J. CLIN. PSYCHOPHARMACOL. 2003 23/6 (657-659) - sum in ENGL.

The study explored whether there is differential efficacy for patients with panic disorder treated with sertraline initially (primary group) versus those switched (transfer group) after intolerance or nonresponse to imipramine in the context of the open 24-week treatment phase of a long-term maintenance/discontinuation study. Similar assessment and treatment procedures were used in the 2 groups and there were no concurrent cognitive behavioral interventions. A consistent pattern suggesting decreased efficacy for the transfer treatment group (n = 11, 68 ± 25 mg/d) compared with the primary treatment group (n = 11, 70 ± 25 mg/d) was found on response rates, univariate repeated measures analysis of variance and within group effect sizes in intent to treat, and completer samples. These preliminary findings concord well with clinical intuition but are contrary to findings in the treatment of depression. Replication studies seem warranted.


Chlorpromazine (CPZ) equivalents can be used to chart relative antipsychotic drug potency of antipsychotic agents. Values of CPZ equivalents per drug are ambiguous in literature. In drug use evaluation studies, antipsychotic doses are frequently compared by use of the defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug if used for its main indication in adults. The DDD is based on review of the available older and recent literature. In this report, we evaluated discrepancy between CPZ-equivalent values and DDD-equivalent values. We plotted CPZ-equivalent values against DDD-equivalent values and performed linear regression to determine the mean relationship between the 2 methods. About 67% of the DDD-equivalent values demonstrated lower potencies for antipsychotic drug compared with CPZ-equivalent values. The slope of the regression line was 0.68 (r² = 0.81). Because we found a great discrepancy between these 2 methods of comparing antipsychotic drug doses, we think further research is necessary to develop a standardized way of antipsychotic drug comparison.

486. Predictors of Clinical Outcome in Schizophrenic Patients Responding to Clozapine - Mairi M.C., Volontier L.S., Dell’Osso B. et al. [Dr. M.C. Mairi, Clinical Psychiatry, ICRCS Ospedale Maggiore, Via F. Sforza 35, 20122 Milano, Italy] - J. CLIN. PSYCHOPHARMACOL. 2003 23/6 (660-664) - sum in ENGL.

Many of the patients who respond better to clozapine (CLZ) than to typical antipsychotics still have residual psychopathology, but CLZ drug resistance data are lacking. The aim of this study was to evaluate the possible predictive factors of a clinical response to CLZ in a group of 20 schizophrenic patients (DSM-IV: 13 males and 7 females with a mean age of 35.5 years ± 7.1 SD) resistant to typical antipsychotics but CLZ responders as assessed by the Brief Psychiatric Rating Scale (BPRS) (> 20% improvement). After a 1-week washout period, CLZ was started at a dose of 25 mg/d, which was increased by the third week up to a maximum of 600 mg/d (mean 365.00 ± 129.88 mg/d SD) and remained unchanged until the end of the study (week 8). The patients showed a significant improvement in the mean scores of the rating scales for positive (SAPS) and negative symptoms of schizophrenia (Scale for the Assessment of Negative Symptoms, SANS) (P < 0.003; P < 0.02). All of the patients included in the study were BPRS responders; 65% were also SAPS and 75% SANS responders (> 20% improvement). The improvement in the SANS score was significantly greater among the female patients (P < 0.05). The SAPS and SANS responders had a significantly higher mean metabolic ratio [MR = (NCLZ/CLZ)] but the nonresponders (P < 0.01), and the percentage of improvement significantly correlated with the increase in MR. This finding suggests that the individual pharmacogenetics indicated by metabolic capacity may be related to clinical response. All of the patients showed a reduction in white blood cell counts, but this was significantly less in the SANS responders than the SANS nonresponders (P = 0.047). The SAPS responders had significantly lower neurophil counts than the nonresponders (P = 0.03). Our results seem to suggest the importance of pharmacodynamic, constitutional, and genetic data over strict pharmacokinetics in determining the clinical response to CLZ.


There is clinical evidence of anxiolytic action of several anti-epileptic drugs. We evaluated the effects of levetiracetam (Keppra®), a new generation anti-epileptic drug, in the plus-maze animal test for anxiety activity. Levetiracetam at 17 and 54 mg/kg intraperitoneally (i.p.) was without effect when tested in naive rats. A modified version of the test was subsequently used in which open-arm exploration was decreased by exposure of the rats to a four-open-arm maze 24 h prior to drug treatment and testing. Under these conditions of enhanced anxiety, levetiracetam, 5.4 to 54 mg/kg, dose-dependently increased open-arm exploration. Chlor diazepoxide 5 mg/kg had similar effects but busiprone 0.1 to 1.0 mg/kg was inactive. The results with levetiracetam substantiate similar similarity of tolerance to the effects of both: a) chronic administration of withdrawal-induced anxiety in mice and in a modified Vogel test in rats and support a potential clinical use of this drug in anxiety states. © 2003 Elsevier B.V. All rights reserved.

488. 5-HT1A receptor full agonist, 8-OH-DPAT, exerts antidepressant-like effects in the forced swim test in ACTH-treated rats - Kitamura Y., Araki H., Shibata K. et al. [Y. Kitamura, Division of Pharmacy, Missasa Medical Center, Okayama University Medical School, 827 Yamada Missasa-cho, Tohaku-Gun, Tottori 682-0192, Japan] - EUR. J. PHARMACOL. 2003 481/1 (75-77) - sum in ENGL.

We examined the effect of adrenocorticotropic hormone (ACTH) on the immobilization of rats in the forced swim test after administration of the 5-HT1A receptor agonist, 8-hydroxy-2-di-n-propylamino tetralin (8-OH-DPAT). Imipramine (3-30 mg/kg, i.p.) or 8-OH-DPAT (0.1-1 mg/kg, s.c.) significantly decreased the duration of immobility in normal rats. The immobility-decreasing effect of imipramine was blocked when ACTH was administered for 14 days. On the other hand, the immobility-decreasing effect induced by 8-OH-DPAT was not blocked by chronic administration...
4.98. Methylenedioxymethylamphetamine (MDMA, 'ecstasy') serves as a robust positive reinforcer in a rat runway procedure - Wakenig G., Sturm K., Saria A. and Zernig G. [Dr. G. Zernig, Division of Neurochemistry, Department of Psychiatry, Anichstrasse 35, AT-6020 Innsbruck, Austria] - PHARMACOLOGY 2003 694 (180-182) - sum in ENGL

Although 'ecstasy' (3,4-methylenedioxymethylamphetamine, MDMA) is, after marijuana, the second most prevalent illegal drug of abuse in European adolescents, animal experimental evidence of MDMA's reinforcing effect has remained scarce, particularly in the rodent model, raising questions about the robustness of MDMA's reinforcing effect under controlled laboratory conditions. In the present rat runway study, Sprague-Dawley and Long-Evans rats were given the opportunity to run for intravenous injections of saline or MDMA (1 mg/kg). MDMA significantly decreased runtimes in both rat strains. Thus, MDMA's positive reinforcing effect can be demonstrated not only across rat strains but also across operant conditioning paradigms. These findings should reassure the drug abuse research community that the investigation of MDMA's reinforcing effect in the inexpensive and widely used rodent model is indeed feasible. Copyright © 2003 S. Karger AG, Basel.


Peripheral activation of the NO-cGMP pathway has been implicated in various nociceptive conditions. The antinoicetotic effect of the FDE-5 inhibitor, sildenafil, alone or in combination with cyclooxygenase inhibitor diclofenac and nimesulide, was assessed in the different animal models of peripheral nociception. In the present study we investigated the possible interaction between cyclooxygenase and NO-cGMP pathway in writhing assay and carrageenan-induced hyperalgesia in mice and rats, respectively. Sildenafil [1-2 mg/kg, i.p. or 50-100 μg/paw, intraplantar (i.pl.)], nimesulide [1-2 mg/kg, i.p. or 25-50 μg/paw, i.pl.] and diclofenac [1-2 mg/kg, i.p. or 25-50 μg/paw, i.pl.] exhibited an antinoicetotic effect in both the models. When ineffective doses of sildenafil (0.5 mg/kg, i.p and 25 μg/paw, i.pl.) were co-administered with ineffective doses of nimesulide (0.5 mg/kg, i.p. and 10 μg/paw, i.pl.) and diclofenac (0.5 mg/kg, i.p. and 10 μg/paw, i.pl.) there was a significant increase in the antinoicetotic effect in both the models of peripheral nociception. Further, the potentiation of the effect was blocked by L-NAME (20 mg/kg, i.p.), 100 μg/paw, i.pl.), a non-selective NOS inhibitor and methylene blue (1 mg/kg, i.p.), a guanylate cyclase inhibitor. L-NAME or methylene blue itself had little or no effect on both the models of hyperalgesia. These results suggest that cyclooxygenase, NO and cGMP are relevant in the peripheral modulation of antinoicetosis, sildenafil induced antinoicetosis, and its potentiation of the effect of the cyclooxygenase inhibitors nimesulide and diclofenac was probably mediated through the activation of the NO-cGMP pathway and inhibition of cyclic GMP degradation. Copyright © 2003 S. Karger AG, Basel.

See also: 529, 530, 533, 551, 567, 579, 580, 594, 610, 624, 625, 693, 694, 695, 722, 723.

5.2. Autonomic and motor nervous system

4.91. Role for standards in assays of botulinum toxins: Inter- national collaborative study of three preparations of botulinum type A toxin - Sesardic D., Leung T. and Das R.G. [D. Sesardic, Division of Bacteriology, Natl. Inst. for Biol. Std-Control, Blanche Lane, Potters Bar, Hertfordshire EN6 3QG, United Kingdom] - BIOLOGICALS 2003 31/4 (265-276) - sum in ENGL

The biological activity of therapeutic preparations of botulinum type A toxin is currently expressed in units defined on the basis of the median lethal intraperitoneal dose of that preparation in mice at 72 h, the LD50 dose. In this study we describe the comparison, by ten laboratories in five countries, of three different formulations of botulinum type A toxin using the mouse lethality test, and also using the relative activities of the preparations. The results of this study show that use of a standard preparation and expression of relative potency gives substantially greater consistency between and within laboratories than when mouse LD50 unit is used to define activity of botulinum toxin. © 2003 The International Association for Biologicals. Published by Elsevier Ltd. All rights reserved.

5.3. Cardiovascular system

4.92. Folic acid supplement decreases the homocysteine increasing effect of filtered coffee. A randomised placebo-controlled study - Strandhagen E., Landaas S. and Thelle D.S. [E. Strandha- gen, Department of Medicine, Cardiovascular Institute, Sahlgrenska Univ. Hospital/Ostra, SE-416 85 Göteborg, Sweden] - EUR. J. CLIN. NUTR. 2003 57/11 (1411-1417) - sum in ENGL

Objective: Elevated levels of plasma total homocysteine (tHcy)- are identified as independent risk factors for cardiovascular disease and for fetal neural tube defects. tHcy levels are negatively associated with folic acid, pyridoxine and cobalamin, and positively associated with coffee consumption and smoking. A total of 600 ml of filtered coffee results in a tHcy increase that 200 μg of folic acid or 40 mg of pyridoxine supplementation might eliminate. Design: Randomised, blinded study with two consecutive trial periods. Set- ting: Free living population. Volunteers. Subjects: A total of 121 healthy, nonsmoking men and women (79%) aged 29-65y. Interventions: (1) A coffee-free period of 3 weeks, (2) 600 ml coffee/day and a supplement of 200 μg folic acid/day or placebo for 4 weeks, (3) 3-week coffee-free period, (4) 600 ml coffee/day and 40 mg pyridoxine/day or placebo for 4 weeks. Main outcome measures: The difference between the change in tHcy in the supplement group and the change in tHcy in the placebo group during the 4-week trial period. Results: Coffee abstention resulted in a tHcy decrease of 1.04 μmol/l for the whole group. In the subsequent coffee period, a further decrease of 0.17 μmol/l was observed in the folic acid group whereas an increase of 1.26 μmol/l was observed in the placebo group, the difference was 1.43 μmol/l (95% Cl: 0.80, 2.07). Pyr- idoxine supplement had no impact on tHcy levels. Conclusions: Supplementation of 200 μg folic acid/day eliminates the tHcy increasing effect of 600 ml filtered coffee in subjects not already on folic acid supplements. A supplement of 40 mg pyridoxine/day does not have the same effect.

4.93. Long-term administration of pravastatin reduces serum lipoprotein(a) levels - Horimoto M., Hasegawa A., Takenaka T. et al. [Dr. M. Horimoto, Division of Cardiovascular Disease, Chitose City Hospital, Hokkou 2-Choume 1-1, Chitose City, Hokkaido 066- 8550, Japan] - INT. J. CLIN. PHARMACOL. THER. 2003 41/11 (524-530) - sum in ENGL

Background: The long-term effect of 3-hydroxy-3-methylgluta- ryl coenzyme A reductase inhibitors on serum lipoprotein(a) (Lp(a)- ) levels has been poorly investigated. Objective: This study sought to examine the effect of 24 months' administration of pravastatin on serum Lp(a) levels. Subjects: 23 patients with coronary artery disease and serum low-density lipoprotein (LDL) cholesterol levels of 120 mg/dl or above were included. Method: Serum levels of lipids and Lp(a) were serially determined after the administration of pravastatin for 24 months. Results: Serum LDL-cholesterol (LDL-C) levels significantly decreased from 1 month after the drug administration and the reduction persisted for 24 months. Lp(a) levels did not decrease at 3 months after the administration but significantly decreased at 12 months or more. The reduction in the Lp(a) levels was not related to the dose of pravastatin. Conclusions: The results indicated that long-term administration of pravastatin for 12 months or more significantly reduced serum Lp(a) levels and the reduction of Lp(a) levels occurred much later than that of LDL-C levels. The delayed reduction in serum Lp(a) levels after the administration may be associated with a retarded inhibition of Lp(a) synthesis by the drug.
497. Experimental and clinical studies show that the probucol derivative AGI-1067 prevents vascular growth - Doggrel S.A. [S.A. Doggrel, Doggrel Biomedical Communications, 47 Caronia Crescent, Lynfield, Auckland, New Zealand] - EXPERT OPIN. IN- VEST. DRUGS 2003 12/11 (1855-1859) - summ in ENGL

AGI-1067 is a derivative of probucol that is a promising new development for the treatment of restenosis and possibly athero- sclerosis. In monkeys fed a high-fat diet for 1 year, AGI-1067 prevented the development of atherosclerosis. In these monkeys, AGI-1067 lowered plasma levels of low-density lipoprotein (LDL)-cholesterol and very low-density lipoprotein cholesterol levels, decreased the atherosclerotic lesion area in the aorta. In a mouse model of acute inflammation, the mRNA for the pro-inflammatory vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 was upregulated and this was inhibited by AGI-1067. AGI-1067 inhibited the TNF-α induction of redox-sensitive inflammatory proteins, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1 and E-selectin, in cell culture. In addition, AGI-1067 is an antioxidant. In the Canadian Antioxidant Restenosis Trial (CART-1) of AGI-1067 in percutaneous coronary interventions, AGI-1067 had no effect on LDL-cholesterol but lowered HDL-cholesterol. At 6 months follow up, the lumen area of the percutaneous coronary interventions segments was greater in patients treated with AGI-1067 than in untreated patients. Restenosis rates were 37.5% in the placebo group and 26% in the AGI-1067 group. The lumen area of reference segments was reduced in the placebo group but increased with the higher doses of AGI-1067. Unlike probucol, AGI-1067 did not alter QTc interval.

498. Diazepam and melatonin effects upon circadian variation of cultured murine myocardocytes - Zhou B., Wang Z., Wan C. et al. [Z. Wang, School of Basic Medical Sciences, Second University Hospital, Peking University Health Science Centre, Beijing 100037, China] - NEUROENDOCRINOL. LEIT. 2005 24/SUPPL. 1 (216-222) - summ in ENGL

We determined that melatonin and diazepam affected the persisting rhythm in contraction rates in cultured murine myocardocytes. The effect of different concentrations of melatonin (10-6M, 10-5M and 10-4M) and diazepam (10-5M, 10-4M and 10-3M) was tested at six different times of day 4h apart in continuous light allowing a condition free-running from the alteration of light and darkness. Circadian variations with graded concentrations of melatonin or diazepam were observed by the cosinor fit of a 24h cosine function and the rejection of the zero-amplitude (no-rhythm) assumption. Melatonin and diazepam induced decreases in time structure or chronome-adjusted averages (MESORs) and amplitudes (measures of extent of predictable change), and generally delayed acrophases and the rejection of the zero-amplitude (no-rhythm) assumption. Melatonin and diazepam induced decreases in time structure or chronome-adjusted averages (MESORs) and amplitudes (measures of extent of predictable change), and generally delayed acrophases and the rejection of the zero-amplitude (no-rhythm) assumption. Melatonin and diazepam induced decreases in time structure or chronome-adjusted averages (MESORs) and amplitudes (measures of extent of predictable change), and generally delayed acrophases and the rejection of the zero-amplitude (no-rhythm) assumption.

A patient treated for essential hypertension monitored her blood pressure and heart rate during an 11-day span. During the first 5 days of monitoring, one 24-hour span was perfectly acceptable; the others showed circadian hyper-amplitude-tension, CHAT, either systolic or diastolic or both. This test demonstrates, in the context of assessing the blood pressure lowering effects of melatonin and losartan potassium, the indispensability of dealing with blood pressure on an individualized time series basis at any age. We here quantified and interpreted melatonin effects on the chronome (time structure) of blood pressure. Whenever possible, in practice, effects upon a variable’s chronome must be interpreted first on an individualized basis before summarizing the results for the population.


Aims: We evaluated the effect of N-acetylcysteine (NAC, infused i.v.), isosorbide 5-mononitrate (ISMN, by gavage), or their combination on cardiac injury in an in vivo rat model of 30-min ischemia followed by 24 hours or 7 days of reperfusion. Results: When administered immediately prior to reperfusion with continuous infusion for 24 h, the combination of NAC + IS5MN reduced infarct size (29 ± 6 vs. 59 ± 4% area-at-risk, p < 0.001) and the infiltration of polymorphonuclear leukocytes (226 ± 15 vs. 315 ± 18 cells mm⁻² of area-at-risk, p = 0.002) to vehicle. NAC or ISMN alone did not reduce infarct size at 24 hours of reperfusion. The same dose regimen of NAC and IS5MN did not reduce infarct size with permanent ischemia for 24 hours not followed by reperfusion. After 7 days of reperfusion (3 days of treatment with NAC + IS5MN or vehicle and 4 days of wash-out), infarct size was similar in the vehicle and NAC + IS5MN groups, but LV end-diastolic pressure and diastolic LV chamber wall stress were significantly lower in the animals treated with NAC + IS5MN (5 ± 1 mmHg and 62 ± 7 dyne mm⁻², respectively) compared to vehicle (9 ± 1 mmHg and 123 ± 18 dyne mm⁻², p < 0.05). Conclusion: We demonstrate in a rat model of cardiac ischemia-reperfusion treated with NAC and IS5MN, according to a regimen that mimicked a clinical situation (drugs started at time of reperfusion), that the short-term benefit seen after 24 h of reperfusion (51% reduction of infarct size) is maintained after one week, possibly through modulation of the inflammatory response to cardiac injury.


The beneficial effects of pyruvate in organ reperfusion injury have been documented, however the therapeutic use of pyruvate has been hindered by the lack of an appropriate delivery method. Pyruvic acid is unstable and high rates of sodium pyruvate infusion are toxic. Dipyruvyl-acetyl-glycerol (DPAG) ester was developed as a novel method for intravenous pyruvate delivery at a high rate without sodium overload. We tested the ability of DPAG to reduce myocardial infarct size when administered after severe myocardial ischemia in an in vivo pig model of ischemia-reperfusion injury. Ischemia was induced by total occlusion of the distal 2/3 of the left anterior descending coronary artery for one hour, followed by two hours of reperfusion. Animals were either untreated (n = 7), or treated with intravenous DPAG (8.0 mg/kg·min⁻¹, n = 8) during the two hours of reperfusion. Infarct size was measured on blinded samples using tetrazolium staining. The DPAG treated group had elevated pyruvate levels (8.22 ± 0.07 mM) and reduced infarct size (20.1 ± 9.3% of the volume at risk compared to 30.8 ± 6.4% in the untreated animals (p < 0.05), with no difference in blood pressure or heart rate between groups. In conclusion, an intravenous infusion of DPAG safely increases arterial pyruvate concentration and reduces myocardial infarct size following myocardial ischemia.

502. Comparison between Ischaemic and Anisomycin-Induced Preconditioning: Role of p38 MAPK - Locher A., Genesis A., Hattingh S. et al. [Dr. A. Locher, Dept. of Med. Physiol., and Biochem., Faculty of Health Science, P.O. Box 19063, Tygerberg 7505, South Africa] - CARDIOVASC. DRUGS THER. 2003 17/3 (217-230) - sum in ENGL.

To further evaluate the significance of p38 MAPK as trigger or mediator in ischaemic preconditioning, anisomycin and SB 203580 were used to manipulate its activation status. Special attention was given to the comparison of the drugs and protocols used. The isolated perfused rat heart, subjected to either 25 min global ischaemia or 35 min regional ischaemia, was used as experimental model. This was preceded by anisomycin (2 or 5 µM; 3 x 5 min; 5 µM: 5 min or 10 min: 5 µM: 10 min + 10 min washout or 20 µM: 20 min) or SB 203580 (2, µM: 3 x 5 min; before and during 3 x 5 min or 1 x 5 min ischaemic preconditioning; 10 min).Endpoints were functional recovery during reperfusion and infarct size. Anisomycin, regardless of the protocol, reduced infarct size, but failed to improve functional recovery. In a number of experiments activation of JNK by anisomycin was blocked by SP 600125 (10 µM). SP 600125 had no effect on the anisomycin-induced reduction in infarct size. SB 203580 when administered for 10 min before sustained ischaemia, improved functional recovery and reduced infarct size. SB 203580 could not abolish the beneficial effects of a multicycle preconditioning protocol, but it significantly reduced the outcome of 1 x 5 min preconditioning. In all hearts improved functional recovery and reduction in infarct size were associated with attenuation of p38 MAPK activation during sustained ischaemia-reperfusion. The results indicate that activation of p38 MAPK acts as a trigger of preconditioning, while attenuation of its activation is a prerequisite for improved recovery and a reduction in infarct size.

503. Effects of Olmesartan, an Angiotensin II Receptor Blocker, on Mechanically-Modulated Genes in Cardiac Myocytes - Oishi R., Yamamoto K., Ueno S. et al. [Dr. K. Yamamoto, Division of Cardiovascular Medicine, Jichi Medical School, Minamikawachi-Machi, Tochigi 329-0498, Japan] - CARDIOVASC. DRUGS THER. 2003 17/3 (231-236) - sum in ENGL.

Background: Angiotensin II plays an important role in cardiac hypertrophy or remodeling. Angiotensin II receptor blockers (ARB) are clinically useful for the treatment of hypertension and heart failure. However, the molecular effects of ARB in the mechanically-stressed myocardium have not been completely defined. We investigated the effects of ARB on mechanically-modulated genes in cardiac myocytes. Methods: We used powerful DNA microarray technology to study the effects of the ARB, CS-886 (olmesartan), on genes modulated in neonatal rat cardiac myocytes cultured in the presence or absence of RNI-6270, an active metabolite of CS-886. Expression profiles of 8000 rat genes using the Affymetrix GeneChap (Rat Genome U34A) were investigated with mRNA obtained from the samples above. Results: Nine genes induced under 4% mechanical strain were significantly suppressed by RNI-6270 in rat cardiac myocytes: monoamine oxidase B, neurenomide B receptor, olfactory receptor, synaptogamin X1, retinol-binding protein, and 4 expressed sequence tags (ESTs) . In contrast, 21 genes suppressed under mechanical strain were significantly restored by RNI-6270: major acute phase alpha 1-protein, Spi-1, Bel-Xl, IAK2, 2 genes encoding demethylation, few genes for receptor, structure, metabolism or ion channel, and 10 ESTs. Conclusions: As some of these genes may be involved in promoting or modulating cardiac remodeling, these findings suggest that ARB may affect cardiovascular morbidity and mortality partially via these molecular alterations.

504. Refractoriness and Conduction Interaction during Modulation of Non-Ischemic Ventricular Fibrillation by Flecainide - Amitzur G., Shenkar N., Mueller M. et al. [Dr. G. Amitzur, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer,
505. Serum MCP-1 and VEGF Levels are not Affected by Inhi-
bitition of the Renin-Angiotensin System in Patients with Acute
Myocardial Infarction - Murakami Y., Kuroskki K., Matsu K.,
et al. [Dr. U. Ikeda, Department of Organ Regeneration, Shinsu
Univ. Grad. Sch. of Medicine, 3-1-1 Asahi, Matsumoto 390-8621,
Japan] - CARDIOVASC. DRUGS THER. 2003 173 (249-255) -
summ in ENGL
Monocyte chemoattractant protein-1 (MCP-1) and vascular en-
gothelial growth factor (VEGF) stimulate angiogenesis in ischemic
 tissues, and both of their expression are stimulated by angiotensin II.
 We measured the serum concentrations of MCP-1 and VEGF in
patients with acute myocardial infarction (AMI) and investigated the
effects of an early administration of angiotensin-converting en-
zyme inhibitor (ACEI) and angiotensin II type 1 receptor blocker
(ARB) on their levels. Thirty-six patients with AMI were divided
randomly into 3 therapeutic groups; the ACEI perindopril, the ARB
candesartan and control (without perindopril and candesartan), and
the drugs were administered within 36 hours after the onset of
AMI. Peripheral blood mononuclear cells (PBMC) obtained from
the patients were incubated for 24 hours. The levels of MCP-1 and
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by ELISA. The serum MCP-1 and VEGF levels in AMI patients
at the time of admission were not significantly different from those
in healthy control subjects, but both MCP-1 and VEGF levels in the
patients were increased significantly after 7 days. There was no
significant difference in the serum MCP-1 and VEGF levels among
the 3 therapeutic groups. The production of MCP-1 and VEGF by
PBMC was also increased in AMI patients compared with healthy
control subjects, and there was also no difference in their production
among the 3 therapeutic groups. In conclusion, circulating MCP-1
and VEGF levels and their production by PBMC are elevated during
the course of AMI, and early administration of ACEI and ARB does
not affect their levels.

506. Calphostin C as a rapid and strong inducer of apoptosis
in human coronary artery smooth muscle cells - Krueger K.D.,
Pazoya J.D., Dobrev I., Core M.G., et al. [K.ido, K. Ido, Agarwal,
Creighton Univ. School of Medicine, CRISS I, 2500 California
Plaza, Omaha, NE 68178, United States] - J. CLIN. PHARMACOL.
2003 43(12) (1299-1306) - summ in ENGL
The authors examine the available clinical and experimental data
supporting the view that homocysteine, an alternative risk factor
for cardiovascular disease, may play a role in the pathogenesis of
essential hypertension. The mechanism of this disease has not
been elucidated, but it may be related to impairment of vascular
endothelial and smooth muscle cell function. Therefore, the occur-
rence of endothelial dysfunction could contribute to alterations of
the endothelium-dependent vasomotor regulation. Elevated homo-
cysteineemia diminishes the vasodilatation by nitric oxide, increases
oxidative stress, stimulates the proliferation of vascular smooth
muscle cells, and alters the elastic properties of the vascular wall.
Thus, homocysteine contributes to elevate the blood pressure. Also
it is known that elevated plasma levels of homocysteine could lead
to oxidant injury to the endothelium. The correction of elevated ho-
mcysteine by administration of vitamins B6 and B12 can prevent this
oxidative stress, could be a useful adjuvant therapy of hypertension.
However, further controlled randomized trials are necessary to establish
the efficacy and tolerability of these potentially therapeutic agents.

507. Differentia
tional va
sconstriction induced by angiotensin II: Role of AT1 and AT2 receptors in isolated C57BL/6J mouse
blood vessels - Zhou Y., Dirksen W.P., Babu G.J. and Periasamy
M. [M. Periasamy, Dept. of Physiology and Cell Biology, Ohio State
Univ. Coll. of Med., 304 Hamilton Hall, 1645 Neil Ave, Colum-
bus, OH 43210, United States] - AM. J. PHYSIOLOG. CARD.
PHYS. 2003 285(4) 846-6 (H2797-H2803) - summ in ENGL
Gene
cally altered mice are increasingly used as experimental models. How-
ever, ANG II responses in mouse blood vessels have not been well defined. Therefore, the aim of this study was to
determine the role of ANG II in regulating major blood vessels in
C57Bl/6J mice with isometric force measurements. The results
showed that in mouse abdominal aorta ANG II induced a concen-
tration-dependent contraction (EC50 4.6 nm) with a maximum
contraction of 75.1 ± 4.9% at 100 nm compared with that of 60
nm K+ . Similarly, femoral artery also exhibited a contractile response of 76.0 ± 3.4% to the maximum concentration of ANG
II (100 nm). In contrast, ANG II (100 nm)-induced contraction
was significantly less in carotid artery 24.5 ± 6.6% and only mainly limited to the endothelium. The nitric oxide synthase
inhibitor Nω-nitro-L-arginine methyl ester and the AT2 antagonist

inhibitor Nω-nitro-L-arginine methyl ester and the AT2 antagonist

505. Serum MCP-1 and VEGF Levels are not Affected by Inhi-
bition of the Renin-Angiotensin System in Patients with Acute
Myocardial Infarction - Murakami Y., Kuroskki K., Matsu K.,
et al. [Dr. U. Ikeda, Department of Organ Regeneration, Shinsu
Univ. Grad. Sch. of Medicine, 3-1-1 Asahi, Matsumoto 390-8621,
Japan] - CARDIOVASC. DRUGS THER. 2003 173 (249-255) -
summ in ENGL
Monocyte chemoattractant protein-1 (MCP-1) and vascular en-
gothelial growth factor (VEGF) stimulate angiogenesis in ischemic
 tissues, and both of their expression are stimulated by angiotensin II.
 We measured the serum concentrations of MCP-1 and VEGF in
patients with acute myocardial infarction (AMI) and investigated the
effects of an early administration of angiotensin-converting en-
zyme inhibitor (ACEI) and angiotensin II type 1 receptor blocker
(ARB) on their levels. Thirty-six patients with AMI were divided
randomly into 3 therapeutic groups; the ACEI perindopril, the ARB
candesartan and control (without perindopril and candesartan), and
the drugs were administered within 36 hours after the onset of
AMI. Peripheral blood mononuclear cells (PBMC) obtained from
the patients were incubated for 24 hours. The levels of MCP-1 and
VEGF in the serum and the supernatant of PBMC were measured
by ELISA. The serum MCP-1 and VEGF levels in AMI patients
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significant difference in the serum MCP-1 and VEGF levels among
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PBMC was also increased in AMI patients compared with healthy
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the course of AMI, and early administration of ACEI and ARB does
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endothelial and smooth muscle cell function. Therefore, the occur-
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oxidative stress, stimulates the proliferation of vascular smooth
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Thus, homocysteine contributes to elevate the blood pressure. Also
it is known that elevated plasma levels of homocysteine could lead
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C57Bl/6J mice with isometric force measurements. The results
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was significantly less in carotid artery 24.5 ± 6.6% and only mainly limited to the endothelium. The nitric oxide synthase
inhibitor Nω-nitro-L-arginine methyl ester and the AT2 antagonist

inhibitor Nω-nitro-L-arginine methyl ester and the AT2 antagonist

Acetylocline releases a non-prostanoid endothelium-derived hyperpolarizing factor (EDHF) and nitric oxide from physiological salt solution perfused rat mesenteric arteries. This study reports an impairment in EDHF-mediated vasodilation in deoxycorticosterone acetate (DOCA)-salt hypertensive versus control normotensive rats. Nitric oxide-mediated vasodilation to acetylcholine was not altered in the animals. We hypothesize that free radical species generated by by-products of arachidonic acid metabolism contribute to impaired EDHF-mediated dilation in DOCA-salt hypertension. With or without reduced nicotinamide adenine dinucleotide phosphate (NADPH) as co-factor, arterial microsomes generate free radical species upon incubation with arachidonic acid. The production of free radicals was significantly higher in DOCA-salt versus control microsomes, and was totally eliminated by adducts. © 2003 Elsevier B.V. All rights reserved.

512. Effect of antiproliferative agents on vascular function in normal and in vitro balloon-injured porcine coronary arteries

- Kennedy S., Walsworth R.M. and Wainwright C.L. [S. Kennedy, Dept. of Physiology and Pharmacology, Strathclyde Inst. of Biol. Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, United Kingdom] - EUR. J. PHARMACOL. 2003 481/1 (101-107) - sum in ENGL

Local infusion of antiproliferative agents following coronary balloon angioplasty is used in vivo. This study examined the effects of the antiproliferative agents paclitaxel (5/β, 20-Epoxy-1,2,4,7,10,13,16,19-Eicosatetraenyl-5,8,11,14-Octadecatrienyl) oxy amino ethyl phosphonic acid, (2,2-dimethyl-1-oxopropoxy) methyl ester, sodium); 10 and 25 M), perillyl alcohol (4-isopropenyl cyclohexenecarbinol; 1 and 2 mM) and Van 10/4 (Decahydro-1,1,4,7-tetramethyl-1H-cycloprop[azulen-4-o-]2-(3-methylpent-2-enoyl)-fucopyranoside); 10 and 50 M), farnesyl protein transferase inhibitor III (FPT III, (EE)-2-[2-Oxo-2-[3,7,11-trimethyl-2,6,10-dodecahydro-1H]-exo amino ethyl] phosphonic acid, (2,2-dimethyl-1-oxopropoxy) methyl ester, sodium); 10 and 25 M), perillyl alcohol (4-isopropenyl-cyclohexencarbinol; 1 and 2 mM) and Van 10/4 (Decahydro-1,1,4,7-tetramethyl-1H-cycloprop[azulen-4-o-][2-(3-methylpent-2-enoyl)-fucopyranoside]; 10 and 25 M) on normal and in vitro balloon-injured porcine coronary arteries. Short-term (30 min) incubation had no effect on contraction or relaxation. Overnight incubation with 25 M Van 10/4 attenuated contraction while perillyl alcohol abolished contractility completely. Endothelin-dependent relaxation was significantly attenuated by the higher concentration of paclitaxel, FPT III and Van 10/4. Stretch injury significantly enhanced sensitivity to 3-morpholinosydnonimine (SN-1) while attenuating relaxation to calcium. Drug incubation (15 min) had no effect on these responses. In conclusion, paclitaxel, FPT III and Van 10/4 have no detrimental effects on vascular function after short-term administration to normal or stretch-injured arteries. © 2003 Elsevier B.V. All rights reserved.

513. Vascular protective effects of dihdydropyridine calcium antagonists.

- Adeagbo A., Bluet MP, Dancey C., and Hallé A. [S.O. Adeagbo, Dept. of Physiology and Biophysics, Health Sciences Center, University of Louisville, Louisville, KY 40292, United States] - EUR. J. PHARMACOL. 2003 481/1 (91-100) - sum in ENGL

Dihydrosyridine calcium antagonists play an important role in the treatment of hypertension and angina pectoris. They lower blood pressure by a well-characterized mechanism of blocking L-type calcium channels in smooth muscle cells. Additionally, there is growing evidence that dihydropyridines also modulate...
endothelial functions by other mechanisms, since macrovascular endothelial cells do not express L-type calcium channels. A number of studies have demonstrated that dihydroydropine calcium antagonists enhance bioavailability of endothelial nitric oxide (NO). Endothelium-derived NO plays a pivotal role in the regulation of vasorelaxation, leukocyte adhesion and platelet aggregation and an impaired NO release is associated with the genesis and progression of atherosclerotic diseases. This review summarizes results from experimental findings that dihydroydropine calcium antagonists increase endothelial NO formation as well as studies which demonstrate these effects in vivo both in animals and humans. Moreover, the influence of dihydroydropine calcium antagonists on the progression of atherosclerosis is discussed. These pleiotropic effects of dihydroydropine calcium antagonists may underlie or contribute to antiatherosclerotic effects of this substance class.

See also: 540, 560, 561, 703, 710, 730.

5.4. Hemopoietic and lymphoeryticular systems


One of the major causes of morbidity and mortality in the developed world is atherosclerosis. Recent research has suggested that the interaction of platelets with the endothelium is important in both the progression of atherosclerosis and the development of the acute complications of the disease. Both of these cells secrete various signalling molecules and express adhesion molecules, which can influence the development of pathological states. Certainly, there may be a vicious cycle in which platelet activation promotes atherosclerosis; a process involving inflammation and the activation of many other cell types (for example, leukocytes and smooth muscle cells), which causes further platelet activation. Therefore, intense effort has been made to develop therapeutic agents that can modulate the function of these cells, with the ultimate aim to retard (or even reverse) the progression of atheroma growth.

515. Thrombopoietin stimulates ex vivo expansion of mature neutrophils in the early stages of differentiation - Terada Y., Hato F., Sakamoto C. et al. [M. Hino, Clin. Hematol/Clinical Diagnostics, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, 545-8585 Osaka, Japan] - ANV. HEMATOL. 2003 82/11 (671-676) - summ in ENGL

We examined the effects of thrombopoietin (TPO) in combination with stem cell factor (SCF), interleukin-3 (IL-3), and granulocyte colony-stimulating factor (G-CSF) on the proliferation and differentiation of human neutrophils. Purified CD34+ hematopoietic progenitor cells were cultivated with SCF, IL-3, and G-CSF for 7 days (early phase), and thereafter nonadherent cells were further cultivated for 9 days with G-CSF alone (late phase). A large number of highly selected neutrophils (>95%) was obtained on day 16. We compared the expansion capacity in the presence or absence of TPO in each culture phase. The significantly larger number of neutrophils was obtained in the presence of TPO in the early culture phase. The number of expanded cells plateaued at day 16. Ultimately, a 550-fold increase in the number of neutrophils was achieved. These neutrophils gained the ability to respond effectively with chemotaxis and superoxide release, and were appropriately primed by G-CSF, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-α, and IL-β for enhanced release of O2. The responsiveness of these cells was identical to that of peripheral blood neutrophils. However, TPO did not accelerate the maturation of neutrophils supported by G-CSF in the late phase of culture. Furthermore, priming effects and triggering effects of TPO on the production of superoxide metabolites from peripheral blood neutrophils were not observed. These results suggest that TPO regulates the proliferation and differentiation of neutrophils in the early stages, but not the late stages, of differentiation.

See also: 545, 546, 547, 556, 618, 619, 623, 631, 635, 643, 644, 727.

5.5. Respiratory system


Aim: To assess the bronchodilatory effect of loradatine in children with mild-to-moderate asthma and to determine whether loradatine interacts with terbutaline. Methods: The effect on pulmonary functions of a 10 mg oral dose of loradatine, with and without inhaled terbutaline powder (0.5 mg), was determined in 13 patients with a mean (SE) age of 10.63 (0.77) years (range from eight to 17 years) at 11 time points during 8 h in a randomized, double-blind, placebo controlled, crossover study. Forced expiratory volume in 1 s (FEV1) was the primary measure of efficacy. Results: Although loradatine alone produced an increase in FEV1 relative to base-line, this was not statistically significant (p > 0.05). Terbutaline with, and without loradatine, significantly increased FEV1 from 1 to 5 h according to baseline (p < 0.004) when compared with the placebo, loradatine significantly increased FEV1 from 150 min to 8 h (p < 0.05). Also, terbutaline alone, or in combination with loradatine, significantly increased FEV1 from 30 min to 7h (p < 0.004, from 30 min to 5 h (p < 0.05). Although the mean increase in FEV1 with terbutaline + loradatine in combination, was greater than with terbutaline alone, the difference was not significant (p > 0.05). Conclusion: Loradatine has a mild bronchodilatory effect in the study period and does not interfere with the bronchodilatory effect of terbutaline in childhood asthma.


Despite concerns in the 1970s and 1980s about the safety of short-acting β2-agonists, it is now generally accepted that these agents, used at appropriate doses, provide safe and effective treatment for asthma symptoms. However, the effects of long-duration action - formoterol and salmeterol - became widely used as maintenance therapy with inhaled corticosteroids (ICS). Both β2-agonists are well tolerated in long-term studies, with no reduction in lung function. However, overuse, indicated by a lack of clinically relevant tolerance development in patients with asthma and COPD. High-dose studies have indicated that formoterol produces systemic effects of similar duration to, but less pronounced than, salbutamol. This suggests that formoterol produces long-lasting bronchodilatation against exercise-induced bronchoconstriction, even in patients receiving regular maintenance therapy; its fast onset of effect (similar to salbutamol) allows formoterol to be used as a rescue agent. Clinically the safety of formoterol and salmeterol has been demonstrated in several studies, both with ICS and alone.

518. Insulin induces a hypercontractile airway smooth muscle phenotype - Gosens R., Nelems S.A., Hiemstra M. et al. [R. Gosens, Department of Molecular Pharmacology, University Centre for Pharmacy, A. Deusingslaan 1, 9713 AV Groningen, Netherlands] - EUR. J. PHARMACOL. 2003 481/1 (125-131) - summ in ENGL

This study aims to investigate the effects of insulin on bovine tracheal smooth muscle phenotype in vitro. Contractility of muscle strips and DNA-synthesis ([1H]thymidine incorporation) of isolated cells were determined as parameters for smooth muscle phenotype. Insulin (1 µM) was mitogenic for bovine tracheal smooth muscle and potentiated DNA-synthesis induced by other growth factors. In contrast, after pretreatment of unpassaged bovine tracheal smooth muscle cells in culture, the mitogenic response induced by growth factors was strongly diminished, with no difference in the basal incorporation. Pretreatment of bovine tracheal smooth muscle strips in organ culture with insulin increased maximal contraction to methacholine and KCl. These results show that insulin acutely augments DNA-synthesis in the presence of other growth factors. In contrast,
insulin pretreatment induces a hypercontractile phenotype with a decreased mitogenic capacity. This mechanism may be involved in the putative negative association between asthma and type I diabetes. In addition, these findings may have implications for the use of aerosolized insulin in diabetes mellitus. © 2003 Elsevier B.V. All rights reserved.

See also: 559, 669.

5.6. Digestive system

519. Contribution of capsaicin-sensitive afferent nerves to rapid recovery from ethanol-induced gastric epithelial damage in rats - Sobue M., Joh T., Oshima T. et al. [Dr. T. Joh, First Dept. of Internal Medicine, Nagoya City Univ. Medical School, 1 Ka- wasumi, Mizhuo-cho, Mizuho-ku, Nagoya 467-8601, Japan] - J. GASTROENTEROL. HEPATOL. 2003 18/10 (1188-1195) - sum in ENGL

Background and Aim: It is well known that capsaicin-sensitive nerve signaling acts as a protective factor against various pathogens. However, the contribution of topical capsaicin-sensitive nerves within the stomach to rapid restitution has not been fully inves- tigated. The present study was therefore conducted focusing on recovery from gastric mucosal damage induced by ethanol in vivo. Methods: Male Sprague-Dawley rats were fasted and anesthetized. Capsaicin (80 μM), a capsaicin-sensitive cation antagonist, was given before the ethanol-capsaicin perfusion. Furthermore, this study was verified using lafutidine, a histamine H2-receptor antagonist, which has a low efficacy on the mucosal damage was exacerbated but recovery was nevertheless more rapid than the control group. With a lower dose of capsaicin (80 μM), mucosal damage was not exacerbated and recovery was enhanced. White capsaicin or lafutidine was administered after the induction of ethanol injury no change was detected regarding the damage. However, recovery was significantly accelerated. Ruthenium red reversed the action of post-treatment with capsaicin on restitution. Conclusions: These results indicate that luminal ad- ministration of capsaicin exerts protection against and accelerates restitution from gastric damage in the early phase after ethanol injury. This action is probably due to activation of topical capsaicin-sensitive afferent nerves. Results: When capsaicin was administered before ethanol treatment, mucosal damage was significantly reduced and recovery was significantly rapid compared to the control. When capsaicin (160 μM) and ethanol were administered simultaneously, the mucosal damage was exacerbated but recovery was nevertheless more rapid than the control group. With a lower dose of capsaicin (80 μM), mucosal damage was not exacerbated and recovery was enhanced. White capsaicin or lafutidine was administered after the induction of ethanol injury no change was detected regarding the damage. However, recovery was significantly accelerated. Ruthenium red reversed the action of post-treatment with capsaicin on restitution. Conclusions: These results indicate that luminal ad- ministration of capsaicin exerts protection against and accelerates restitution from gastric damage in the early phase after ethanol injury. This action is probably due to activation of topical capsaicin-sensitive afferent nerves in the rat. © 2003 Blackwell Publishing Asia Pty Ltd.

520. Long-term administration of Salvia miltiorrhiza amelio- rates carbon tetrachloride-induced hepatic fibrosis in rats - Lee T.-Y., Yang G.-J., Chiu J.-H. and Lin H.-C. [H.-C. Lin, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei 11217, Taiwan] - J. PHARM. PHARMACOL. 2003 55/11 (1561-1568) - sum in ENGL

Carbon tetrachloride (CCl4) is metabolized by cytochrome P450 to form a reactive trichloromethyl radical that triggers a chain of lipid peroxidation. These changes lead to cell injury, and chronic liver injury leads to excessive deposition of collagen in liver, result- ing in liver fibrosis. The aim of this study was to evaluate the effects of long-term Salvia miltiorrhiza administration in CCl4- induced hepatic injury in rats. Salvia miltiorrhiza (10, 25 or 50 mg kg⁻¹ twice a day) was given for 9 weeks, beginning at the same time as the injections of CCl4. Rats receiving CCl4 alone showed a decreased hepatic glutathione level and an increased glutathione- S-transferase content. The hepatic thiobarbituric acid-reactive substance levels were increased. CCl4 also caused a prominent collagen deposition in liver histology that was further supported by the increased hepatic mRNA expression of transforming growth factor-β1, tissue inhibitor of metalloproteinase-1 and procollagen I. Salvia miltiorrhiza administration led to a dose-dependent increase in hepatic glutathione levels and a decrease in peroxidation prod- ucts. Additionally, it reduced the mRNA expression of markers for hepatic fibrogenesis. In conclusion, long-term administration of Salvia miltiorrhiza in rats ameliorated the CCl4-induced hepatic injury that probably related to a reduced oxidant stress and degree of hepatic fibrosis.


Purpose. To investigate the inhibitory activity of casein on proteases in detail, the effect of digested products of casein itself on trypsin and chymotrypsin in rat small intestine was examined. Methods. Male Sprague-Dawley rats weighing 200-300 g were used as the animal model. The luminal content of the jejunum was prepared, and the enzymatic activities of trypsin and chymotrypsin were determined using a specific substrate for each protease. Therefore, the effect of enzymatic digested products of casein on the proteases was examined. Results. The inhibitory activity of trypsin-digested casein against trypsin decreased as its digestion proceeded, but its inhibitory activity against chymotrypsin can be more effective. On the other hand, the inhibitory activity of chymotrypsin-digested casein against chymotrypsin decreased with the degree of diges- tion, but no change in the inhibitory activity against trypsin was observed. Even the completely digested products of casein with trypsin or chymotrypsin showed inhibitory activities against the two proteases. Conclusions. It was suggested that not only the intact casein but also the products digested with trypsin or chymotrypsin contribute to the inhibitory effect of casein on the proteases in the intestinal lumen.

See also: 549, 550, 555, 558, 570, 571, 578, 591, 597, 600, 603, 616, 648, 653, 709, 734, 739, 746.

5.7. Urinary system


Objective. Therapy of elevated cholesterol serum concentrations is often necessary in patients with kidney transplant. However, the pharmacokinetics of HMG-CoA reductase inhibitors when admin- istered in combination with sirolimus and cyclosporin A (CsA) have not been determined. The aim of this study was to investigate the pharmacokinetics of cerivastatin when administered in combination with sirolimus in patients with kidney transplants, and to review the literature with regard to the differences in pharmacological behav- ior between sirolimus, CsA and tacrolimus. Methods. Patients (n = 7) with a stable and functioning kidney transplant and elevated LDL cholesterol serum concentrations were included in the study. After an observation period of 3 months, and whilst receiving sirolimus and CsA, cerivastatin (0.2 mg daily) was administered for a period of 3 months. Pharmacokinetic parameters were calculated on Day 1 and 3 months after initiation of cerivastatin therapy. Routine laboratory parameters and clinical adverse events were monitored throughout the study period. Results: Single-dose cerivastatin AUC was 2 to 3-fold higher in comparison to published values obtained in healthy subjects. The accumulation ratio of cerivastatin (after 3 months/Day 1) was 1.6. Sirolimus and CsA trough levels, and the sirolimus AUC did not differ after single dose and multiple doses of cerivastatin. Conclusions: The combination therapy of cerivastatin with sirolimus and CsA leads to a significant increase in cerivastatin exposure. Additional drug monitoring of sirolimus and CsA is not necessary.

Dutasteride is a new 5-alpha reductase inhibitor for the treatment of men with moderate to severe lower urinary tract symptoms secondary to benign prostate hyperplasia. It has been available in the UK since March 2003. It is a competitive inhibitor of both type I and type II isozymes of the 5-alpha reductase enzyme that converts testosterone to the more potent androgen, dihydrotestosterone. Randomized controlled studies have shown dutasteride to be statistically more effective than placebo in reducing lower urinary tract symptoms and increasing maximum urinary flow rates. This is a consequence of a reduction in serum dihydrotestosterone and hence dependent prostate volume. Dutasteride has also shown to decrease the absolute risk of urinary retention and the need for prostate-related surgery when compared to placebo taken over a 24-month period. In this review article we discuss the pharmacology and clinical effects of dutasteride, a new dual-acting 5-alpha reductase inhibitor.

524. Renal epithelial gene expression profile and bismuth-induced resistance against cisplatin nephrotoxicity - Leussink H.T., Baatik J.J., Broekhuizen-van den Berg T.M. et al. [G.B. van der Vouet, Toxicology Laboratory, Leiden University Medical Center, PO Box 9608, 2300 RC Leiden, Netherlands] - HUM. EXP. TOXICOL. 2003 22/10 (535-540) - sum in ENGL.

Nephrotoxicity is the most important dose-limiting factor in cisplatin-based anti-neoplastic treatment. Pretreatment with bismuth salts, used as pharmaceuticals to treat gastric disorders, has been demonstrated to reduce cisplatin-induced renal cell death in clinical settings and during in vivo and in vitro animal experiments. To investigate the genomic basis of this renoprotective effect, we exposed NRK-52E cells, a cell line of rat proximal tubular epithelial origin, to 33 μM Bi^{3+} for 12 hours, which made them resistant to cisplatin-induced apoptosis. Differentially expressed genes in treated and untreated NRK-52E cells were detected by subtraction PCR and microarray techniques. Genes found to be down regulated (0.17-0.31-times) were cytochrome c oxidase subunit I, BAR (an apoptosis regulator), heat-shock protein 70-like protein, and three proteins belonging to the translation machinery (ribosomal proteins S7 and L17, and S1, a member of the elongation factor 1-alpha family). The only up-regulated gene was glutathione S-transferase 2-transferase subunit 3A (1.89-times). Guided by the expression levels of these genes, it may be possible to improve renoprotective treatments during anti-neoplastic therapies.

525. Pharmacological effects of darifenacin on human isolated urinary bladder - Miyazaki K., Yoshida M., Murakami S. et al. [M. Yoshida, Department of Urology, Kumamoto University, School of Medicine, 1-1-1 Honjo, Kumamoto 860-8556, Japan] - PHARMACOLOGY 2003 69/4 (205-211) - sum in ENGL.

Darifenacin [1-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-3-pyrrolodinyl]-2,2-diphenylethlamide] is a novel antimuscarinic drug currently undergoing phase III trials for the treatment of overactive bladder. We investigated the functional antagonist potency of darifenacin, and the antimuscarinic drugs propiverine, oxybutynin and atropine, on human detrusor smooth muscle. Urinary bladder specimens were obtained from 20 patients who underwent total cystectomy for malignant bladder tumor. Using an organ-bath technique, the effects of the compounds on carbachol, KCl, CaCl2 or electrical field stimulation (EFS)-induced contractions of the tissues were evaluated. The order of antagonist potency (pA2 values) at the muscarinic M3 receptors was: darifenacin (9.34)> atropine (9.26)> oxybutynin (7.74)> propiverine (7.68). Darifenacin and atropine, at concentrations up to 10^{-6} mol/l, did not inhibit the KCl- and CaCl2-induced contractions (concentrations 80 and 5 mmol/l, respectively), while propiverine and oxybutynin (10^{-5} mol/l) significantly inhibited these contractions. Pretreatment with darifenacin (10^{-9}-10^{-6} mol/l), propiverine (10^{-6}-10^{-5} mol/l), oxybutynin (10^{-5}-10^{-4} mol/l) and atropine (10^{-4}-10^{-3} mol/l) significantly inhibited maximum EFS-induced contractions. Darifenacin inhibited contractions of human detrusor smooth muscle only through its anti-muscarinic action, while propiverine and oxybutynin had both antimuscarinic and Ca^{2+} channel antagonist actions. These findings indicate that darifenacin is a potent (antagonist at the M3 receptor and support its use as a treatment for overactive bladder. Copyright © 2003 S. Karger AG, Basel.

See also: 724.

5.8. Reproductive system

526. Effect of cyproterone acetate on alpha1-adrenoceptor subtypes in rat vas deferens - Campos M., Morais P.L. and Pupo A.S. [A.S. Pupo, Departamento de Farmacologia, Instituto de Biocibernética, UNESP, 18618-000 Botucatu, SP, Brazil; M.E. Beksinska, Reproductive Health Research Unit, Dept. of Obstetrics and Gynaecology, University of the Witwatersrand, 143 Salmon

527. Hyperhomocysteinemia may be a resistance factor in tocolytic treatment with β mimetics - Celik H., Ayar A. and Tug N. [Dr. H. Celik, Dept. of Obstetrics and Gynecology, School of Medicine, Frat University, Elazig TR 23119, Turkey] - MED. HYPOTHESES 2003 65/5-6 (580-582) - sum in ENGL.

Homocysteine may be an intermediate amino acid in the methionine metabolism which does not take place in the structure of proteins. Plasma homocysteine levels can be elevated by a variety of genetic and nutritional factors. Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases and common obstetric problems. Mildly elevated levels of homocysteine have been implicated in a number of disease processes such as atherosclerotic vascular disease and adverse obstetrical outcome. It was shown that the presence of high homocysteine concentrations in the in vitro system had an activating role in myometrial contractions. It is hypothesized that hyperhomocysteinemia in pregnancy is associated with labor in consequence of myometrial contractions. Hyperhomocysteineemia, therefore, could be a treatable cause of this important public health and obstetric concern. © 2003 Elsevier Ltd. All rights reserved.

528. Detection of raised FSH levels among older women using dopemodroxpropogesterone acetate and norethisterone enant - Beksininska M.E., Smitt J.A., Kleinschmidt I. et al. [M.E. Beksiniska, Reproductive Health Research Unit, Dept. of Obstetrics and Gynaecology, University of the Witwatersrand, 143 Salon
The objective of this study was to investigate whether follicle-stimulating hormone (FSH) levels can be used reliably to indicate approaching menopause in older (aged 40–49), long-term users of depomedroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). One-hundred and seventeen women using DMPA, 60 NET-EN users and 161 nonusers of contraception were recruited. At recruitment, serum FSH levels were measured and questions were asked regarding menopausal symptoms, menstrual cycle and date of last injection. Results of the recruitment blood test showed that 32% of the nonusers had FSH levels in the menopausal range (12.8 mIU/mL) compared to 28% of the DMPA users and 9% of the NET-EN group. After adjusting for age, there was no significant difference between the 3 groups (p = 0.13). An increase of 1 year in age increased the FSH level by 3 mIU/mL (p < 0.001). All the hormonal contraceptive users were between 1 day and 12 weeks of their injection interval. Many had been using the injectable contraceptive method for over 10 years and almost all were amenorrheic at the time of recruitment. The data show that a raised FSH level can be detected during use of DMPA and NET-EN and could be used as a menopausal indicator without interrupting method use in this group of contraceptive users. © 2003 Elsevier Inc. All rights reserved.

See also: 541, 542, 543, 544, 564, 613.

5.9. Endocrine system

529. Neuropeptide Y and energy homeostasis: Insights from Y receptor knockout models - Herzog H, H. Herzog, Neurobiology Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia - EUR. J. PHARMACOL. 2003 480/1-3 (21-29) - sumam in ENGL

The complex system has evolved to regulate food intake and to maintain energy homeostasis. A series of short-term hormonal and neural signals that derive from the gastrointestinal tract, such as ghrelin initiate meals, and insulin and leptin, together with circulating nutrients, indicate long-term energy stores. All these signals act on central nervous system sites which converge on the hypothalamus, an area that contains a large number of peptide and other neurotransmitters that influence food intake with neuropeptide Y (NPY) being one of the most prominent ones. Five Y receptors are known which mediate the action of neuropeptide Y and its two other family members, peptide YY and pancreatic polypeptide. Elevated neuropeptide Y expression in the hypothalamus leads to the development of obesity and its related phenotypes. Type II diabetes and cardiovascular disease. The wide availability of specific pharmacological tools and the considerable number of Y receptors have made it difficult to delineate their individual contributions to the regulation of energy homeostasis. However, recent studies analysing transgenic and knockout neuropeptide Y and Y receptor mouse models have started to unravel some of the individual functions of these Y receptors potentially also helping to develop novel therapeutics for a variety of physiological disorders including obesity. © 2003 Elsevier B.V. All rights reserved.


The Siberian hamster, Phodopus sungorus, is a powerful model of physiological body weight regulation. This seasonal model offers the potential to distinguish between the compensatory neuroendocrine systems that defend body weight against imposed negative energy balance, and those that are involved in the programming of the level of body weight that will be defended - a seasonally appropriate body weight. Of the known, studied, components of the hypothalamic energy balance system, the anorexigenic peptide, cocaine- and amphetamine-regulated transcript (CART), is the only candidate where gene expression changes in a manner consistent with a role in initiating or sustaining photoperiod-induced differences in body weight trajectory. Siberian hamsters effect a reversible biannual switch in leptin sensitivity in which only short day (SD)-acclimated hamsters that have undergone a reduction in body weight, adiposity and plasma leptin are sensitive to peripheral exogenous leptin. The suppressor of cytokine signalling protein, SOCS3, appears to be the molecular correlate of this seasonal sensitivity. © 2003 Elsevier B.V. All rights reserved.

531. Reduced dopaminergic tone in hypothalamic neural circuits: Expression of a "thirsty" genotype underlying the metabolic syndrome? - Pijl H, H. Pijl, Department of Internal Medicine, Leiden University Medical Center, C1-R39, PO Box 9600, 2300 RC Leiden, Netherlands - EUR. J. PHARMACOL. 2003 480/1-3 (125-131) - sumam in ENGL

The "thirsty" genotype hypothesis postulates that the genetically determined ability to grow obese and insulin resistant in times of food abundance confers a survival advantage in times of famine. Obviously, this ability poses a major health threat in modern times, where food is always available in large quantities. In the last 10-15 years, many genes encoding pathways that orchestrate energy balance and fuel flux have been discovered. This paper summarizes the evidence that diminished dopaminergic tone in the hypothalamic nuclei contributes to the "thirsty" genotype/phenotype. Reduced dopaminergic neurotransmission in the suprachiasmatic nucleus of seasonally obese animals appears to drive noradrenaline and NPY mediated transmissions in other nuclei to induce the obesity syndrome at the appropriate time of year. Treatment with dopamine D2 receptor agonists can fully reverse the metabolic syndrome in these animals. Similar mechanisms are operative in non-seasonal obese animal models. In man, treatment with dopamine D2 receptor antagonists induces obesity and type 2 diabetes mellitus, whereas dopamine D2 receptor activation ameliorates the metabolic profile in obese nondiabetic and diabetic humans. Various loss of function mutations of the dopamine D2 receptor gene are associated with overweight in humans. In concert, the data support the notion that diminution of dopaminergic (dopamine D2 receptor mediated) transmission in relevant hypothalamic nuclei sets the stage for efficient partitioning of ingested nutrients to contribute to a phenotype that is not so thirsty anymore. © 2003 Elsevier B.V. All rights reserved.


Previously, we reported on the synthesis and estrogen receptor (ER) interaction of imidazoles, which had to be 1-alkyl-4,5-bis(2-halo-4-hydroxyphenyl) substituted for a high relative binding affinity (RBA > 1 %). This led to the assumption that a shielding of the polar heterocyclic system is a prerequisite for ER binding. In continuation of this study we synthesized 2,4,5-tris(4-hydroxyphenyl)imidazoles with Cl- or F-atoms in the ortho-positions of the aromatic rings and evaluated whether they mediate sufficient hydrophobicity for ER interaction. 2-(2,6-Dichloro-3/4-hydroxyphenyl)-4,5-bis(2-halo-4-hydroxyphenyl)imidazoles were synthesized by reaction of the respective methoxy-substituted benzil with either the 2,6-dichloro-4-methoxy- or the 2,6-dichloro-3-methoxybenzaldehyde in ammonium acetate solution. The required ether cleavage was performed subsequently with BBr3. In the competition experiment with [H]estradiol the imidazoles with the a-c2-standing (2,6-dichloro-4-hydroxyphenyl) ring showed an RBA > 0.02 %, but did not activate the luciferase gene in estrogen receptor positive MCF-7-2a breast cancer cells, stably transfected with the plasmid EREluc. In the test for antagonistic potency only the 2-(2,6-dichloro-4-hydroxyphenyl)-4,5-bis(4-hydroxyphenyl)imidazoles 3 antagonized the effects of 1 nM estradiol slightly. From these data, it can be concluded that a c2-standing 2,6-dichloro-4-hydroxyphenyl ring is not appropriate to optimize the ER interaction of 4,5-(4-hydroxyphenyl)imidazoles.

533. Neuroendocrinology of insulin resistance: Metabolic and endocrine aspects of adiposity - Van Dijk G, De Vries K, Ben-
Abdominal obesity is a major risk factor to affect the insulin resistance syndrome. It is proposed that abdominal obesity exposes the liver to elevated levels of free fatty acids, which activate a neuroendocrine reflex, leading to increased circulating levels of glucocorticoids. Besides directly attenuating peripheral insulin signaling, glucocorticoids oppose the activity of central nervous regulatory systems that stimulate insulin action. Among the factors that promote insulin action is leptin. Leptin regulates peripheral fuel partitioning and insulin action mainly through hypothalamic neuronal networks, which in turn, regulate endocrine activity of adipose tissue in a way comparable to thiazolidinediones. These are a class of insulin-sensitizing drugs, which exert their antidiabetic effects through the gamma isoform of peroxisome proliferator-activated receptor (PPAR-γ). Since glucocorticoids oppose leptin action at several levels of control (including the central nervous system, CNS), it is argued that subjects easily develop obesity and associated metabolic disorders. © 2003 Elsevier B.V. All rights reserved.


Nefazodone is a potent and selective inhibitor of cytochrome P450 3A4 (CYP3A4), an enzyme pathway responsible for the biotransformation of a number of steroid compounds. The potential therefore exists that nefazodone inhibits the disposition of methylprednisolone. In this open label, repeated measures study, the effect of 9 days of nefazodone administration on the pharmacokinetic disposition of a single 0.6 mg/kg intravenous dose of methylprednisolone was assessed. Additionally the effect of concomitant nefazodone use on the methylprednisolone concentration-time curve was significant (p<0.02). The duration of cortisol suppression after methylprednisolone administration was longer (≥ 32 vs. 3.32 ± 3.43 hours) during nefazodone administration.


Autoimmune β-cell destruction occurs directly by cell-mediated cytotoxicity or indirectly by cytokines released from infiltrating lymphocytes. Cytokines (IL-1, IFN-γ) modify or induce expression of MHC antigens and ICAM-1 on β-cells which can lead to an improved binding of T-lymphocytes to β-cells and finally to an enhanced cell-mediated cytotoxicity. Cytokines also induce Fas-expression and inducible nitric oxide synthase (iNOS) causing generation of nitric oxide (NO) which is toxic for β-cells. The iNOS inhibitor aminoguanidine (AG) delays diabetes onset, but does not reduce diabetes incidence. We wanted to know whether AG inhibits cytokine-induced expression of Fas, MHC antigens and ICAM-1 on β-cells of LEW.1W and BB/O rats islets after culture with IL-1, IFN-γ, NO was completely inhibited by 5.0mmol/L AG (P<0.005), apparent clearance was lower (28.7 ± 7.2 vs. 14.6 ± 7.8 L/h·P<0.02) and the terminal elimination half-life was longer (2.28 ± 0.49 vs. 3.32 ± 0.95 hours; P<0.02). The duration of cortisol suppression after methylprednisolone administration was longer (≥ 32 vs. 23.3 ± 3.43 hours) during nefazodone administration.

536. Thyroid over-expression of type 1 and type 2 deiodinase may account for the syndrome of low thyroid and increasing triiodothyronine during propylthiouracil treatment - Weetman A.P., Shepherdley C.A., Mansell P. et al. [A.P. Weetman, The University of Sheffield, Division of Clinical Sciences, Northern General Hospital, Sheffield S5 7AU, United Kingdom] - EUR. J. ENDOCRINOL. 2003 149/5 (443-447) - sum in ENGL

Although propylthiouracil inhibits type 1 deiodinase, leading to a more rapid fall in triiodothyronine (T3) than thyroxine (T4)-levels in patients treated for hyperthyroidism, we report a patient with Graves’ disease whose free T3 paradoxically rose during such treatment, despite low free T4 levels and increasing doses of propylthiouracil. A similar response has previously been associated with high levels of thyroid stimulating antibodies, but it has been unclear why there should be a dichotomy in the circulating thyroid hormone profile. Thyroid tissue from our patient contained very high type 1, and, especially, type 2 deiodinase, in contrast to other patients treated with Graves’ disease, which were most likely secondary to high levels of thyroid stimulating antibodies. This unusual response to propylthiouracil is important to recognise therapeutically and represents a further situation in which abnormal expression of deiodinase enzymes has clinical significance.

See also: 554, 560, 566, 568, 569, 740.

6. PHARMACOLOGICAL AGENTS

538. Usefulness of microspheres composed of gelatin with various cross-linking density - Iwanaga K., Yabuta T., Kakemi M. et al. [K. Iwanaga, Department of Pharmaceutical Sciences, Osaka Univ. Pharmaceutical Sci., 4-20-1 Nachara, Takatsuki-city, Osaka 569-1094, Japan] - J. MICROENCAPSULATION 2003 20/6 (767-776) - sum in ENGL

The release rate of insulin, as a model peptide, from gelatin microspheres (GM) prepared with gelatin having various cross-linking densities in vitro was examined. The release of insulin from GM showed the burst effect, followed by a slow release phase regardless of the cross-linking density of gelatin. The total amount of insulin released in 2 weeks decreased with increasing cross-linking density of gelatin. The release rate of insulin within 6 h was well correlated with the cross-linking density of gelatin. The remaining amounts of both insulin and GM after injection of insulin incorporated in GM to mice femoral muscle tissue were also examined in vivo. Both insulin and GM rapidly disappeared from the injection site.

Biologically adhesive delivery systems offer important advantages over conventional drug-delivery systems. In this paper, microspheres intended as a sustained release carrier for oral or nasal administration have been prepared by associating a known bioadhesive polymer, poly(acrylic acid), in gelatin microspheres. A model drug oxprenolol hydrochloride was chosen. It was found that some of the formulation variables can influence the characteristics of the beads in a controlled manner. The microstructure of the microspheres studied by X-ray diffraction, thermal analysis and optical microscopy showed the absence of drug crystals in microspheres and a lowering in the glass transition temperature. The dynamic swelling of the beads obeyed the square root of time and a shift from the diffusional to the relaxational process dependent on the content of poly(acrylic acid) in gelatin microspheres was observed. As expected, drug release from gelatin/poly(acrylic acid) microspheres was influenced by the poly(acrylic acid) content in beads, by the particle size of microspheres and by the pH of the medium. The mechanism of release was analysed by applying the empirical exponential equation and by calculation of the approximate contribution of the diffusional and relaxational mechanisms to the anomalous release process by fitting the data to the coupled Fickian/Case II equation. In vitro and in vivo experiments in rats showed good adhesive characteristics of the gelatin/poly(acrylic acid) microspheres, which were greater if the poly(acrylic acid) content was greater. A significant retardation in gastric and intestinal emptying time of the beads was observed. This was also suggested by the bioavailability of the model drug after intragastric and intranasal administration of the microspheres. The pharmacokinetic parameters after microsphere administration were more appropriate to a slow release drug-delivery system. The work suggests the potential of this pharmaceutical delivery system as an alternative controlled-release dosage form, either for oral or nasal administration.

540. Use of bisoprolol in heart failure. The BISOCOR observa-
tional study (Spain) - EMPLEO DE BISOPROLOL EN LA INSUFICIENCIA CARDIÁCA. RESULTADOS DEL ESTUDIO BISOCOR - González-Juanteay J.R., Alegria Ezquerra E., García Saavedra V. et al. [Prof. J.R. González-Juanteay, Servicio de Cardiología, Hospital Clínico Universitario, Avda. Chuopana s/n, 15706 Vidian Š. Compostela A Coruna, Spain] - REV. ESP. CARDIOL 2003 56/9 (873-879) - sum in SPAN, ENGL

Introduction and objectives. The benefits of beta blockers in heart failure are highly dependent on dosage. This study aimed to analyze the degree of concordance between targeted (CHIBS II) and achieved doses of bisoprolol in a group of patients with stable heart failure on conventional treatment. We also evaluated functional parameters, adverse effects and the reasons for withdrawal or drop-out. Patients and method. The study group consisted of 334 patients with heart failure who entered the individual dose (study) group (n = 131) or the standard dose (control) group (n = 131). Results: In the study group, 101 patients (77.1%) had an appropriate response (defined as ≤ 14 oocytes), compared with 86 (65.6%) in the control group (P = 0.05). Fewer than five oocytes were retrieved in two patients (1.5%) in the study group, compared with 14 patients (10.7%) in the control group (P < 0.05). By comparison, > 14 oocytes were retrieved from 27 patients (20.6%) in the study group and from 26 (19.8%) control patients (P = NS). Eighty-six per cent of the individual dose patients did not require any dose adjustment on day 8, compared with 45% of the standard dose patients (P < 0.01). The ongoing pregnancy rate per initiated cycle was 36.6% in the study group and 24.4% in the control group (P < 0.01). One patient (0.8%) in the study group, and four patients (3.1%) in the control group, were hospitalized due to ovarian hyperstimulation syndrome. Conclusions: An individual dose regimen in a well-defined 'standard' patient population increased the proportion of appropriate ovarian responses and decreased the need for dose adjustments during controlled ovarian stimulation. A higher ongoing pregnancy rate was observed in the individual dose group.

541. A prospective randomized clinical trial comparing an in-
dividual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients un-
deringoing IVF/ICSI treatment - Popovic-Todorovic B., Loft A., Egdrup Bredikjær H. et al. [B. Popovic-Todorovic, Fertility Clinic 4071, Rigshospitalet, Copenhagen University Hospital, Blegdam-
svæg 5, 2100 Copenhagen, Denmark] - HUM. REPROD. 2003 18/11 (2275-2282) - sum in ENGL

Background: The study aim was to compare the use of individu-
al rFSH doses between 100 and 250 IU/day (calculated using the rFSH dose normogram) with a standard dose of rFSH of 150 IU/day. Methods: This prospective randomized dual-centre clinical trial included 267 first IVF/ICSI cycles using the long agonist protocol in 'standard' patients. Following down-regulation, patients were randomized using computer-generated lists using 'clusters of 10' into the individual dose (study) group (n = 131) or the standard dose (control) group (n = 131). Results: In the study group, 101 patients (77.1%) had an appropriate response (defined as ≤ 14 oocytes), compared with 86 (65.6%) in the control group (P = 0.05). Fewer than five oocytes were retrieved in two patients (1.5%) in the study group, compared with 14 patients (10.7%) in the control group (P < 0.05). By comparison, > 14 oocytes were retrieved from 27 patients (20.6%) in the study group and from 26 (19.8%) control patients (P = NS). Eighty-six per cent of the individual dose patients did not require any dose adjustment on day 8, compared with 45% of the standard dose patients (P < 0.01). The ongoing pregnancy rate per initiated cycle was 36.6% in the study group and 24.4% in the control group (P < 0.01). One patient (0.8%) in the study group, and four patients (3.1%) in the control group, were hospitalized due to ovar-
ian hyperstimulation syndrome. Conclusions: An individual dose regimen in a well-defined 'standard' patient population increased the proportion of appropriate ovarian responses and decreased the need for dose adjustments during controlled ovarian stimulation. A higher ongoing pregnancy rate was observed in the individual dose group.

542. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation - Tang O.S., Chan C.C.W., Ng E.H.Y. et al. [O.S. Tang, Dept. of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong SAR, Hong Kong] - HUM. REPROD. 2003 18/11 (2315-2318) - sum in ENGL

Background: A combination of mifepristone and misoprostol provides an effective method of medical abortion for early preg-
nancy. This is the first randomized trial comparing the use of sublingual misoprostol with vaginal misoprostol in combination with mifepristone for termination of early pregnancies up to 63 days. Methods: A total of 224 women who requested legal termination of pregnancy up to 63 days were randomized by computer-generated list into two groups and given 200 mg of oral mifepristone followed 48 h later by either 800 µg of sublingual (n = 112) or vaginal (n = 112) misoprostol. Results: Complete abortion occurred in 98.2% (95% CI: 93-99) of women in the sublingual group and 93.8% (95% CI: 88-97) in the vaginal group. There were three ongoing pregnancies in the vaginal group but none in the sublingual group. The median duration of vaginal bleeding was 17 days. There was no serious complication. Fever, chills and gastrointestinal side-
effects (nausea, vomiting and diarrhoea) were significantly more common in the sublingual group. Conclusions: The combination of mifepristone and misoprostol is effective for medical abortion up to 63 days. Both the sublingual and vaginal are effective routes of administration. Further randomized trials are required to find out the optimal dose of sublingual misoprostol that effect would give the highest complete abortion rate and lowest incidence of side-effects.

Background: Desmopressin, a synthetic analogue of the natural hormone vasopressin, stimulates endogenous haemostasis and exerts a powerful myometrial and vasconstrictor action in a variety of pharmacological preparations. Both mechanisms of action may have therapeutic value for the treatment of intrauterine device (IUD)-related menorrhagia, which is believed to be caused not only by altered local haemostasis but also according to a new hypothesis-by decreased vascular uterine resistance. The aim of this prospective study was to evaluate the effect of vasopressin drug on menstrual blood loss and on changes, if any, in uterine flow impedance. Mefenamic acid, which is commonly used to treat IUD-related menorrhagia, was administered as a comparison. Methods: Twenty-four women with IUD-induced menorrhagia were recruited and randomly allocated to treatment with either desmopressin or mefenamic acid. Menstrual blood loss (measured by pictorial blood loss assessment chart) and uterine artery resistance (measured with transvaginal colour Doppler) performed in two pretreatment periods were compared with 3-month treatment periods. Results: Menstrual blood loss was significantly reduced in both treatment groups. In the desmopressin group, the effect was clinically useful and lasted at least 1 year.

544. High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2) - Eijkemans M.J.C., Imani B., Mulders A.G.M.G.J. et al. [B.C.J.M. Fauser, Division of Reproductive Medicine, Dept. of Obstetrics and Gynaecology, Erasmus MC-Univ. Med. Ctr. Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands] - HUM. REPROD. 2003 18/11 (2357-2362) - sum in ENGL

Background: Medical induction of ovulation using clomiphene citrate (CC) as first line and exogenous gonadotrophin in second line forms the classical treatment algorithm in normogonadotrophic anovulatory infertility. Because the chances of success following classical ovulation induction are not well established, a shift in first-line therapy can be observed towards alternative treatment. The study aim was to: (i) reliably assess the probability of singleton live birth following classical induction of ovulation; and (ii) construct a prediction model, based on individual patient characteristics assessed upon standardized initial screening, to help identify patients with poor chances of success. Methods: A total of 240 consecutive women visiting a specialist academic fertility unit with a history of infertility, oligomenorrhoea or amenorrhoea, and normal FSH and estradiol serum concentration (WHO group 2) was prospectively followed. The women had not been previously treated with ovulation-inducing agents. All patients commenced with CC. Patients who did not ovulate within three treatment cycles of incremental daily doses up to 150 mg for 5 consecutive days or ovulatory CC patients who did not conceive within six cycles, subsequently underwent gonadotrophin induction of ovulation applying a step-down dose regimen. The main outcome measure was pregnancy resulting in singleton live birth. Cox regression was used to construct a multivariable prediction model. Results: Overall, there were 134 pregnancies ending in a singleton live birth (56% of women). The cumulative pregnancy rate after 12 and 24 months of follow-up was 50% and 71% respectively. Polycystic ovary syndrome (PCOS) patients (49%), clearly non-PCOS patients (13%) and the in-between group did not differ in prognosis (P = 0.9). The multivariable Cox regression model contained the woman’s age, the insulin:glucose ratio and duration of infertility. With a cut-off value of 30% for low chance, the model predicted probabilities at 12 months lower than this cut-off for 25 out of 240 patients (10.4%). Conclusions: Classical ovulation induction produces very good results in normogonadotrophic anovulatory infertility. Alternative treatment options may not be indicated as first-line therapy in these patients, except for subgroups with poor prognosis. These women can be identified by older age, longer duration of infertility and higher insulin:glucose ratio.

545. Pharmacokinetics and anticogulant properties of the factor VIIa-tissue factor inhibitor recombinant Nematode Anticoagulant Protein c2 following subcutaneous administration in man: Dependence on the stoichiometric binding to circulating factor X - Vlasuk G.P., Bradbury A., Lopez-Kinninger L. et al. [Dr. G.P. Vlasuk, Corvas International, Inc., 3030 Science Park Road, San Diego, CA 92121, United States] - THROMB. HAEMOST. 2003 90/5 (803-812) - sum in ENGL

Recombinant Nematode Anticoagulant Protein c2 (rNAPc2) is a potent (K_i=10 pM), inhibitor of the tissue factor (TFI-VIIa/TF) complex that requires the prerequisite binding to zymogen or activated factor X (IX). In two double blind, placebo-controlled, sequential dose-escalation phase I studies, rNAPc2 was found to be safe and well tolerated following single and repeat subcutaneous administrations in healthy human male volunteers at doses ranging from 0.3 to 5 µg/kg. There was a dose-dependent elevation of the prothrombin time reaching almost 4-fold above the baseline value in the highest dose group that directly correlated with rNAPc2 plasma concentrations. Plasma half-life of rNAPc2 was 1.5-2 hours.


N-Acetyl L-cysteine (NAC) is widely used to treat obstructive bronchopulmonary diseases. It has thiol reactive properties, accounting for its mucolytic property. Clopidogrel is a potent antithrombotic compound, metabolised by the liver which generates an active metabolite. The aim of the present study was to determine if NAC interferes with the antiaggregating activity of clopidogrel. For this purpose, NAC (100 µM) was incubated with platelets from rats treated or not with clopidogrel (5 mg/kg, PO, -2 h). Clopidogrel treatment strongly inhibited aggregation but this effect was not modified by NAC. In another experiment, a low concentration of the active metabolite of clopidogrel (0.3 ± 0.1 µg/ml) was incubated with platelets from men or rats, in the absence or presence of NAC (100 µM). When stimulated by ADP (2.5 µM), platelet aggregation was inhibited by the active metabolite when incubated alone. In the presence of NAC, the inhibition by the active metabolite was not modified, therefore clearly indicating that NAC cannot reduce the thiol reactive part of the active metabolite of clopidogrel and does not interfere with its antiaggregating activity. Moreover, in rats, the inhibition by NAC (150 mg/kg), the activity of clopidogrel (5 or 10 mg/kg) against ADP-induced platelet aggregation was neither inhibited nor increased. This demonstrates that the generation of the active metabolite of clopidogrel is not affected by NAC. In conclusion, we have found that NAC does not restore the "normal" properties of P2Y12 on platelets from clopidogrel-treated animals, it does not interfere with the antithrombotic activity of the active metabolite of clopidogrel, and does not interfere with the generation of the active metabolite.
547. Mechanisms of the priming effect of low doses of lipopolysaccharides on leukocyte-dependent platelet aggregation in whole blood - Montrucciu G., Bosco O., Del Sorbo L. et al. [Prof. Dr. G. Camussi, Dipartimento di Medicina Interna, Università degli Studi di Torino, C.so Dogliotti 14, 10126 Turin, Italy] - THROMB. HAEMOST. 2003 90(5) (92-8B) - sum in ENG

Several studies focused on the ability of bacterial lipopolysaccharides (LPS) in triggering platelet and/or leukocyte activation. The aim of this study was to investigate the molecular mechanisms involved in the aggregation of platelets and in their interaction with leukocytes in whole blood after stimulation with low doses of LPS. LPS did not directly induce platelet aggregation in whole blood, but they primed the aggregation of platelets induced by epinephrine, adenosine diphosphor and arachidonic acid. As shown by cytofluorimetry, platelets neither bind FITC-LPS, nor express the LPS-receptors CD14 and toll-like receptor 4 (TLR4). After LPS, transmigration of polymorphonuclear leukocytes (PMNs) and the monocytic cell line THP-I. Furthermore, by using specific ELISAs we could show that AS-IV completely abolished LPS- and TNFα-induced nuclear translocation of NF-κB and NF-κB DNA binding activity in endothelial cells. We conclude that the ability of AS-IV to inhibit the NF-κB pathway might be one underlying mechanism contributing to its anti-inflammatory potential in vivo.


The regulated expression of adhesion molecules on the surface of endothelial cells is a key process in the pathogenesis of inflammation. The saponin astragaloside IV (AS-IV), a 3-O-β-D-glucopyranosyl-4-O-β-D-glucopyranosylglucocorticosterol purified from the Chinese medicinal herb Astragalus membranaceus (Fisch) Bge. has been shown to have anti-inflammatory effects in vivo. In this study we have investigated the effect of AS-IV on cytokine- and LPS-stimulated expression of adhesion molecules in and leukocyte adhesion to endothelial cells. We have demonstrated that AS-IV significantly reduced the adhesion promoting activity of LPS-stimulated HUVECs for polymorph-nuclear leukocytes (PMNs) and the monocytic cell line THP-I. Furthermore, by using specific cell ELISAs we could show that AS-IV decreased the LPS-induced expression of E-selectin and VCAM-1 on the surface of HUVECs in a dose and time dependent manner, whereas the expression of ICAM-1 was not affected by AS-IV. AS-IV also face of HUVECs in a dose and time dependent manner, whereas the expression of ICAM-1 was not affected by AS-IV. AS-IV also

549. Efficacy of esomapezole in controlling reflux symptoms, intraoesophageal, and intragastric pH in patients with Barrett's esophagus - Yeh R.W., Gerson L.B. and Trudalopoulous G. [Dr. G. Trudalopoulou, Gastroenterology Section (111-GL), VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, United States] - DIS. ESOPHAGUS 2003 16/3 (204-209) - sum in ENG

Barrett’s esophagus is a metaplastic condition associated with gastroesophageal reflux disease and an increased risk for adenocarcinoma. Acid plays a significant role in the development and progression of Barrett’s esophagus and high dose proton pump inhibitor (PPI) therapy is often needed. The aim of this study is to assess the efficacy of esomapezole, a new potent PPI, on symptoms relief and intraoesophageal and intra-gastric acid suppression in patients with Barrett’s esophagus (BE). Patients were evaluated by standardized questionnaires and dual sensor 24-h pH monitoring while receiving esomapezole at a dose (40-80 mg/day) needed for control of symptoms. Analyses of intraoesophageal and intragasttric pH profiles were then made. Thirteen patients, mostly men, were studied. All tolerated esomapezole (40-80 mg/day) with good symptom control. Sixty-two percent of patients with BE had abnormal intraoesophageal pH profiles despite adequate symptocontrol on esomapezole which was associated with significant breakthrough of intraoesophageal acid control, particularly at night. Low nocturnal intra-gastric pH correlated highly with nocturnal intraoesophageal acid reflux (P=0.004) and there was a relative failure of nocturnal intra-gastric acid control with esomapezole. A high percentage of patients with BE continue to exhibit pathologic GERD and low intragastric pH despite esomapezole for reflux symptom control. For an antisecretory treatment aimed at chemoprevention of esophageal adenocarcinoma to be effective, higher PPI dosing confirmed by pH monitoring may be necessary.


Botulinum toxin (BT) injection is an alternative treatment of achalasia. The aim of the study was to examine outcomes of patients treated with BT in the Czech Republic. Since 1997, 49 patients with achalasia have been treated with BT. We prospectively evaluated the effect of BT injection on 41 patients during a median follow-up of 24 months (range 9-62). Esophageal manometry was performed before and at 3-5 months after the injection. In 16 patients, BT was injected from the antegrade angle only (subgroup A), in 15 patients, BT was injected from both retrograde and antegrade angles (subgroup B) and, in 10 patients, BT injection was combined with subsequent balloon dilatation (subgroup C). Immediate clinical response was achieved in 93% of patients. Clinical remission was sustained beyond 3 months in 83% of patients (responders) - Fourteen responders (41%) did not experience a relapse during the median of 22 months. Twenty responders (59%) experienced symptomatic relapse approximately 8 months after the injection. Ten relapsers underwent BT reinjection, five (50%) of them were asymptomatic for another 14 months. The remaining five (50%) patients reported a second relapse approximately 6 months after the reinjection. Median duration of the symptom-free period was 11.5 months after the first BT injection, and 10.5 months after the second (P = 0.21). We did not find any significant predictor of a favorable outcome; responders tended to be older and had a lower basal lower-esophageal-sphincter pressure. Patients in subgroup C were more likely to be in remission at 1 and 2 years as compared with patients in subgroup A. BT injection is an effective treatment of achalasia in the short term. However, almost 75% of patients experience a relapse within 2 years. BT injection should therefore be reserved for patients at risk for more invasive procedures or for patients who prefer this treatment.


TP-38 is a recombinant chimeric targeted toxin composed of the EGFR binding ligand TGF-α and a genetically engineered form of the Pseudomonas exotoxin, PE-38. After in vitro and in vivo animal studies that showed specific activity and defined the maximum tolerated dose (MTD), we investigated this agent in a Phase I trial. The primary objective of this study was to determine the MTD and dose limiting toxicity of TP-38 delivered by convection-enhanced...
delivery in patients with recurrent malignant brain tumors. Twenty patients were enrolled in the study and doses were escalated from 25 ng/mL to 100 with a 40 mL infusion volume delivered by two catheters. One patient developed Grade IV fatigue at the 100 ng/mL dose, but the MTD has not been established. The overall median survival after TP-38 for all patients was 23 weeks whereas for those without radiographic evidence of residual disease at the time of therapy, the median survival was 31.9 weeks. Overall, 3 of 15 patients, with residual disease at the time of therapy, have demonstrated radiographic responses and one patient with a complete response and has survived greater than 83 weeks.

552. The potential of chitosan in ocular drug delivery - Alonso M.J. and Sánchez A. (M.J. Alonso, Dept. of Pharm./Pharmaceut. Technol., Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain) - J. PHARM. PHARMACOL. 2003 55/11 (1451-1463) - sum in ENGL

This paper presents an overview of the potential of chitosan-based systems for improving the retention and biodistribution of drugs applied topically onto the eye. Besides its low toxicity and good ocular tolerance, chitosan exhibits favourable biological behaviour, such as bioadhesion- and permeability-enhancing properties, and also interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. The review summarizes the techniques for the production of chitosan gels, chitosan-coated colloidal systems and chitosan nanoparticles, and describes their mechanism of action upon contact with the ocular mucosa. The results reported until now have provided evidence of the potential of chitosan gels for enhancing and prolonging the retention of drugs on the eye surface. On the other hand, chitosan-based colloidal systems were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal systems containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticles containing ciclespiron). Finally, the tolerance, toxicity and biodegradation of the carriers under evaluation were reviewed.

553. Kinetic studies of the degradation of an aminopenicillin antibiotic (amoxicillin trihydrate) in aqueous solution using heat conduction microcalorimetry - Chaddha R., Kashid N. and Jain D.V.S. (R. Chaddha, Pharmaceutical Chemistry Division, Univ. Inst. of Pharmaceut. Sciences, Panjab University, Chandigarh 160014, India) - J. PHARM. PHARMACOL. 2003 55/11 (1495-1503) - sum in ENGL

Recent developments in isothermal microcalorimetry allow the direct determination of kinetic and thermodynamic parameters for slow reactions from studies conducted at appropriate temperatures and under designated environmental control. The degradation kinetics of amoxicillin trihydrate has been investigated as a function of pH and under designated environmental control. The degradation kinetics in aqueous solution followed pseudo-first-order kinetics under our experimental conditions. The enthalpy of degradation reaction was found to be exothermic in nature. The values of the rate constant k for individual steps were determined from the values of the overall rate constants at different pH. Energy of activation of overall reaction as a function of pH and for individual rate constants was determined. The log k–pH profiles indicated specific-acid and specific-base catalysis and there were inflection points near pH 3 and pH 7 corresponding to the pKa1 and pKa2 values. Quantitatively, there was good correlation between calorimetric determined half-lives and the literature value in the acidic region determined by other methods at 310.15 K. The presence of a -lactam ring and of the -amino groups in the C-6 side chain played a critical role in the degradation of amoxicillin trihydrate and thewitterionic form of the drug was found to be more stable.

554. Transdermal isophoroside of insulin. Part 1: A study on the issues associated with the use of platinum electrodes for transdermal iontophoretic delivery of peptides, using insulin as a model peptide. Insulin permeation was studied using full-thickness rat skin by varying the donor solution pH as a function of electrode polarity. The stability of insulin under the iontophoretic conditions was assessed using TLC. SDS-polyacrylamide gel electrophoresis and HPLC. Large pH shifts were observed during anodal iontophoresis (AI), when the donor solution pH was above the isoelectric point of insulin and in cathodal iontophoresis (CI), when the donor solution pH was below the isoelectric point of insulin. The direction and magnitude of electrosoretic flow was influenced by pH of the donor solution and the electrode polarity. On the other hand, the buffer used to maintain the pH governed the contribution of electrorepulsion to the overall transport of insulin. Electrochemical degradation of insulin was significant during AI at pH 7.4. Among the pH investigated, AI of insulin at pH 3.6 and CI at pH 8.35 were better, as the pH shift was relatively less and electrophoretically more stable during iontophoresis as compared with other pH. In summary, the pH shift caused by platinum electrodes had a significant influence on the permeation and stability of insulin.


We have studied the issues associated with the use of platinum electrodes for transdermal iontophoretic delivery of peptides, using insulin as a model peptide. Insulin permeation was studied using full-thickness rat skin by varying the donor solution pH as a function of electrode polarity. The stability of insulin under the iontophoretic conditions was assessed using TLC. SDS-polyacrylamide gel electrophoresis and HPLC. Large pH shifts were observed during anodal iontophoresis (AI), when the donor solution pH was above the isoelectric point of insulin and in cathodal iontophoresis (CI), when the donor solution pH was below the isoelectric point of insulin. The direction and magnitude of electrosoretic flow was influenced by pH of the donor solution and the electrode polarity. On the other hand, the buffer used to maintain the pH governed the contribution of electrorepulsion to the overall transport of insulin. Electrochemical degradation of insulin was significant during AI at pH 7.4. Among the pH investigated, AI of insulin at pH 3.6 and CI at pH 8.35 were better, as the pH shift was relatively less and electrophoretically more stable during iontophoresis as compared with other pH. In summary, the pH shift caused by platinum electrodes had a significant influence on the permeation and stability of insulin.
The effect of Montelukast on bronchial provocation tests of asthmatic patients - Berkman N., Avidal A., Bardach E. et al. [Dr. N. Berkman, Institute of Pulmonology, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel] - ISR. MED. ASSOC. J. 2003 5/11 (778-781) - summ in ENGL

Background: Leukotriene antagonist therapy in asthmatic patients alleviates symptoms and improves exercise tolerance, however the effect of these drugs on bronchial firovaction tests and exhaled nitric oxide levels are less clearly established. Objective: To determine the effect of, montelukast treatment on airway hyperresponsiveness to exercise, methacholine and adenosine-5′-monophosphate and on exhaled nitric oxide levels in steroid-naive asthmatics. Methods: Following a 2 week run-in period, 20 mild to moderate asthmatics were enrolled in an open label 6 week trial of oral montelukast-sodium therapy. Bronchial hyperreactivity (exercise, methacholine and adenosine-5′-monophosphate challenges) and exhaled nitric oxide levels were measured before and after the 6 week period. Results: Montelukast treatment resulted in a significant improvement in treatment tolerance in median ΔFEV1 20.0% (range 0-50) prior to treatment vs. 15.0% (range 0-50) post-treatment (P = 0.029). A significant difference was also observed for exhaled NO following therapy: median NO 16.0 ppb (range 7-41) vs. 13.0 (range 4.8-26) (P = 0.016). No change was seen in baseline lung function tests (FEV1, MEF50) or in the bronchial responsiveness (P<0.05) for methacholine in all patients.

Conclusions: This study demonstrates that the leukotriene antagonist montelukast-sodium reduces bronchial hyperreactivity in response to exercise and reduces exhaled nitric oxide levels but has little effect on bronchial responsiveness to methacholine and adenosine challenges.

560. Cardiovascular disease in type 2 diabetes: Epidemiology, risk factors and therapeutic modalities - Khamaisi M., Wexler L.D., Skrha J. et al. [M. Khamaisi, Diabetes Center, Department of Internal Medicine, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel] - ISR. MED. ASSOC. J. 2003 5/11 (801-806) - summ in ENGL

Macrovascular complications associated with chronic hyperglycemia in type 2 diabetes mellitus is a major global health problem that is currently on the rise. Accelerated cardiovascular and cerebrovascular atherosclerosis is the major cause of mortality in patients with type 2 diabetes. Many of the risk factors for cardiovascular disease are operative or even exacerbated in diabetic patients, including hypercholesterolemia, hypertriglyceridemia, hypertension, central obesity, and smoking. Other diabetes-specific factors, such as increased levels of plasminogen activator 1 and fibrinogen, chronic inflammation, genet susceptible, and accelerated glycosylation end-products-mediated vascular damage, are thought to play a role in the development of CVD among patients with type 2 diabetes. Further studies will hopefully elucidate the clinical relevance of such factors. In addition, recent studies indicate that hyperglycemia is an important and independent risk factor for CVD. Increased risk of CVD is directly related to elevated 1 and 2 hour post-prandial blood glucose averages, as well as to fasting hyperglycemia. Thus, specific treatment regimens designed to reduce the development rate of cardiovascular complications in patients with type 2 diabetes must consider the impact of risk factors and their control, as well as the need for optimal metabolic and glycemic control.

561. Lercanidipine vs lacidipine in isolated systolic hypertension - Millar-Carg M., Shafti B., Greenough A. et al. [Dr. C. McDonald, Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW, United Kingdom] - J. HUM. HYPERTENS. 2003 17/1 (799-806) - summ in ENGL

This randomised, double-blind, double-dummy, parallel group, multicentre study compared the efficacy and tolerability of lercanidipine with lacidipine. Elderly patients with isolated systolic hypertension (supine blood pressure ≥ 160/95 mmHg) were enrolled and underwent a placebo run-in period of 14-27 days before random allocation to lercanidipine tablets 10 mg once daily (n=111) or lacidipine tablets 2 mg once daily (n = 111) for the assessment period (112-160 days). Titration to lercanidipine 20 mg once daily (two 10 mg tablets) or lacidipine 4 mg once daily (two 2 mg tablets) was allowed after 8 weeks, if required. Both treatments decreased supine and standing systolic and diastolic blood pressure between the end of the run-in period and the end of the assessment period.
and telangiectasia, while grading scales are most commonly used for erythema and telangiectasias. Color scales are popular for erythema and pustules, erythema, and telangiectasia. Manual lesional counts areLetterally judged by evaluating the effect of the intervention on papules and pustules, erythema, and telangiectasia. The presence of both lovastatin and uconazole resulted in a significant decrease in expression of genes involved in ergosterol synthesis, prenylation and dolichol synthesis. This study examines gene expression of the sterol pathway in response to lovastatin, an inhibitor of HMG-CoA reductase (H-Rugy), and uconazole, an inhibitor of 14α-lanosterol demethylase (ErG11p). Minimum inhibitory concentration (MIC) studies indicated that lovastatin acts synergistically with uconazole in vitro. Semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) results indicated that genes in the early part of the sterol pathway, such as HMGI and ErG20, did not alter expression in the presence of both lovastatin and uconazole, whereas genes in the later part of the sterol pathway, such as ERG9 and ERG11, had increased expression in response to these drugs in mid-logarithmic growth. Genes involved in prenylation, such as RAM1 and RAM2, also respond to these drugs in mid-logarithmic growth, although another prenylation gene, CDC43, was not affected. After 24 h of growth, the relative expression of ERG20, ERG9, and ERG11 remained unchanged or increased in the presence of both drugs, while all other genes decreased in expression under all drug treatments.


Background: Rosacea is a relatively common disorder that may affect individuals of all races, particularly those of northern European descent. The onset generally occurs in individuals between the ages of 20 and 50 years. Rosacea may be classified into several subtypes and variants. Although individuals with rosacea may not pass through all of the stages, the primary features of the disorder include frequent flushing and blushing, nontransient erythema, the presence of papules and pustules, and telangiectasia. Many agents have been used to treat rosacea stigmata, especially because none of these is uniformly effective. Aim: To identify the parameters that are used to evaluate the response to therapy when different agents are used to treat rosacea. For a given parameter, to determine whether the different trials are consistent in the manner in which this variable has been measured. Methods: The reports on the efficacy and safety of the different drug therapies used to treat rosacea were identified. We searched MEDLINE (1966 to June 2002) for studies where rosacea was treated. The parameters used to evaluate the efficacy of therapy were determined. For each parameter, the ways in which it has been measured were identified. Results: Efficacy of treatment is generally judged by evaluating the effect of the intervention on papules and pustules, erythema, and telangiectasia. Manual lesional counts of papules and pustules are usually performed. There is, however, substantial variation in the methodology chosen for comparison of erythema and telangiectasia. Color scales are popular for erythema and telangiectasia, while grading scales are most commonly used for physician and patient evaluations. Conclusions: For each of the parameters that are commonly used to measure the efficacy of treatments for rosacea, the different approaches by which it has been measured in the various trials have been highlighted; these dissimilarities can make it problematic to compare between clinical trials. A greater degree of uniformity in the manner in which the various parameters are evaluated would enable a more objective comparison between the studies.


Direct effects of PRL on Sertoli cell proliferation were investigated by using Sertoli cell primary cultures isolated from both prepubertal rat and porcine testes. PRL metabolic effects were analyzed in Sertoli cell primary cultures. Exposure to physiological doses of PRL resulted in a significant increase (+50-60%) of basal DNA synthesis, as reflected by the pattern of [3H] thymidine incorporation during culture; significant increases in lactate secretion (about 50%), androgen binding protein (ABP) production (about 30%) and basal protein synthesis (25-30%), as reflected in the augmented [3H] valine incorporation, were also evident. Taken together, these data suggest that PRL and its receptor, on Sertoli cell proliferation and metabolism, demonstrate that Sertoli cells are a potential target for PRL action at testicular level during pre-pubertal development. ©2003, Editrice Kurtis.

565. Intravenous ibandronate in men with osteoporosis: An open pilot study over 2 years - Lamy O., Sandini L., Pache I. et al. [Dr. O. Lamy, Department of Internal Medicine, CHU, BH10/CH-1011 Lausanne, Switzerland] - J. ENDOCRINOL. INVEST. 2003 26/8 (728-732) - summa in ENGL

In the treatment of osteoporosis, the tolerance of oral bisphosphonates is often low. The high potency of ibandronate allows iv bolus injections that can be repeated every 2 to 3 months. However, the best dose and time interval of the treatment with iv ibandronate is still debated. Efficacy of 2-mg ibandronate injected every 3 months was tested in men with osteoporosis over 2 yr, in a prospective, open study. Seventeen men with primary osteoporosis, mean age 57±12 yr (range: 40-73), received 2-mg ibandronate iv every 3 months over 2 yr. All got 1 g/day calcium and 880 IU/day vita- min D for 2 yr. Bone mineral density (BMD) increased after 2 yr by 6.7±1.5% (mean change±SEM) at lumbar spine (p<0.001), by 3.2±0.8% at trochanter (p<0.001) and by 1.4±1.1% at femoral neck (ns). Serum β-crosslaps and osteocalcin decreased significantly by 30-45 and 30%, respectively, during the 2 yr of treatment. Serum calcium increased from the lower to the middle tertile of the normal range during the 2 yr of the study. The observed decrease of bone remodeling and the increase of BMD are of the same magnitude as those described with oral bisphosphonates. The increase of plasma calcium the positive effect of the supplementation with calcium and vitamin D. These results suggest that 3 months are a good interval between two doses of iv ibandronate, when 2 mg are given. ©2003, Editrice Kurtis.

566. Rapid desensitisation of the GH secretagogue (ghrelin) receptor to hexarelin in vitro - Orkin R.D., New D.I., Norman D. et al. [Dr. M. Korbonits, Department of Endocrinology, St. Bartholomew’s Hospital, Dominon House, Unit 1.1, 59 Bartholomew Close, London EC1A 7BE, United Kingdom] - J. ENDOCRINOL. INVEST. 2003 26/8 (743-747) - summa in ENGL

Ghrelin, the recently identified hormone with GH-secreting and appetite-inducing effects, acts on the ghrelin secretagogue receptor (GHS-R). GHS-R belongs to the G protein-coupled 7 transmembrane domain receptors and activates the phospholipase C pathway; it then leads to the release of GH from somatotroph cells via an elevation of intracellular calcium concentration. Both in vivo and in vitro studies demonstrated that the effect of GH secretagogues (GHS) could be desensitised similar to most receptor stimulation systems. We have studied whether acute desensitisation of the GHS-R occurs in response to the GHS hexarelin in vitro in terms of intracellular calcium concentration. Chinese hamster ovary cells were transiently transfected with DNA encoding the human 24-aa GHS-R. The presence of messenger RNA was confirmed with...
RT-PCR, while no GHS-R was observed in mock-transfected cells. Calcium responses to the peptide GHS analogue hexarelin were measured using the fluorescent indicator fura-2. Cells were stimulated with the peptide GHS, hexarelin, at concentrations between 10^{-10} and 10^{-8} M. Cells transfected with the GHS-R cDNA demonstrated a significant and specific calcium response to hexarelin that was not observed in mock-transfected cells. Marked desensitisation of the calcium response to hexarelin was observed 2-5 min after the first dose of hexarelin (10^{-8} M) was administered. These data show directly for the first time the desensitisation of the GHS receptor signal at the second messenger level. The desensitisation of the receptor may play a major role in the regulation of effect of circulating or locally produced ghrilin both in the GH and in the appetite-regulating system or in other systems where ghrelin has been shown to be active, such as the cardiovascular system or cell proliferation. ©2003, Editrice Kurtis.

567. All-trans retinoic acid- and N-(4-hydroxyphenyl)-retinamide-induced growth arrest and apoptosis in orbital fibroblasts in Graves’ disease - Fasqualli D, Bellastella A, Colantuoni V, et al. [Dr. D Pasquale, Istituto di Endocrinologia, Seconda Università di Napoli, Building 16, Via Pansini 5, 80131 Napoli, Italy] - METAB. CLIN. EXP. 2003 52/11 (1387-1392) - summary in ENGL.

In this study, we evaluated by reverse transcription-polymerase chain reaction (RT-PCR) the expression pattern of retinoic acid receptors (RARα, β, and γ and cellular retinoic acid binding protein-I (CRBP-I) genes in 12 primary cultures of fibroblasts (F) from orbital tissue of Graves’ ophtalmopathy (GO) patients. We also studied the in vitro effects of all-trans retinoic acid (RA) and N-(4-hydroxyphenyl)-retinamide (4HPR), a less toxic and better tolerated synthetic derivative of RA, on cell morphology, growth, apoptosis, and cyclic adenosine monophosphate (cAMP) accumulation. All primary cultures expressed RARα, β, and γ, and CRBP-I. F treated with RA and 4HPR (10^{-7} mol/L) presented morphologic changes and significantly inhibited cell growth after 72 hours. At 96 hours of drug exposure, apoptosis was detected in 15% and 50% of RA- and 4HPR (10^{-7} mol/L)-treated cells, and p53 protein increased in cell lysates. 4HPR induced a 70% decrease of Bcl-2 protein. After 30 minutes of RA and 4HPR (10^{-7} mol/L) exposure, a 20% decrease of basal cAMP accumulation was seen, and forskolin cAMP-induced increase was abolished. The expression of RARα, β, and γ, and CRBP-I in primary cultures of FGO indicates that they are targets for retinoids. Moreover, we show that RA and 4HPR are able to induce morphologic changes, inhibition of cell growth, and apoptosis in FGO exerting their effects through RAR-modulated pathways. The rapid inhibition of cAMP accumulation indicates that a novel nonclassic retinoid pathway may also be involved. Finally, the potent in vitro effects of 4HPR, a retinoid derivative with fewer adverse reactions in vivo, could justify further investigations on a clinical application of retinoids in GO. © 2003 Elsevier Inc. All rights reserved.

568. Contrasting effects of nateglinide and rosiglitazone on in-sulin secretion and phosphodiesterase-C activation - Zawalich W.S., Tesz G. and Zawalich K.C. [Dr. W.S. Zawalich, Yale University, School of Nursing, 100 Church St. South, New Haven, CT 06536-0740, United States] - METAB. CLIN. EXP. 2003 52/11 (1393-1399) - summary in ENGL.

When stimulated with 6 mmol/L glucose, a minimal, transient insulin secretory response was observed from perfused rat islets. The inclusion of 5 μmol/L nateglinide significantly amplified release. Elevating glucose to 8 or 10 mmol/L resulted in an increasing insulin secretory response that was again markedly potentiated by the further inclusion of nateglinide. The calcium channel antagonist, nitrendipine, abolished secretion to 8 mmol/L glucose plus nateglinide. Unlike nateglinide, rosiglitazone (5 μmol/L), troglitazone (1 to 10 μmol/L), or darglitazone (10 μmol/L), 3 peroxisome proliferator-activated receptor gamma (PPARγ) agonists, were without any acute stimulatory effect on insulin release in the simultaneous presence of 6 to 10 mmol/L glucose. Glucose (8 to 10 mmol/L) significantly increased inositol phosphate accumulation. Nateglinide amplified this response. Nitrendipine reduced inositol phosphate (IP) accumulation in response to the combination of 8 mmol/L glucose plus 5 μmol/L nateglinide. Rosiglitazone had no effect on IP accumulation. These results confirm the efficacy of nateglinide as a potent glucose-dependent insulin secretagogue that exerts its stimulatory effect, at least in part, through the activation of phosphodiesterase C (PLC). No acute potentiating effect of rosiglitazone on either insulin secretion or IP accumulation could be detected in isolated rat islets. © 2003 Elsevier Inc. All rights reserved.

569. Milrinone, a selective phosphodiesterase 3 inhibitor, stimulates lipolysis, endogenous glucose production, and insulin secretion - Cheung P., Yang G. and Boden G. [Dr. G. Boden, Temple University Hospital, 3401 N Broad St., Philadelphia, PA 19140, United States] - METAB. CLIN. EXP. 2003 52/11 (1496-1500) - summary in ENGL.

In vivo effects of milrinone, a selective phosphodiesterase 3 (PDE-3) inhibitor, on plasma free fatty acids (FFA), glucose, and insulin levels were examined in alert rats. In dose response studies, intravenous injection of 1, 5 or 25 μmol/kg of milrinone provoked an immediate increase in plasma concentrations of FFA and insulin, while glucose levels rose only in response to the 5- and 25-μmol/kg doses. During euclidean-hyperinsulineemic (-450 μmol/L)-clamps, intravenous injection of milrinone (25 μmol/kg) completely inhibited insulin suppression of lipolysis and of endogenous glucose production, while having no effect on insulin-stimulated glucose uptake (ISGU). To explore the reason why ISGU was not affected, we performed reverse-transcription polymerase chain reaction (RT-PCR) with RNA from skeletal muscle, fat, and liver. The results showed that PDE-3B mRNA was expressed in adipose tissue and liver, but it was not detected in skeletal muscle. We conclude that PDE-3B plays a major role in the inhibitory action of insulin on lipolysis in fat and on glucose production in liver and, in addition, seems to be involved in insulin secretion in pancreatic β cells. © 2003 Elsevier Inc. All rights reserved.

570. Effect of tetramethylpyrazine on exocrine pancreatic and bile secretion - Zhao W.-C., Zhu J.-X., Tang N. et al. [Prof. H.-C. Chan, Department of Physiology, Faculty of Medicine, Chinese University of Hong Kong, Shatin, NT, Hong Kong] - WORLD J. GASTROENTEROL. 2003 9/11 (2505-2508) - summary in ENGL.

Aim: To investigate the effect of tetramethylpyrazine (lignostazine, TMP) on the secretion of exocrine pancreas (and biliary).

Methods: In vivo study, we investigated the effect of TMP on the secretion of the pancreatic-bile juice (PBJ) in rats. Using human pancreatic duct cell line, CAPAN-1, combined with the short-circuit current (Isc) technique we further studied the effect of TMP on the pancreatic anion secretion. Results: Administration of TMP (80 mg/kg, ip) significantly increased the secretion of PBJ (P<0.05), but the pH of PBJ and the secretion of pancreatic protein were not significantly affected. Basolateral addition of TMP produced a dose-dependent increase in Isc (EGF=1.56 μmol/L), which contained a fast transient Isc response followed by a slow decay. Apical application of CT channel blockers, DPC (1 mmol/L), decreased the response by about 67.1 % (P<0.001), whereas amiloride (100 μmol/L), a epithelial sodium channel blockers, had no effect. Removal of extracellular HCO3− abolished TMP-induced increase in Isc by about 74.4 % (P<0.001), but the removal of external CT did not.

Conclusion: TMP could stimulate the secretion of PBJ, especially pancreatic ductal HCO3−secretion via cAMP or cGMP-dependent pathway. It need further study to investigate the roles of cAMP or cGMP in the effect of TMP on the secretion of exocrine pancreas.

571. Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms - Du W.-D., Yuan Z.-R., Sun J. et al. [Dr. W.-D. Du, Department of Surgery, Huadong Hospital, No. 221 Yanan Xilu, Shanghai 200040, China] - WORLD J. GASTROENTEROL. 2003 9/11 (2565-2569) - summary in ENGL.

Aim: To observe the therapeutic efficacy of high-dose vitamin C (Vit. C) on acute pancreatitis (AP), and to explore its potential mechanisms. Methods: Eighty-four AP patients were divided into treatment group and control group, 40 healthy subjects were taken as normal group. In the treatment group, Vit. C (10 g/day) was given intravenously for 5 days, whereas in the control group, Vit.
C (1 g/day) was given intravenously for 5 days. Symptoms, physical signs, duration of hospitalization, complications and mortality rate were monitored. Meanwhile, serum amylase, urine amylase and leukocyte counts were also determined. The concentration of plasma vitamin C (P-VC), plasma lipid peroxide (P-LPO), plasma vitamin E (P-VE), plasma β-carotene (P-B-Car), whole blood glutathione (WB-GSH) and the activity of erythrocyte superoxide dismutase (E-SOD) and erythrocyte catalase (E-CAT) as well as T lymphocyte subphenotype were measured by spectrophotometry in the normal group and before and after treatment with Vit. C in the treatment and the control group. Results: Compared with the normal group, the average values of P-VC, P-VE, P-β-Car, WB-GSH and the activity of E-SOD and E-CAT in AP patients were significantly decreased and the average value of P-LPO was significantly increased, especially in severe acute pancreatitis (SAP) patients (P<0.05). P-VC, P=0.045; P-VE, P=0.013; P=0.016; WB-GSH, P=0.039; E-SOD, P=0.019; E-CAT, P=0.020; P-LPO, P=0.038). Compared with the normal group, CD4 and CD8 positive cells in AP patients were significantly decreased. The ratio of CD4/CD8 and CD4 positive cells were decreased, especially in SAP patients (P<0.05). CD4/CD8, P=0.019; Fever and vomiting disappeared, and leukocyte counts and amylase in urine and blood become normal quicker in the treatment group than in the control group. Moreover, patients in treatment group also had a higher cure rate, a lower complication rate and a shorter in ward-days compared with those in he control group. After treatment, the average value of P-VC was significantly higher and the values of SILD, TNF-α, IL-6 and IL-8 were significantly lower in the treatment group than in the control group (P<0.05; P-VC, P=0.045; SILD-2R, P=0.012; TNF-α, P=0.030; IL-6, P=0.015; and IL-8, P=0.043). In addition, the ratio of CD4/CD8 and CD4 positive cells in the patients of treatment group were significantly higher than that of the control group after treatment (P<0.05). CD4/CD8, P=0.039; CD4, P=0.024). Conclusion: High-dose vitamin C has therapeutic efficacy on acute pancreatitis. The potential mechanisms include promotion of anti-oxidizing ability of AP patients, blocking of lipid peroxidation in the plasma and improvement of cellular immune function.

572. Primary sensory neuronal rescue with systemic acetyl-L-carnitine following peripheral axotomy. A dose-response analysis - Wilson A.D.H., Hart A., Brannstrom T. et al. [Dr. G. Terenghi, Blond McIndoe Research Laboratory, Plastic/Reconstructive Surgery Res., University of Manchester, Stipholt Building, Oxford Road, Manchester M13 9PT, United Kingdom] - BR. J. PLAST. SURG. 2003 56/8 (732-739) - summa in ENGL. The loss of a large proportion of primary sensory neurons after peripheral nerve axotomy is well documented. As a consequence of this loss, the innervation density attained on completion of regeneration will never be normal, regardless of how well the individual surviving neurons regenerate. Acetyl-L-carnitine (ALCAR), an endogenous peptide in man, has been demonstrated to protect sensory neurons, thereby avoiding loss after peripheral nerve injury. In this study we examined the dose-response effect of ALCAR on the primary sensory neurons in the rat dorsal root ganglia (DRG) 2 weeks after sciotic nerve axotomy. Six groups of adult rats (n = 5) underwent unilateral sciatic nerve axotomy, without repair, followed by 2 weeks systemic treatment with one of five doses of ALCAR (range 0.5-50 mg/kg/day), or normal saline. L4 and L5 dorsal root ganglia were then harvested bilaterally and sensory neuronal cell counts obtained using the optical dissecto technique. ALCAR eliminated neuronal loss at higher doses (50 and 10 mg/kg/day), while lower doses did result in loss (12% at 5 mg/kg/day, p<0.05; 19% at 1 mg/kg/day, p<0.001; 25% at 0.5 mg/kg/day, p<0.001) compared to contralateral control ganglia. Treatment with normal saline resulted in a 25% (p<0.001) loss, demonstrating no protective effect in accordance with previous studies. ALCAR preserves the sensory neuronal cell population after axotomy in a dose-responsive manner and as such, has potential for improving the clinical outcome following peripheral nerve trauma when doses in excess of 10 mg/kg/day are employed. © 2003 The British Association of Plastic Surgeons. Published by Elsevier Ltd. All rights reserved.

6.1. Anesthetics

573. Effects of Lidocaine on Shock-Induced Vulnerability - Li N., Nikolski V. and Efmov I.R. [Dr. I.R. Efmov, Department of Biomedical Engineering, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106-7207, United States] - J. CARDIOVASC. ELECTROPHYSIOL. 2003 14/10 SUPPL. (S237-S248) - summa in ENGL. Introduction: Lidocaine is known to increase the defibrillation threshold (DFT) of monophasic shocks (MS) and have no effect on DFT of biphasic shocks (BS). The aim of this study was to enhance our understanding of the mechanisms of vulnerability and defibrillation through the investigation of this difference. Methods and Results: We studied the effect of 15 μM lidocaine on shock-induced vulnerability using fluorescent imaging of Langendorff-perfused rabbit hearts. Vulnerability was assessed as vulnerable window with shock strengths of 15 to 150 V and vulnerable period (VP) with shock delivery phase of 0% to 100% of action potential duration (% APD). With MS, lidocaine caused a significant increase in both the upper limit of vulnerability (ULV: 17 ± 17 V vs 120 ± 1.5 V, P<0.01) and upper limit of VP (91 ± 8 % APD vs 110 ± 2 % APD, P<0.01). With BS, lidocaine had no effect on ULV (40 ± 3.4 V vs 45 ± 4.5 V) and did not increase the upper limit of VP (81 ± 4 % APD vs 91 ± 11 % APD, P<0.01). Lidocaine caused reduction of the conduction velocity during pacing (0.58 ± 0.08 m/s vs 0.44 ± 0.05 m/s, P<0.01), shock-induced break excitation (0.82 ± 0.17 m/s vs 0.30 ± 0.07 m/s, P<0.01), and post-excitation recovery (0.34 ± 0.07 m/s vs 0.19 ± 0.08 m/s, P<0.01). Lidocaine had no effect on shock-induced virtual electrode polarization. Conclusion: Lidocaine increased MS ULV due to slowing of shock-induced break-excitation wavefronts, which resulted in enhanced probability of survival of virtual electrode induced phase singularity. Lidocaine had no effect on BS ULV because no break excitation was induced by BS. Reduction of conduction velocity by lidocaine resulted in increased dispersion of repolarization and led to upper limit of VP increase for both MS and BS.

574. GABA A receptor modulation by the novel intravenous general anesthetic E-6375 - Pati D., Belelli D., Callahan H. et al. [J.J. Lambert, Neuroscience Institute, Dept. of Pharmacology, and Neuroscience, University of Dundee, Dundee DD1 9SY, United Kingdom] - NEUROPHARMACOLOGY 2003 45/8 (1029-1040) - summa in ENGL. E-6375 (4-butoxy-2-[4-(2-cyanobenzoyl)-1-piperazinyl] pyrimidine hydrochloride) is a new intravenous general anesthetic with an anesthetic potency, in mice, comparable to propofol, or etomidate. Here, we examined the effect of E-6375 upon the GABA A receptor, a putative target of intravenous anesthetic action. E-6375 reversibly enhanced GABA-evoked currents mediated by recombinant GABA A 1(3)/γ2 receptors expressed in Xenopus laevis oocytes, with little effect on NMDA- and kainate-evoked currents mediated by NR1A/2R2A and GluR1/GluR2 glutamate receptors, respectively. E-6375 prolonged the decay of GABA-evoked miniature inhibitory postsynaptic currents recorded from rat Purkinje neurones demonstrating the anaesthetic also enhanced the activity of synaptic GABA A receptors. The GABA A receptor activation of E-6375 on recombinant GABA A receptors was unaffected by the subtype of GABA A receptor isoforms that discriminate between GABA A receptor subtypes, or by the presence of the γ2 subunit. Receptors incorporating β3 or β2, subunits were more sensitive to modulation by E-6375 than those containing the β1 subunit. The selectivity of E-6375 was largely governed by the identity (serine or asparagine)- of a single amino acid residue within the second transmembrane domain of the β subunit. The various in vivo actions of general anesthetics may be mediated by GABA A receptor isoforms that have a differential distribution within the CNS. The identity of the anaesthetic also enhanced the activity of GABA A receptor subtypes may augur the development of general anesthetics with an improved therapeutic profile. © 2003 Elsevier Ltd. All rights reserved.

575. A Comparison of a Triple-Injection Axillary Brachial Plexus Block with the Humeral Approach - March X., Pardina B., Torrejón S. et al. [Dr. X. March, Servei d Anestesi i Reanimació, Hosp. Univer. Girona Dr. Josep Trueta, Av. de França

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management has significant impact on clinical and economic outcomes. Negative clinical outcomes of inadequately managed acute postoperative pain include extended hospitalization, compromised prognosis, higher morbidity and mortality, and the development of a chronic pain state as a result of neuronal plasticity. Although estimating the economic burden of postoperative pain is difficult, this burden is considerable and results from direct costs due to excess health-care resource use, as well as indirect costs due to reduced patient functionality and productivity. These latter factors also have a significant adverse impact on patients’ quality of life and may be associated with the development of depression and anxiety. Thus, improved clinical outcomes are dependent not only on the availability of effective drugs but also on their appropriate utilization. A multimodal approach incorporating different drugs and techniques is effective in reducing postoperative pain but is limited by the currently available therapies. The efficacy of opioids is well established, but there are concerns about dependency, respiratory depression and side-effects, that have special clinical significance in patients undergoing surgical procedures. Cyclooxygenase-2-specific inhibitors such as celecoxib, rofecoxib, and valdecoxib, were developed to provide the capacity of non-specific NSAIDs while limiting associated toxicity. These agents have demonstrated analgesic efficacy and an opioid-sparing effect in a variety of surgical procedures, suggesting their value as an alternative to non-specific NSAIDs. Further studies are needed to determine the impact of these drugs on clinical and economic outcomes when used in a programme of postsurgical pain management.

578. Liver Enzyme Modification in Undernourished Rats Treated with Acetaminophen (Span) - MODIFICACIÓN DE ENZIMAS HEPÁTICAS EN RATAS DESNUTRIDAS TRATADAS CON ACETAMINOFEN - González-Mendoza M. and Víchez-Fernández N. [M. González-Mendoza, Avenida Principal de La Pedregosa, Mérida-Mérida, Venezuela] - GAC. MED. MEX. 2003 139/5 (429-433) - summary in ENGL, SPAN

Acetaminophen is used as an analgesic and antipyretic. Due to its relative safety at therapeutic dose, it is frequently used in children and in pregnant women. We evaluated the effect of a dose equivalent to the therapeutic dose of Acetaminophen in undernourished rats: 72 Wistar male rats of 18 weeks of age, with weight between 270 and 280 g, were distributed randomly in four groups: A, normal without food restriction; B, normal without food restriction treated with Acetaminophen (100 mg/kg); C, undernourished by food restriction and D, undernourished by food restriction treated with Acetaminophen (100 mg/kg). The results showed decreasing of body and hepatic weight in undernourished rats and in undernourished treated with Acetaminophen, significant decrease of serum albumin concentration (p < 0.001). It was demonstrated that activity of the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase significantly decreased (p < 0.001) in the group of undernourished rats treated with Acetaminophen compared with the other groups. We concluded that the Acetaminophen induces hepatic lesions in undernourished rats treated with a single non-toxic dose of 100 mg/kg of weight, probably as a consequence of the inherent susceptibility to malnutrition.


Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological modality used clinically to relieve pain. Central involvement of serotonin and endogenous opioids are implicated in TENS-induced analgesia. Activation of spinal cholinergic receptors is antinoceptive and these receptors interact with opioid and serotonin receptors. In the current study, the possible involvement of spinal cholinergic receptors in TENS analgesia was investigated in rats. Hyperalgesia was induced by inflaming one knee joint with 3% kaolin-carrageenan and assessed by measuring paw withdrawal

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s/n, 17007 Girona, Spain] - REG. ANESTH. PAIN MED. 2003 28/6 (504-508) - summary in ENGL

Background and Objectives: This prospective, randomized, and single-blind study compared effectiveness, performance, onset, and total anesthetic time and complications of the multiple axillary block (median, radial, and musculocutaneous nerves) with the humeral approach. Methods: One hundred patients were randomly assigned to 2 groups. In group A (axillary) median, radial, and musculocutaneous nerves were located by a nerve stimulator and injections were made. In group H (humeral) all 4 terminal nerves of the brachial plexus were located and injections were made. A total of 40 mL mepivacaine of 1% was used. Results: Complete sensory block of all 6 peripheral nerves occurred in 94% and 79% of patients in groups A and H, respectively (P < 0.05). The time to perform the block was shorter in group A (8 ± 4 minutes vs 11 ± 4 minutes; P < 0.001), onset time was shorter in group A (16 ± 8 minutes vs 21 ± 9 minutes; P < 0.05); total anesthetic time was shorter in group A (24 ± 8 minutes vs 33 ± 10 minutes; P < 0.001). Complete motor block was greater in group A (88% vs 66%; P < 0.05). More vascular punctures occurred in group A (22 vs 8%; P < 0.05). Conclusion: The triple-injection axillary block was more effective than the humeral approach as it was associated with more cases of sensory and complete motor block and gave shorter performance and onset times.

576. Lateral Approach to the Sciatic Nerve in the Popliteal Fossa: A Comparison between 1.5% Mepivacaine and 0.75% Ropivacaine - Taboada M., Cortés J., Rodríguez J. et al. [Dr. M. Taboada, Department of Anesthesiology, Hosp. Clin. Univ. de Santiago, Travessa da Choupama s/n, 15706 Santiago de Compostela, Spain] - REG. ANESTH. PAIN MED. 2003 28/6 (516-520) - summary in ENGL

Background and Objectives: Ropivacaine and mepivacaine are commonly used local anesthetics for peripheral nerve blockade. The purpose of the present study was to compare onset time, quality of anaesthesia, and duration of analgesia with ropivacaine 0.75% and mepivacaine 1.5% for lateral popliteal nerve block. Methods: Fifty American Society of Anesthesiologists (ASA) physical status I or II patients scheduled for foot and ankle surgery with calc tourniquet under lateral popliteal sciatic nerve block were randomly assigned to receive 30 mL of either ropivacaine 0.75% or mepivacaine 1.5%. Time required for onset of sensory and motor block, resolution of motor block, onset of postsurgical pain, and time of first analgesic medication were recorded. Results: The 2 groups were similar with regard to demographic variables and duration of surgery. Onset of sensory and motor block was significantly shorter in the mepivacaine group (9.9 ± 3.3 min and 14.7 ± 5.6 min, respectively) than in the ropivacaine group (18.1 ± 6.1 min and 23.6 ± 5.5 min, respectively) (P < 0.001). Resolution of motor block occurred later in the ropivacaine group than in the mepivacaine group (P < 0.001), and duration of postoperative analgesia was significantly longer in the ropivacaine group (19 ± 3.4 h) compared with the mepivacaine group (5.9 ± 1.1 h) (P < 0.001). Analgesic requirements were higher in mepivacaine group than in the ropivacaine group (P < 0.001). There were 2 failed blocks, one in each group. Conclusions: Both ropivacaine and mepivacaine provided effective sciatic nerve blockade. Mepivacaine 1.5% displayed a significantly shorter onset time than ropivacaine 0.75%. Postoperatively, ropivacaine 0.75% resulted in longer-lasting analgesia and less need for oral pain medication.

6.2. Opiates and other analgesics

577. The burden of acute postoperative pain and the potential role of the COX-2-specific inhibitors - Stephens J., Laskin B., Paushos C. et al. [J. Stephens, Abt Associates Clinical Trials, HERQuoless Group, 4800 Montgomery Lane, Bethesda, MD 20814, United States] - RHEUMATOLOGY (UK) 2003 42/SUPPL. 3 (iii40-ii35) - summary in ENGL

Pain has been recognized as a problem of global proportions, and postoperative pain is one of the most common types of pain. Postoperative pain is acute and, although it is preventable and/or treatable, it is often undertreated. Lack of appropriate analgesic

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latency (PWL) to heat before and 4 h after injection. The non-selective nicotinic antagonist mecamylamine (30 μg) or one of the muscarinic subtype antagonists: pirenzepine (M1,1 g), methoctramine (M2,1 g), 4-DAMP (M1,1 g), or saline was administered intrathecally just prior to TENS treatment. Low or high frequency TENS was then applied to the inflamed knee and PWL was determined again. Pirenzepine and 4-DAMP significantly attenuated the antihyperalgesic effects of low and high frequency TENS while mecamylamine and methoctramine had no effects, compared to saline control. The results show that TENS-induced antihyperalgesia is mediated partially by activation of spinal muscarinic receptors but not spinal nicotinic receptors. Further, the results also indicate that spinal M1 and M3 muscarinic receptor subtypes mediate the muscarinic component of TENS antihyperalgesia. © 2003 Elsevier Ltd. All rights reserved.


Several anatomical, biochemical and pharmacological evidence support the existence of bidirectional interactions between cannabinoid and opioid systems. The present review is focused on the participation of the endogenous opioid system in the antinociceptive and emotional-like responses induced by cannabinoids, and the development of tolerance to cannabinoid pharmacological effects. Cannabinoid and opioid agonists produce antinociception by acting on similar structures within the central nervous system, and a peripheral mechanism has also been proposed for both compounds. Pharmacological studies have suggested that the endogenous opioid system could be involved in cannabinoid antinociception and the development of cannabinoid tolerance. Recent studies using knockout mice have also demonstrated the role of the opioid system in cannabinoid antinociception and tolerance, although some discrepancies with the previous pharmacological results have been reported when using knockout mice. On the other hand, cannabinoid administration can induce antinociceptive-like responses that are mediated at least in part by an endogenous opioid activity on μ and δ-opioid receptors. © 2003 Elsevier B.V./ECNP. All rights reserved.


The discovery of endogenous opioids has markedly influenced the research on the biology of drug dependence. Evidence has been presented that these brain substances are self-administered by laboratory animals. This finding, among others, has led to the hypothesis that endogenous opioids are involved in reinforcing habits, including dependence on drugs of abuse. The course of drug dependence is presented as a continuum from no drug use via regular use to an actual dependence on the drug. Specific brain opioid systems belonging to four conceptualized brain circuits are described to be involved during the different phases of the drug dependence continuum. More recent research to delineate the role of endogenous opioid systems in drug dependence has focussed on genetic research in humans and animals. Among others, the findings obtained from studies of opioid receptor and opioid peptide precursor knockout mice provided further support for a role of endogenous opioid systems in drug dependence, in agreement with previous pharmacological studies. © 2003 Elsevier B.V./ECNP. All rights reserved.

582. Analgesic properties of Capraria biflora leaves aqueous extract - Acosta S.L., Muro L.V., Sacerio A.L. et al. [S.L. Acosta, Pharmacy Department, Chemical and Pharmacy School, Central University of Las Villas, Carretera a Camagüey Km. 5.5, Santa Clara, Villa Clara, Cuba] - FITOTERAPIA 2003 74/7-8 (686-688) - summ in ENGL

The analgesic properties of dried leaves of Capraria biflora were investigated. The aqueous extract (50-200 mg kg⁻¹) produced moderate inhibition of acetic acid-induced writhing in mice. At the same doses, a better analgesic effect was observed on the hot plate test. © 2003 Elsevier B.V. All rights reserved.


Purpose. Pregabalin is being evaluated for the treatment of neuropathic pain. Two phase 2 studies were simulated to determine how precisely the dose that caused a one-point reduction in the pain score could be estimated. The likelihood of demonstrating at least one point change for each available dose strength was also calculated.

Methods. A pharmacokinetic-pharmacodynamic (PK/PD) model relating pain relief to gabapentin plasma concentrations was derived from a phase 3 study. The PK component of the model was modified to reflect pregabalin PK. The PD component was modified by scaling the gabapentin concentration-effect relationship to reflect pregabalin potency, which was based on preclinical data. Uncertainty about the potency difference and the steepness of the concentration-response slope necessitated simulating a distribution of outcomes for a series of PK/PD models. Results. Analysis of the simulated data suggested that after accounting for the uncertainty, there was an 80% chance that the dose defining the clinical feature was within 45% of the true value. The likelihood of estimating a dose that was within an acceptable predefined precision range relatively to a known value approximated 60%. The minimum dose that should be studied to have a reasonable chance of estimating the dose that caused a one-point change was 300 mg. Conclusions. Doses that identify predefined response may be imprecisely estimated, suggesting that replication of a similar outcome may be elusive in a confirmatory study. Quantification of this precision provides a rationale for phase 2 trial design and dose selection for confirmatory studies.

See also: 606, 744.

6.3. Antiinflammatory agents

584. Inhibition of Mg²⁺-dependent adhesion of polymorphonuclear leukocytes by serum hemopexin: Differences in divalent-cation dependency of cell adhesion in the presence and absence of serum - Suzuki K., Kobayashi N., Doi T. et al. [Dr. K. Suzuki, Department of Biology, School of Education, Waseda University, Shinjuku-ku, Tokyo 169-0051, Japan] - CELL STRUCT. FUNCTION. 2003 28/4 (243-253) - summ in ENGL

Circulating and nonadherent polymorphonuclear leukocytes (PMNs) become activated to attain adhesive state in an integrin-dependent manner by various stimuli, and perform a variety of microbicidal functions such as phagocytosis and superoxide production. We found that, in the absence of serum, physiological concentration of hemopexin has a strong inhibitory action on Mg²⁺-dependent adhesion of PMA-activated PMNs to fibrinogen- and serum-coated surfaces. Under these conditions, Ca²⁺ had no effect on Mg²⁺-dependent adhesion or the adhesion-inhibitory activity of hemopexin. In contrast, PMNs suspended in serum containing sufficient amounts of hemopexin to inhibit adhesion showed marked adherence, which was inhibited by EGTA. Next, we prepared a small-molecule fraction of serum by ultrafiltration followed by boiling. PMA-activated PMNs was found to adhere in the presence of both hemopexin and the small-molecule fraction, and the adhesion was enhanced by exogenous Ca²⁺. EGTA abolished the effect of the small molecule fraction. The data suggest that serum contains adhesion-promoting factor(s) which allows PMNs to adhere despite the presence of hemopexin and that Ca²⁺ is required for adhesion-promoting activity. Further study of hemopexin may provide clues for new therapeutic strategies aimed at interfering with PMN adhesion to control inflammation and tissue injury.

585. Channelling of patients taking NSAIDs or cyclooxygenase-2-specific inhibitors and its effect on interpretation of outcomes
When new drugs with improved safety or efficacy are introduced, they may be preferentially prescribed to specific populations of patients. Safety and efficacy may be underestimated if such channeling effects are not recognized. Meloxicam and cyclooxygenase (COX)-2-specific inhibitors were developed as safer alternatives to non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis and rheumatoid arthritis. Studies of the use of meloxicam and COX-2-specific inhibitors demonstrate that both of these drugs are being prescribed to patients at increased risk of gastrointestinal adverse drug events. In the case of COX-2-specific inhibitors, this channeling appears to represent a prescribing pattern consistent with current recommendations. Subsequent analysis of the data, after adjusting for channeling bias, showed that the risk of gastrointestinal toxicity for meloxicam was similar to that for other NSAIDs, while COX-2-specific inhibitors reduced the risk of developing gastrointestinal adverse drug events by approximately 60%. These studies serve as examples of observed channeling bias and highlight the need for adjusting for channeling in order to provide a valid assessment of relevant outcomes for drugs likely to be preferentially prescribed to specific populations.


Cycooxygenase (COX)-2-specific inhibitors were developed to circumvent the gastrointestinal toxicity of non-specific non-steroidal anti-inflammatory drugs while maintaining efficacy. However, the higher acquisition cost of COX-2-specific inhibitors has resulted in the implementation of a programme for cost containment in the Ontario public drug program. This programme consists of limited use (LU) criteria that need to be met for drug reimbursement of patients with osteoarthritis (OA) or rheumatoid arthritis (RA). Determining the proportion of patients eligible for reimbursement for celecoxib according to the LU criteria (based on prior treatment failure and the presence or history of serious ulcer-related gastrointestinal complications) can provide an indication of the extent of adherence to suggested guidelines. Using a patient-based survey and an analysis of the Ontario Drug Benefit Program database, the proportion of patients prescribed celecoxib who met rigorous or pragmatic definitions of the LU criteria was determined. The extent of coprescription of gastroprotective agents among patients taking celecoxib was also determined. Using the pragmatic definition, the majority of patients in the patient survey (53% for OA and 81% for RA) met the LU criteria. Similarly, in the database analysis, the majority of patients (76% for OA and 78% for RA) met the LU criteria. These data suggest that physician prescribing of celecoxib is consistent with the LU criteria. Concomitant prescription of gastroprotective agents in patients taking celecoxib was approximately 40%. It is recommended that further investigations be performed to determine the long-term impact of LU criteria on clinical and economic outcomes, since these criteria may also serve to restrict use in patients who may benefit from taking COX-2-specific inhibitors.

587. Persistence of use of COX-2-specific inhibitors and non-specific non-steroidal anti-inflammatory drugs (NSAIDs) in Quebec - Moride Y., Dautret T., Rochon S. and Lavoie F. [Y. Moride, Faculty of Pharmacy, Université de Montréal, C.P. 6128 Succ. Centre-Ville, Montréal, Qué. H3T 3J7, Canada] - RHEUMATOLOGY (UK) 2003 42/3SUPPL. 3 (iii17-iii22) - sum in ENGL

The effectiveness of pharmacological therapies is dependent in part on patient persistency with the prescribed therapeutic regimen. In the case of non-specific non-steroidal anti-inflammatory drugs (NSAIDs), effectiveness is often compromised by undesirable side-effects, poor compliance or discontinuation of therapy. While patterns of utilization of non-specific NSAIDs have been investigated, few data are available on the patterns of persistency for cyclooxygenase (COX)-2-specific inhibitors. We used a provincial health-care system database in Quebec, Canada, to determine the duration of treatment in new users of COX-2-specific inhibitors and non-specific NSAIDs over the first 3 months of treatment, and to characterize the factors associated with treatment persistency. Results demonstrate that the median duration of treatment was longer among patients initially prescribed COX-2-specific inhibitors (30 days and 23 days for celecoxib or rofecoxib, respectively) than in those prescribed non-selective NSAIDs (10 days). Although the percentage of patients remaining on COX-2-specific drugs declined over the course of treatment, few patients on either celecoxib or rofecoxib switched drugs, either to the other COX-2-specific inhibitor or to non-specific NSAIDs. Factors associated with persistent drug use were: COX-2-specific inhibitors, age, and the use of gastroprotective agents either at treatment initiation or during follow-up. Dosage, chronic disease score and prescriber's specialty were only marginally associated with persistency. Prior use of gastroprotective agents was associated with lower persistency. Although the limitations of this study, which included lack of information on the indication for the prescription and the reason for switch or discontinuation, preclude definite conclusions regarding patterns of use of these drugs, the data suggest that the use of COX-2-specific inhibitors may result in increased persistency with treatment.

588. Inhibitory effects of anti-rheumatic agent T-614 on immunoglobulin production by cultured B cells and rheumatoid synovial tissues engrafted into SCID mice - Tanaka K., Yamamoto T., Akawa Y. et al. [K. Tanaka, Research Laboratories, Toyama Chemical Co. Ltd., Shimooku 2-4-1, Toyama 930-8508, Japan] - RHEUMATOLOGY (UK) 2003 42/11 (1365-1371) - sum in ENGL

Objective. To clarify the pharmacological action of an anti-rheumatic agent T-614, we investigated its effects on immunoglobulin (Ig) production by cultured B cells and Ig secretion from synovial tissues of patients with rheumatoid arthritis (RA) using SCID mice engrafted with human RA tissue (SCID-HuRAg). Methods. Murine B cells were prepared from murine spleen by a T-cell depletion method. The cells were cultured with lipopolysaccharide (LPS) and/or interleukin 4 (IL-4) in the absence or presence of T-614. Human B cells were isolated from peripheral blood of healthy donors and the Ig production was induced by co-culture with autologous T cells and anti-CD3 antibody. SCID-HuRAg was prepared according to our previous method. T-614 was orally administered to the mice once daily for 4 weeks starting on the fourth week after the implantation. Then, peripheral blood was obtained and the implanted tissues were removed. Igs in the culture media or the sera were determined by enzyme-linked immunosorbent assay (ELISA). Results. In murine B-cell cultures, T-614 significantly decreased not only the IgM production stimulated with LPS but IgG1 production induced by LPS and IL-4. Regarding human B cells stimulated with T cells, it also inhibited IgM and IgG production. In SCID-HuRAg mice, high concentrations of polyclonal human IgG were detectable in the sera of all mice. A significant decrease in the IgG1 level was observed in the T-614-treated group compared with the control group. Conclusions. We showed that T-614 inhibited Ig production by the cultured B cells and also decreased the high level of human IgG observed in SCID-HuRAg mice. T-614 may support its effect on plasma Ig in RA patients and provide insights into mechanisms of its anti-rheumatic effect.

589. The effects of Zintona EC (a ginger extract) on symptomatic gonarthrosis - Wigler I., Grotto L., Caspi D. and Yaron M. [Prof. M. Yaron, Department of Rheumatology, Tel Aviv Sourasky Medical Center, Weizmann Street 6, Tel Aviv 64239, Israel] - OSTEOARTHRITIS CARTILAGE 2003 11/1 (783-789) - sum in ENGL

Objective: Evaluation of the effect of a ginger extract (Zintona EC) on patients suffering from gonarthrosis. Material and methods: Twenty-nine patients (6 men and 23 women) with symptomatic gonarthrosis (ACR criteria), in the age range 42-85 years, were included after randomization in a double blind, placebo controlled, crossover study of 6 months duration. The treatment group was given a ginger extract (250 mg of Zingiberis Rhizoma per capsule, qid), while the placebo group received the same number of identical looking capsules per day. The crossover occurred after 3 months of therapy. Results were evaluated by a 100 mm visual analog scale (VAS) of pain on movement and of handicap. Results: Eight patients dropped out because of inefficacy, three from group
(ginger extract first) and five from group 2 (placebo first). One patient from group 1 and one from group 2 dropped out because of heartburn (while they were on ginger extract). Twenty patients completed the study period of 24 weeks and 19 of that 48 weeks follow-up. By the end of 24 weeks there was a highly statistically significant difference between the VAS of pain and handicap of the two groups (P<0.001). However, at crossover both groups showed a statistically significant decrease in VAS of pain on movement and of handicap, but the differences between the groups did not reach statistical significance. Conclusions: Zintona EC was as effective as placebo during the first 3 months of the study, but at the end of 6 months, 3 months after crossover, the ginger extract group showed a significant superiority over the placebo group. © 2003 OsteoArthritis Research Society International. Published by Elsevier Ltd. All rights reserved.


Objectives: To describe an in vivo model in the rat in which change in weight distribution is used as a measure of disease progression and efficacy of acetaminophen and two nonsteroidal anti-inflammatory drugs (NSAIDs) in a model of monosodium iodoacetate (MIA)-induced osteoarthritis (OA). Methods: Intrararticular injections of MIA and saline were administered to male Wistar rats (175-200 g) into the right and left knee joints, respectively. Changes in hind paw weight distribution between the right (osteoarthritic) and left (contralateral control) limbs were utilized as an index of joint discomfort. Acetaminophen and two archetypal, orally administered NSAIDs, naproxen and rofecoxib, were examined for their ability to decrease MIA-induced change in weight distribution. Results: A concentration-dependent increase in change in hind paw weight distribution was noted after intrarticular injection of MIA. Both naproxen and rofecoxib demonstrated the capacity to significantly (P<0.05) decrease hind paw weight distribution in a dose-dependent fashion, indicating that change in weight distribution associated with MIA injection is susceptible to pharmacological intervention. Conclusion: The determination of differences in hind paw weight distribution in the rat MIA model of OA is a technically straightforward, reproducible method that is predictive of the effects of anti-inflammatory and analgesic agents. This system may be useful for the discovery of novel pharmacologic agents in human OA. © 2003 © 2003 OsteoArthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

591. Effects of aspirin and indomethacin on endothelial cell proliferation in vitro - Hartwich R.D. and Brown N.J. [Dr. N. Kalia, Department of Biomedical Science, Alfred Denny Building, University of Sheffield, Western Bank, Sheffield S10 2TN, United Kingdom] - J. GASTROENTEROL. HEPATOOL. 2003 18/10 (1180-1187) - summ in ENGL.

Background and Aim: Non-steroidal anti-inflammatory drugs (NSAID) are associated with delayed peptic ulcer healing. ulcer healing is dependent on angiogenesis, which requires endothelial cell (EC) proliferation. The present study aimed to determine whether NSAID and prostaglandin E2 (PGE2) inhibited EC proliferation in vitro. Methods: Effects of 50 µM aspirin (10 µM-1 mM), indomethacin (10 µM-1 mM) and PGE2 (1 µM-0.1 mM) on the proliferation, viability and cell cycle of human dermal microvascular (HuDMEC) and human umbilical vein (HUVEC) EC were assessed using dual staining cell viability, 3-(4,5-dimethyl)-2-thiazolyl-2,5-diphenyl-2H-tetrazolium bromide and flow cytometry assays. Results: Proliferation of HuDMEC and HUVEC was significantly inhibited by 0.1 mM indomethacin, 1 mM aspirin and 100 µM PGE2, with a significant (P < 0.05) increase in EC necrosis with 1 mM indomethacin and 100 µM PGE2. No effects on cell cycle were demonstrated. Conclusions: High concentrations of NSAID inhibit both HuDMEC and HUVEC proliferation in vitro by cytotoxic (indomethacin) or cytostatic (aspirin and indomethacin) mechanisms. Interestingly, PGE2 was also antiproliferative. Inhibition of EC proliferation may prevent angiogenesis at the ulcer site, which may in part explain the delayed ulcer healing associated with NSAID. © 2003 Blackwell Publishing Asia Pty Ltd.


In this article, a flow system developed for the amperometric determination of a great variety of pharmaceuticals that are known to lead the rapid poisoning of the working electrode surface is described. The referred system was made of two parallel flow channels that shared the voltammetric detector of tubular configuration, whose movement in the manifold followed the concept of multi-site location of detector. In this way, after each measurement, the conditioning of the working electrode was possible through the passage by its surface of a regeneration solution without implying the alteration of the carrier that flowed in the analytical channel of the manifold. The methodology proposed was evaluated through the determination of two drugs belonging to two distinct therapeutic groups: an antihypertensive (diltiazem) and a non-steroid anti-inflammatory (nimesulide). The results obtained after evaluation of various pharmaceutical formulations of the Peconmuaceous were in the case of diltiazem compared with those supplied by the reference US Pharmacopoeia XXIV method, with no statistically significant differences having been observed for a confidence interval of 95%. This antihypertensive method exists, a series of recovery experiments were proceeded with and a mean value of 101.1% with a R.S.D. of 0.7% was obtained. © 2003 Elsevier B.V. All rights reserved.

593. Comparison of UV and tandem mass spectrometric detection for the high-performance liquid chromatographic determination of diclofenac in microdialysis samples - Mayer B.X., Namiranian K., Delghanyar P. et al. [B.X. Mayer, Department of Clinical Pharmacology, Div. of Clinical Pharmacokinetics, Vienna University School of Medicine, Währinger Gürtel 18-20, 1090 Vienna, Austria] - J. PHARM. BIOMED. ANAL. 2003 33/4 (745-754) - summ in ENGL.

High-performance liquid chromatography (HPLC) was used to analyze microdialysis samples obtained in vivo from human subcutaneous adipose tissue after topical application of the nonsteroidal anti-inflammatory drug diclofenac. For the reliable determination of diclofenac two different detection principles were applied in two different laboratories. One HPLC method utilized UV-detection at 280 nm, the other one used selected reaction monitoring mass spectrometry (MS). The HPLC-UV and -MS methods offered low limits of quantification of 10 and 1 ng/ml and an accuracy between 94.0-126.7 and 89.3-110.9%, respectively. However, a comparison showed that the HPLC-UV method failed to determine diclofenac in biological matrices, as both false negative and positive values were found. HPLC-MS is clearly superior to HPLC-UV due to a much more selective detection, increased sensitivity and shorter run times. © 2003 Elsevier B.V. All rights reserved.


In this study, 4-(5-chloro-2-(3H)-benzoazol-3-yl)butanoic acid and its ethyl ester as well as its ten new amide derivatives have been synthesized. Their structures have been elucidated by IR, 1H-NMR spectra and elemental analyses. The compounds were screened for antinociceptive and anti-inflammatory activities. The highest antinociceptive and anti-inflammatory activities were exhibited by Compound 11 which has carbocyclic acid structure. A various decrease in antinociceptive and anti-inflammatory activity was observed by amidation of the carboxylic acid moiety of this compound.

595. Receptor density dictates the behavior of a subset of steroid ligands in glucocorticoid receptor-mediated transrepression -
Zhao Q., Pang J., Furuta M.F. and Trzaskos J.M. [Q. Zhao, Department of Immunology, Bristol-Myers Squibb, Route 206 and Province Line Road, Princeton, NJ 08540, United States] - INT. IMMUNOPHARMACOL. 2003 3/13-14 (1803-1817) - sum in ENGL

By co-expressing glucocorticoid receptor (GR) and transcriptional reporter systems in GR-deficient Cos-7 cells, we profiled potency and efficacy of a panel of GR ligands as a function of GR expression levels (density). Our results show that potency and efficacy for GR full agonists, such as dexamethasone, in these transrepression assays are affected by receptor density. Intriguingly, receptor density dramatically influenced the behavior of the GR antagonist RU486 or the GR agonist medroxyprogesterone acetate (MPA). At high receptor density, both MPA and RU486 behaved as full agonists in transrepression: reducing GR density, however, resulted in conversion of these ligands from full agonist to full antagonists. In contrast, varying GR density could not convert cortisol and budesonide from GR agonists to antagonists. These results have clearly demonstrated, for the first time, an effect of receptor density on the agonist and antagonist properties of RU486 and MPA in GR-mediated transrepression. © 2003 Elsevier B.V. All rights reserved.

596. Effects of tramadol on synovial fluid concentrations of substances of interest and intensity of pain in patients with knee osteoarthritis: Comparison with paracetamol - Bianchi M., Brogmin M., Balzarini P. et al. [M. Bianchi, Department of Pharmacology, University of Milan, Via Vanvitelli, 32, 20129 Milano, Italy] - INT. IMMUNOPHARMACOL. 2003 3/13-14 (1901-1908) - sum in ENGL

Both the analgesic drugs tramadol and paracetamol are widely used for the symptomatic therapy of osteoarthritis (OA). The aim of this double-blind, randomised study in patients with knee OA was to compare their effects on synovial fluid concentrations of interleukin (IL)-6 and substance P (SP). Moreover, we evaluated plasma and synovial fluid concentrations of tramadol and its active metabolite (O-desmethyl-tramadol, M1) after oral treatment with this drug. Twenty patients were enrolled. A group of 10 patients received tramadol (50 mg three times a day), and another group of 10 patients was treated with paracetamol (500 mg three times a day) for 7 days. Both drugs significantly reduced the intensity of joint pain. The synovial fluid concentrations of SP were significantly reduced only by the treatment with tramadol. In this group of patients, IL-6 synovial fluid concentrations were slightly, but significantly, decreased. Paracetamol did not significantly change the synovial fluid concentrations of SP and IL-6. After oral administration, a considerable amount of tramadol was measurable in synovial fluid. Both in plasma and synovial fluid the concentrations of M1 were markedly lower than those of tramadol, with a T/M1 ratio of 14.7±4.6 and 9.3±3.9, respectively. These data demonstrate that the activity of tramadol may involve the modulation of inflammatory mediators. Moreover, they indicate that after oral treatment with tramadol, both the parent drug and its active metabolite can penetrate into synovial fluid. © 2003 Elsevier B.V. All rights reserved.


In this study, we have evaluated the efficacy of dosmalfate, a new flavonoid derivative compound, for the prevention and treatment of experimental colitis. To induce colitis, BALB/c mice received 5% dextran sulphate sodium (DSS) in their drinking water during 5-7 days. Colitis was quantified by a clinical damage score, colon length, weight loss, stool consistency and rectal bleeding. Inflammatory response was assessed by neutrophil infiltration, determined by histology and myeloperoxidase (MPO)-activity. Interleukin (IL)-1β, pro-inflammatory (PG)E2 and (PG)D2 concentrations in colonic tissue, histological and histochemical analysis of the lesions were also measured. Dosmalfate (400-800 mg/kg body weight, p.o.) ameliorated severe colitis reduced the degree of inflammation through reduction of neutrophil infiltration and IL-1β/1-6 levels. (PG)E2 and (PG)D2 synthesis were significantly reduced in colitis control group and treatment with dosmalfate abolished the decrease in PG synthesis in colon mucosa. We conclude that dosmalfate is protective in acute DSS-induced colitis. The beneficial effects seem to be related to a decrease of neutrophil infiltration, absence of up-regulation of IL-1β and increase of PG production in colon mucosa. © 2003 Published by Elsevier B.V.

598. Monegatone furoate degradation and metabolism in human biological fluids and tissues - Teng X.W., Cutler D.J. and Davies N.M. [N.M. Davies, Dept. of Pharmaceutical Sciences, College of Pharmacy, Washington State University, PO Box 646534, Pullman, WA 99164-6534, United States] - BIOPHARM. DRUG DISPOS. 2003 24/8 (321-333) - sum in ENGL

The in vitro metabolic and non-metabolic degradation kinetics of monegatone furoate (MF) was investigated in selected human biological fluids and subcellular fractions of tissues. Qualitative and quantitative differences in transformation profiles of MF were observed among human biological media. Degradation was the major event in plasma and urine with four new degradation products identified; A: 17-(2-furoate)-, B: 9α, 21β-dichloro-11β, 23α-dihydroxy-16α-methylpregna-1,4,17,20-tetraen-3-one-21 (2-furoate), C: 21β-chloro-23α-hydroxy-16α-methyl-9α,11β-oxidoepropregna-1,4,17,20-tetraen-3-one-21 (2-furoate), and D: 21-β-hydroxy-16α-methyl-9α,11β-oxidoepropregna-1,4-diene-3,20-dione. A, B and C were predominant and D was minor in plasma while A and C were predominant in urine. Hydrolysis of the 17-ester bond of MF was not a major event in plasma. The turnover of MF in plasma was faster than that in phosphate buffers of pH 7.4. Metabolism of MF occurred primarily and rapidly in liver, appreciably in intestine, but negligibly in in vitro lung tissue. While 6β-hydroxylation was a major metabolic pathway for MF in microsomes of both human liver and intestine, other parallel and subsequent metabolism pathways could also be involved. If these degradation and metabolic products are also formed and active in humans in vivo, both MF and its 'active' products need to be taken into account when determining the systemic bioavailability of MF and in establishing concentration-effect relationships with this drug. Copyright © 2003 John Wiley & Sons, Ltd.
is intended to be an antagonist of LPS to reduce the morbidity and mortality associated with sepsis syndrome. This study assessed the pharmacokinetics (PK) of ES564 in patients with impaired hepatic function. ES564 was administered via intermittent intravenous infusion every 12 hours for six times to 24 hepatic-impaired patients (12 each to Child-Pugh Classifications A and B) and 24 matching healthy volunteers. Plasma samples were analyzed by LC/MS/MS. A one-compartment model resulted in good and comparable fits for all volunteers. Regardless of liver disease state, none of the PK parameters compared (i.e., Cmax, CL, t1/2, V, AUC (0-24), AUC(0-∞), Cmax, C0, and Css) exhibited any difference between these two groups. This suggested that the exposure of ES564 in volunteers was independent of hepatic function. Thus, no dose adjustment is needed in patients with hepatic impairment classified as Child-Pugh A and B.

601. Different in vitro activity of flurbiprofen and its enantiomers on human articular cartilage – Panico A.M., Cardile V., Vittorio F. et al. [A.M. Panico, Dept. of Pharmacological Sciences, Faculty of Pharmacy, University of Catania, Via A. Doria 6, 95125 Catania, Italy] - FARMACO 2003 58/12 (1339-1344) - sumin in ENGL

The 2-arylpicolonic acid derivatives or ‘proﬁrns’ are an important group of non-steroidal anti-inﬂammatory drugs that have been used for the symptomatic treatment of various forms of arthritis. These compounds are chiral and the majority of them are still marketed as racemate although it is known that the (S)- form is the principal effective in the cyclooxygenase inhibition. However, recent findings suggest that certain pharmacological effect of 2-arylpicolonic acids cannot be attributed exclusively to the (S)-(+)-enantiomer. To obtain further insights into the pharmacological effect of proﬁrns, the present study investigated the in vitro activity of racemic and pure enantiomers of flurbiprofen on the production of nitric oxide and glycosaminoglycans, key molecules involved in cartilage destruction. The human culture of articular cartilage stimulated with interleukin-1/3 (IL-1/3), which plays an important role in the degradation of cartilage, has been established, as a pro-inﬂammatory model, for reproducing the mechanisms involved in the pathophysiology of arthritic diseases. Our results show that mainly (S)-(+)-flurbiprofen decreases, at therapeutic concentrations, the IL-1β-induced cartilage destruction. © 2003 Elsevier SAS. All rights reserved.

602. Colchicine induces membrane-associated activation of matrix metalloproteinases-2 in osteosarcoma cells in an S100A4-dependent manner – Loennechen T., Mathisen B., Hansen J. et al. [J.-O. Winberg, Department of Biochemistry, Institute of Medical Biology, University of Tromso, 9037 Tromso, Norway] - BIOCHIM. BIOPHYS. ACTA 2003 1662/1 (2341-2355) - sumin in ENGL

Like the metastasis-associated protein S100A4, matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are important in physiological and pathological conditions. Previously, we showed that S100A4 is involved in the regulation of MMPs and TIMPs, and in the present work we have investigated whether the anti-inﬂammatory and microtubule-disrupting drug colchicine has an effect on the expression of these proteins in osteosarcoma cell lines (OS) with high and low levels of S100A4. Colchicine treatment of the various OS cells resulted in an increased expression of MT1-MMP and TIMP-2 mRNA, and a corresponding increase of these two proteins in isolated cell membranes. Colchicine-treated cells produced more of the activated form of MMP-2 than control cells. However, the drug did not affect the amount of MMP-2 and TIMP-1 mRNA or protein, and it reduced the S100A4 mRNA expression. Isolated cell membranes from the colchicine-treated cells were more effective in activating exogenous proMMP-2 than membranes from control cells, and inhibitory studies indicated that it was the colchicine-induced increase in MT1-MMP that caused the increased activation of endogenous MMP-2. A peptide inhibitor of nuclear factor-β nuclear translocation, SN50, blocked the colchicine-induced activation of proMMP-2 and reduced the synthesis of MMP-2 in colchicine-treated cells, but not in control cells. It can be concluded that colchicine modulates the expression of MT1-MMP and TIMP-2 and hence the activation of proMMP-2 independently of the S100A4 level in osteosarcoma cells. © 2003 Elsevier Inc. All rights reserved.

603. Ameliorative effects of sodium ferulate on experimental colitis and their mechanisms in rats - Dong W.-G., Lu S.-Y., Yu B.-P. et al. [W. Dong, Department of Gastroenterology, Renmin Hospital, Wuhan University, 238 Jiefang Road, Wuhan 430060, Hubei Province, China] - WORLD J. GASTROENTEROL. 2003 9/11 (2533-2538) - sumin in ENGL

AIM: To investigate the ameliorative effects of sodium ferulate (SF) on acetic acid-induced colitis and their mechanisms in rats. METHODS: The colitis model of Sprague-Dawley rats was induced by intracolon enema with 8 % (V/V) of acetic acid. The experimental animals were randomly divided into model control, 5-aminosalicicylic acid therapy group and three dose of SF therapy groups. The 5 groups were treated intracolonically with normal saline, 5-aminosalicylic acid (100 mg.kg-1), and SF at the doses of 400 mg.kg-1, 800 mg.kg-1 respectively and daily (8: 00 am) for 7 days 24 h following the induction of colitis. A normal control group of rats custered with normal saline instead of acetic acid was also included in the study. Pathological changes of the colonic mucosa were evaluated by the colon mucosa damage index (CMDI) and the histopathological score (HS). The insulted colonic mucosa was sampled for a variety of determinations at the end of experiment when the animals were sacriﬁced. Colonic activities of myeloperoxidase (MPO) and superoxide dismutase (SOD), and levels of malondialdehyde (MDA) and nitric oxide (NO) were assessed with ultraviolet spectrophotometry. Colonic contents of prostaglandin E2 (PGE2) and thromboxane B2 (TXB2) were determined by radioimmunoassay. The expressions of inducible nitric oxide synthase (iNOS), cyclo-oxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB) p65 in the colonic tissue were detected with immunohistochemistry.

RESULTS: Enhanced colonic mucosal injury, inﬂammatory response and oxidative stress were observed in the animals clystered with acetic acid, which manifested as the significant increase of CMDI, HS, MPO activities, MDA and NO levels, PGE2 and TXB2 contents, as well as the expressions of iNOS, COX-2, NF-κB p65 proteins in the colonic mucosa, although the colonic SOD activity was signiﬁcantly decreased compared with the normal control (CMDI: 2.9±0.6 vs 0.0±0.0; HS: 4.3±0.9 vs 0.7±0.1; MPO: 98.1±26.9 vs 24.8±11.5; MDA: 57.5±13.26 vs 9.21±3.15; NO: 0.33±0.092 vs 0.176±0.045; PGE2: 186.2±96.2 vs 42.8±32.8; TXB2: 34.26±13.51 vs 8.83±3.75; INOS: 0.36±0.026 vs 0.053±0.015; COX-2: 0.296±0.028 vs 0.034±0.013; NF-κB p65: 0.314±0.026 vs 0.039±0.012; SOD: 28.33±1.17 vs 36.14±1.91; P<0.01). However, these parameters were found to be signiﬁcantly ameliorated in rats treated locally with SF at the given dose protocols, especially at 400 mg.kg-1 and 800 mg.kg-1 doses (CMDI: 1.8±0.6, 1.6±0.9; HS: 3.3±0.9, 3.1±0.9; MPO: 63.8±30.5, 36.2±14.2; MDA: 41.8±10.62, 37.3±4.88; NO: 0.247±0.042, 0.216±0.033; PGE2: 77.2±26.9, 58.4±23.9; TXB2: 18.0±7.14; 15.52±8.62; INOS:0.175±0.018, 0.106±0.019; COX-2: 0.064±0.018,0.036±0.014; NF-κB: 0.215±0.019, 0.189±0.028; P<0.01). Moreover, a therapeutic dose protocol of 800 mg.kg-1 SF was observed as effective as 100 mg.kg-1 of 5-ASA in the amelioration of colonic mucosal injury as evaluated by CMDI and HS. CONCLUSION: Administration of SF intracolonically may have important therapeutic effects on the rat model of colitis induced by acetic acid enema, which was probably due to the mechanism of antioxidation, inhibition of arachidonic acid metabolism and NF-κB expression.

604. Thalidomide inhibits UVB-induced mouse keratinocyte apoptosis by both TNF-α-dependent and TNF-α-independent pathways - Lu K.Q., Brenneman S., Burns Jr. R. et al. [Dr. A. Gaspari, Department of Dermatology, Univ. of Maryland School of Medicine, 405 W. Redwood St., Baltimore, MD 21201, United States] - PHOTODERMATOL. PHOTOMED. 2003 19/6 (272-280) - sumin in ENGL

Background: Thalidomide is an anti-inflammatory pharmacologic agent that has been utilized as a therapy for a number of dermatologic diseases. Its anti-inflammatory properties have been attributed to its ability to antagonize tumor necrosis factor alpha (TNFα) production by monocytes. However, its mechanism of
action in the skin is not known. Purpose: To test our hypothesis that thalidomide may antagonize TNF-α production in the skin, we used a mouse model for acute ultraviolet-B (UVB) exposure, a known stimulus for inducing this cytokine. Results: A single bolus dose of thalidomide (either 100 or 400 mg/kg) given immediately before UVB exposure (40-120 mJ/cm²) inhibited, in a dose-dependent manner, sunburn cell formation (i.e. keratinocyte (KC) apoptosis as defined by histologic appearance and confirmed by terminal deoxynucleotidyl transferase mediated biotinylated dUTP nick end labelling staining) in mouse skin biopsy specimens. However, this agent did not affect the formation of cyclobutane pyrimidine dimers, a measure of UVB-induced DNA damage, which is an early event associated with apoptosis. RNAse protection assays confirmed that high (400 mg/kg), but not low (100mg/kg), doses of thalidomide inhibited the UVB-induced increase in steady-state TNF-α mRNA. Additionally, in our in vitro data using neonatal mouse KCs showed that thalidomide prevented UVB-induced cell death (TUNEL assay). The antipapoptotic effects of thalidomide can be reversed by the addition of exogenous recombinant mouse TNF-α and hence reconstituting UVB-induced programmed cell death. The inhibition of sunburn cell formation by low-dose thalidomide in the absence of TNF-α inhibition suggests that other, unidentified mechanisms of apoptosis inhibition are active. Conclusions: These data suggest that the anti-inflammatory effects of thalidomide can affect UVB injury, and may, in part, explain its action in photosensitivity diseases such as cutaneous lupus erythematosus.

605. Design of PEGylated soluble tumor necrosis factor receptor type I (PEG-sTNF-R1) for chronic inflammatory diseases - Edwards III C.K., Martin S.W., Seely J. et al. [Dr. C.K. Edwards III, RBA Dermatology U.S.A., Berlex Biosciences, Richmond, CA 94804, United States] - ADV.DUG.DEVI REV. 2003 55/10 (1315-1336) - sumin in ENG.

A recombinant C-terminal truncated form of the human soluble tumor necrosis factor receptor type I (sTNF-R1) was produced in E. coli. This soluble receptor contains the first 2.6 of the 4 domains of the intact sTNF-R1 molecule. A monopeGylated form of this molecule was produced using a 30 kD methoxyPEG aldehyde with approximately 85% selectivity for the N-terminal amine group.

This molecule was shown to be less immunogenic in primates than the full length (4.0 domain) molecule or other versions of sTNF-R1 which were either PEGylated at different sites or with different molecular weight PEGs. The 30 kD PEG also has a longer serum half-life to the molecule than lower molecular weight PEGs. This molecule markedly blunts the inflammatory response in a number of rheumatoid arthritis animal models. In addition, phase I/II and early phase II data in humans indicate that PEG-sTNF-R1 is non-immunogenic and that weekly dosing with this drug can reduce the number of tender and swollen joints in rheumatoid arthritis patients. PEG sTNF-R1 has comparable American College of Rheumatology (ACR) efficacy scores as other anti-TNF molecules currently used to treat rheumatoid arthritis patients. © 2003 Elsevier B.V. All rights reserved.

606. Thiophenes and furans derivatives: A new class of potential pharmaceutical agents - Meotti F.C., Silva D.O., Dos Santos A.R.S. et al. [C.W. Nogueira, Departamento de Quimica, Centro de Ciencias Naturais e Exatas, Universidade Federal de Santa Maria, Santa Maria, CEP-97105-900, RS, Brazil] - ENVIRON. TOXICOL. PHARMACOL. 2003 15/1 (37-44) - sumin in ENGL.

A new class of potential pharmacological thiophenes and furans compounds has been prepared. The obtained thiophenes and furans derivatives were screened for anti-inflammatory, antinociceptive and antioxidant activity in rats. In vitro hepatic ALA-D activity was also evaluated. Thiophene 2 exhibited higher anti-inflammatory effect than thiophenes 1 and 3. However, compound 1 demonstrated a lower IC₅₀ for lipid peroxidation than 2 and 3 in liver and brain. Furans compounds 4-6 presented similar anti-inflammatory activity. The acetylenic furans 4 and 5 inhibited scarcely lipid peroxidation at low concentration as 10 μM. Conversely, furan compound 6 was the most effective against lipid peroxidation in liver. Furans 4 and 5 inhibited lipid peroxidation, in brain, only in high concentrations. In contrast, furan 6 protected (90%) against lipid peroxidation at 10 μM. Thiophene 1 was devoid of anti-inflammatory activity but was efficient in reducing acetic acid-induced constriction. Conversely, it analogue furan 4 presented anti-inflammatory and antinociceptive activity. Thioephene and furan inhibited hepatic ALA-D only at high concentrations. All compounds displayed antioxidant activity however the anti-inflammatory activity is not related to antioxidant potential. © 2003 Elsevier B.V. All rights reserved.

See also: 703, 714, 729.

6.4. Antineoplastic agents

607. Characterization of cell death induced by ethacrynic acid in a human colon cancer cell line DLD-1 and suppression by N-acetyl-L-cysteine - Aizawa S., Oookawa K., Kudo T. et al. [S. Tsuichi, Second Department of BPR, Okayama Univ. School of Medicine, 5 Zaizufu, Hiroaki, Aomori 036-8562, Japan] - CANCER SCI. 2003 94/10 (886-893) - sumin in ENG.

Since ethacrynic acid (EA), an SH modifer as well as glutathione S-transferase (GST) inhibitor, has been suggested to induce apoptosis in some cell lines, its effects on a human colon cancer cell line DLD-1 were examined. EA enhanced cell proliferation at 20-40 μM, while it caused cell death at 60 μM. GST inhibitors did not block cell death and DNA ladder formation was not detected. Poly(ADP-ribose) polymerase, however, was cleaved into an 82-kDa fragment, different from an 85-kDa fragment that is specific for apoptosis. The 82-kDa fragment was not recognized by antibody against PARP fragment cleaved by caspase 3. N-Acetyl-L-cysteine (NAC) completely inhibited EA-induced cell death, but 3(2)-butyl-4-hydroxyanisole or pyrroliodinedithio-carbamate ammonium salt did not. Glutathione (GSH) levels were dose-dependently increased in cells treated with EA and this increase was hardly affected by NAC addition. Mitogen-activated protein kinase (MAPK) kinase (MEK1), extracellular signal-regulated kinase (ERK1) and GST P1-1 were increased in cells treated with 25-75 μM EA, while c-Jun N-terminal kinase (JNK1) and p38 MAPK were markedly decreased by 100 μM EA. NAC repressed EA-induced alterations in these MAPKs and GST P1-1. p38 MAPK inhibitors, SB203580 and FR167653, dose-dependently enhanced EA-induced cell death. An MEK inhibitor, U0126, did not affect EA-induced cell death. These studies revealed that EA induced cell death concomitantly with a novel BAPF fragmentation, but without DNA fragmentation. p38 MAPK was suggested to play an inhibitory role in EA-induced cell death.


Fenretinide (N-4-hydroxyphenylretinamide [4-HPR]) is a synthetic retinoid that has been examined in in vitro assays, preclinical animal models and clinical trials as a cancer chemopreventive agent. Its pharmacology, toxicity and mechanisms of action initially suggested an increased therapeutic index relative to native retinoids for the control of tumours of the breast, prostate, bladder, colon, cervix and head and neck. Although fenretinide at the doses and schedules used in several pivotal Phase II and III clinical trials has not proven to be efficacious in reducing the incidence of cancer or in retarding the development of preneoplastic lesions, encouraging observations regarding unanticipated preventative activity, such as for ovarian cancer control, have arisen from these studies. Research in cancer therapy and the elucidation of molecular pathways activated by fenretinide have also yielded clues about how this agent might be better used in a preclinical setting. Current trials are underwarp to re-examine both dose and schedule of fenretinide administration as well as the target tissues of interest. Investigations of potential synergism between fenretinide and other candidate chemopreventive molecules with complementary mechanisms of action may support future assessments of this prototype cancer prevention drug or its newer analogues.

609. Preclinical and clinical results with the natural marine product ET-743 - D'Incalci M. and Jimeno J. [M. D'Incalci, Department of Oncology, Ist. Ric. Farmacologiche Mario Negri, Via
ET-743 is a unique property of ET-743 and is of potential importance for the drug activity when administered alone or in combination with other drugs. ET-743 showed striking antitumour activity against sensitive and resistant human xenografts. The dose-limiting toxicities in animal models, hepatobiliary events, were of concern, but the pattern of the reversibility noted in monkeys and the evidence of a positive therapeutic index in tumour-bearing nude mice prompted its clinical development. The Phase I programme investigated different schedules of administration, with the dose-limiting toxicities being neutropenia and fatigue. As anticipated in the preclinical models, reversible non-cumulative transaminitis was a prevalent finding from one-third of the maximum tolerated dose level; long-lasting objective responses in pretreated resistant patients were noted, including consistent efficacy data in mesenchymal tumours. The Phase II data for ET-743 administered as a single agent has established a clinical role for the compound in advanced pretreated soft tissue sarcoma and a promising potential in pretreated ovarian and breast cancer. ET-743 combined with other drugs (i.e., cisplatin, paclitaxel or doxorubicin) showed more than additive effects in several preclinical systems and initial clinical results (e.g., a combination of ET-743 with cisplatin) appear to confirm the preclinical findings. In summary, ET-743 is a new drug with a novel mode of action, which has demonstrated activity in human tumours resistant to the available anticancer drugs. Further comparative studies are needed to define the role of ET-743 alone or in combination in cancer chemotherapy.


ET-743 (Yondelis™, trabectedin) is a natural marine product with antitumour properties derived from the tunicate Ecteinascidia turbinate. ET-743 binds to the N2 position of guanine in the minor groove of DNA, with some degree of sequence specificity, altering the transcription regulation of induced genes. Cells that are deficient in nucleotide excision repair, hypersensitive to UV rays, cisplatin and conventional alkylating agents, are resistant to ET-743. The synthesized 1,4-dihydropyridines were subjected to various chemical and biological investigations to evaluate their ability to cross the blood-brain barrier (BBB). The synthesized 1,4-dihydropyridine ammonium salt type redox system is described as a general and flexible method for site-specific and sustained delivery of drugs to the brain. This concept was used in the present investigation as a model to deliver an alkylating antitumour agent into the brain. A bis-chloroethylamine drug was hooked to 1,4-dihydropyridine chemical delivery system (CDS) through an amide linkage. Five new target compounds (23-27) of the 1,4-dihydropyridine CDS type were synthesized through the reduction of five new pyridinium quaternary intermediates (18-22). The synthesized 1,4-dihydropyridines were subjected to various chemical and biological investigations to evaluate their ability to cross the blood-brain barrier (BBB), and to be oxidized biologically into their corresponding quaternary compounds.

The in vitro oxidation studies showed that 1-benzyl-3-[(N-[2-bis-2-chloroethyl]aminoethyl)]-1,4-dihydropyridine (23) and 1-[(4-nitrobenzyl)-3-[(N-[2-bis-2-chloroethyl]aminoethyl)]-1,4-dihydropyridine (27) could be oxidized into their corresponding quaternary compounds 18 and 22, respectively, at an adequate rate, which ensure the release of the carried anticancer drug. In vivo studies showed that compound 23 was able to cross the BBB at detectable concentrations. On the other hand, the in vitro alkylation activity studies revealed that 1-[(4-nitrobenzyl)-3-[(N-[2-bis-2-chloroethyl]aminoethyl)]-1,4-dihydropyridine bromide (22) is an alkylating agent with activity comparable to the known drug chlorambucil.

611. Bisphosphonate Actions on Cancer - Yoneda T., Hashimoto N. and Hiraga T. - CALCH. TISSUE INT. 2003 73/4 (315-318) - sum in ENGL

Bisphosphonates (BPs) suppress cancer cell colonization in bone associated with cancers such as breast cancer and multiple myeloma. The mechanism of the suppressive action of BPs is thought to be due to an inhibition of osteoclastic bone resorption which releases bone-resorptive growth factors that feed cancer cells colonizing bone. Recently, data are accumulating that BP suppresses growth and induces apoptosis in cancer cells in culture, suggesting that BP directly influences survival of cancer cells in an osteoclast-independent manner. These results raise the possibility that BP inhibits cancer cell viability in an osteoclast-independent manner. However, evidence is limited that BP reduces tumor growth in non-bone sites in cancer patients. In this review, we discuss the effectiveness of BP on breast cancer colonization in non-bone sites and our results in animal models with metastases. With currently available clinical and in vivo experimental data, BPs are definitely beneficial for the treatment of cancer patients who manifest clinically detectable bone metastases. However, it is not recommended that BP be given as a preventative to patients with visceral metastases and of no evidence of bone metastases. Whether individual BP with different chemical structure has unique biological or biochemical action is an intriguing question but open at the moment.

612. Use of mathematical derivatives (time-domain differentiation) on chromatographic data to enhance the detection and quantification of an unknown 'riders' peak - Ford S.J., Elliott M.A. and Halbert G.W. (S.J. For Cancer Research Centre, Dept. of Pharmaceutical Formulation Unit, Dept. of Pharmaceutical Sciences, University of Strathclyde, 204 George Street, Glasgow, G1 1XW, United Kingdom) - J. PHARM. BIOMED. ANAL. 2003 33/4 (563-570) - sum in ENGL

Two samples of an anticancer prodrug, AQN4, were submitted for HPLC assay and showed an unidentified impurity that eluted as a 'rider' on the tail of the main peak. Mathematical differentiation of the chromatograms offered several advantages over conventional skinned integration. A combination of the second derivative amplitude and simple linear regression gave a novel method for estimating the true peak area of the impurity peak. All the calculation steps were carried out using a widely available spreadsheet program. © 2003 Elsevier B.V. All rights reserved.

613. Growth factor receptor tyrosine kinase inhibitors: clinical development and potential for prostate cancer therapy - Blackledge G., Sellers W.R. and Smith M.R. [Dr. G. Blackledge, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom] - J. UROL. 2003 170/6 II (S77-S83) - sum in ENGL

Purpose: The development of effective, novel, targeted cancer therapies with minimal side effects has long been a goal in cancer research. A key group of targets identified for drug development consists of the receptor tyrosine kinases, which have pivotal roles in the growth factor signaling that is subverted in carcinogenesis and in the host processes, such as angiogenesis, involved in tumor progression. Materials and Methods: A literature review of the role of receptor tyrosine kinases in human malignancies is followed by a discussion of the potential use of inhibitors of receptor tyrosine kinases as anticancer therapy, focusing on the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa, ZD1839, AstraZeneca, Macclesfield, United Kingdom). Results: Several small molecule inhibitors that are specific to individual receptor tyrosine kinases have been developed and a number of these potential anticancer agents are progressing through clinical trials. Various surrogate end points are being assessed to demonstrate the activity of these inhibitors against their targets. Results from studies of gefitinib alone and with the antiandrogen bicalutamide in both hormone dependent and independent prostate xenografts suggested that gefitinib may have potential as monotherapy and combination therapy in the treatment of both forms of the disease. Gefitinib is currently undergoing further preclinical and clinical evaluation for the treatment of prostate cancer. Conclusions: A number of tyrosine kinase inhibitors, including gefitinib, are progressing through clinical development and are beginning to provide new treatment options for a range of malignancies.

614. Apoptosis-mediated selective killing of malignant cells by cardiac steroids: Maintenance of cytotoxicity and loss of cardiac activity of chemically modified derivatives - Daniel D., Sasai C., Kopp B. et al. [C. Sasai, Dept. of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Im Neuenheimer
We analyzed the cytotoxic effect of six steroids belonging to the bufadienolide family on malignant T lymphoblasts and normal peripheral blood mononuclear cells (PBMC). One compound, derivative X of a new cardioactive steroid, was a natural bufadienolide glycoside (hellebrin) with cardiac activity. The other five compounds were chemically modified derivatives that did not contain cardioactive groups. We found that these steroids were able to cause time-dependent apoptosis in Jurkat T lymphoblasts, whereas they only minimally affected PBMC. Preferential killing of malignant cells was induced by the natural cardiac substance hellebrin and by three of the five chemically modified non-cardioactive derivatives. The substances caused mitochondrial transmembrane potential disruption and internucleosomal DNA fragmentation in tumor cells. The cytoplasmic and nuclear events of bufadienolide-induced apoptosis were strongly inhibited in the presence of caspase 8, caspase 9, or caspase 3 inhibitors, as well as in the presence of the broad-spectrum caspase inhibitor Z-VAD-FMK. Overexpression of Bcl-2 significantly protected bufadienolide-treated cells from phosphatidylinerse translocation, transmembrane potential disruption, and internucleosomal DNA fragmentation. Our results show that the antitumor activity of bufadienolides is linked to the known human lymphoblasts by initiating apoptosis via the classical caspase-dependent pathway. Apoptosis-inducing agents specific for tumor cells might be ideal anti-tumor drugs. The therapeutic use of bufadienolides and nuclear events of bufadienolide-induced apoptosis may provide new ways of inducing tumor-specific cytotoxicity and apoptosis, thus aiding cancer chemotherapy. © 2003 Elsevier Ltd. All rights reserved.

615. Classification of anticaner drugs - A new system based on therapeutic targets - Espinosa E., Zamora P., Feili J. and González Barón M. [E. Espinosa, Servicio de Oncologia Medica, Hospital La Paz, Po de la Castellana, 28046 Madrid, Spain] - CANCER TREAT. REV. 2003 29/6 (515-523) - summ in ENGL

The arrival of a great number of new antineoplastic agents has made it necessary to reclassify all of them. Anticancer drugs may act at different levels: cancer cells, endothelium, extracellular matrix, the immune system or host cells. The tumour cell can be targeted at the DNA, RNA or protein level. Most classical chemotherapeutic agents interact with tumour DNA, whereas monoclonal antibodies and small molecules are directed against proteins. The endothelium and extracellular matrix may be affected also by specific antibodies and small molecules. © 2003 Elsevier Ltd. All rights reserved.

616. Oesophageal cancer: New developments in systemic therapy - Iason D.H. [Dr. D.H. Iason, Gastrointestinal Oncology Service, Department of Medicine, Mem. Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10011, United States] - CANCER TREAT. REV. 2003 29/6 (525-532) - summ in ENGL

Oesophageal cancer is a rare but highly virulent malignancy in the United States and Western countries, and adenocarcinoma of the oesophagus has seen the most rapid rate of increase of any solid tumour malignancy. Systemic metastatic disease is present in 50% of patients at diagnosis, and in the remaining 50% of patients presenting initially with loco-regional disease, systemic metastatic disease will develop in the vast majority of these patients. Combined chemotherapy and radiotherapy is the standard of care in the nonsurgical management of oesophageal cancer. Preoperative chemoradiotherapy followed by surgery continues to be actively studied in the surgical management of locally advanced oesophageal cancer. Pathologic complete responses are seen in 20-40% of patients, with five-year survival achieved in 25-35% of patients. The limited efficacy of convenional chemotherapeutic agents, which have a modest effect on the majority of patients, has led to the development of novel therapies. Novel therapeutic strategies include the use of biologically targeted therapies, with the aim of altering the complex biology of solid tumour development. Although recent advances in understanding of intracellular pH have been shown to be critically important for many cellular functions, pH regulation has not been fully investigated in the field of cancer. It has, however, been shown that cellular pH is crucial for biological functions such as cell proliferation, invasion and metastasis, drug resistance and apoptosis. Hypoxic conditions are often observed during the development of solid tumours and lead to intracellular and extracellular acidosis. Cellular acidosis has been shown to be a trigger in the early phase of apoptosis and leads to activation of endonucleases inducing DNA fragmentation. To avoid intracellular acidification under such conditions, pH regulators are thought to be up-regulated in tumour cells. Four major types of pH regulator have been identified: the proton pump, the sodium-proton exchanger family (NHE), the bicarbonate transporter family (BCT) and the monocarboxylate transporter family (MCT). Here, we describe the structure and function of pH regulators expressed in tumour tissue. Understanding pH regulation in tumour cells may provide new ways of inducing tumour-specific apoptosis, thus aiding cancer therapy. © 2003 Elsevier Ltd. All rights reserved.

618. HA1A-1 selectively induces apoptosis in Bcl-2-overexpressing leukemia/lymphoma cells, and enhances cytarabine-induced cell death - Lickliter J.D., Wood N.J., Johnson L. et al. [Dr. J.D. Lickliter, Queensland Inst. of Medical Research, Royal Brisbane Hospital, Post Office, Herston, QLD 4006, Australia] - LEUKEMIA 2003 17/11 (2074-2080) - summ in ENGL

The Bcl-2 oncprotein is commonly overexpressed in hematopoietic malignancy, where it promotes the survival of neoplastic cells. Recently, a small molecule (HA14-1) was reported to bind the surface pocket of Bcl-2 that mediates antiapoptotic interactions, triggering apoptosis in a Bcl-2-transfected cell line. We investigated the activity of this compound in a panel of malignant hematopoietic cell lines. Consistent with its proposed role as a Bcl-2 inhibitor, HA14-1 was most cytotoxic in lines expressing high levels of Bcl-2. In addition, at lower concentrations (5-12.5 μM), the compound predominantly triggered apoptosis. However, at concentrations two-fold higher than this and above, increasing primary necrosis was observed, suggesting the onset of interactions supplementary to Bcl-2 inhibition. In experiments on primary cells, 2.5 μM HA14-1 induced extensive apoptosis in acute leukemic blasts, but also suppressed normal hematopoietic colony formation to <50% of baseline. Importantly, low-concentration HA14-1 (5 μM) was nontoxic to normal colony-forming cells, whereas it enhanced the cytotoxicity of the antileukemia drug cytarabine in Bcl-2-positive lymphoblastic leukemia cells. In conclusion, our results indicate that HA14-1 at low concentration selectively triggers apoptosis in malignant hematopoietic cells that over-express Bcl-2. Agents of this class may have particular utility in combination with cytotoxic chemotherapy drugs.

619. Regulation and targeting of antiapoptotic XIAP in acute myeloid leukemia - Carter B.Z., Milella M., Tsoo T. et al. [Dr. M. Andreeff, Sect. of Molec. Hematology/Therapy, The University of Texas, MD Anderson Cancer Ctr., 1515 Holcombe Boulevard, Houston, TX 77030, United States] - LEUKEMIA 2003 17/11 (2081-2089) - summ in ENGL

XIAP is a member of the inhibitors-of-apoptosis family of proteins, which inhibit caspases and block cell death, with prognostic importance in AML. Here we demonstrate that cytokines regulate the expression of XIAP in leukemic cell lines and primary AML blasts. Inhibition of phosphatidylinositol-3 kinase (PI3K) with LY294002 and of the mitogen-activated protein kinase (MAPK) receptor kinase cascade by PD098059 resulted in decreased XIAP levels (34±8 and 23±5.7%, respectively). We then generated OCI-AML3 cells
with constitutively phosphorylated Akt (p473-Akt) by retroviral gene transfer. Neither these nor Akt inhibitor-treated OCl-AML3 cells showed changes in XIP levels, suggesting that XIP expression is regulated by PI3K downstream effectors other than Akt. The induction of XIP expression by cytokines through PI3K/MAPK pathways is consistent with its role in cell survival. Exposure of leukemia cells to chemotherapeutic agents decreased XIP protein levels by caspase-dependent XIP cleavage. Targeting XIP by XIP antisense oligonucleotide resulted in downregulation of XIP activation of caspases and cell death, and sensitized HL-60 cells to Ara-C. Our results suggest that XIP is regulated by cytokines through PI3K, and to a lesser degree through MAPK pathways. Selective downregulation of XIP and apoptosis might be of therapeutic benefit to leukemic patients.

620. Sustained activation of c-jun-terminal kinase (JNK) is closely related to arsenic trioxide-induced apoptosis in an acute myeloid leukemia (M2)-derived cell line, NKM-1 - Kajiguchi T., Yamamoto K., Hossain K. et al. [Dr. N. Emi, First Dept. of Internal Medicine, Nagoya Univ, Graduate Sch. of Medicine, Nagoya, 466-8550, Japan] - LEUKEMIA 2003 17/11 (2189-2195) - sum in ENG

High concentrations (greater than 5 μM) of arsenic trioxide (As2O3) have been reported to be able to induce apoptosis in several malignant cells. We explored cell lines in which apoptosis was induced with a therapeutic concentration (1-2 μM) of As2O3, and found that 1 μM of As2O3 induced apoptosis in the NKM-1 cell line, which was established from a patient with acute myeloid leukemia (M2). Apoptosis induced by 1 μM of As2O3 in NKM-1 cells was accompanied by an increased cellular content of H2O2, a decreased mitochondrial membrane potential (ΔΨm), and activation of caspase-3. C-jun-terminal kinase (JNK) was activated only in NKM-1 cells and arsenic-sensitive NB4 cells, but not in arsenic-insensitive HL-60 cells. Activation of JNK in NKM-1 was sustained from 6 to 24 h after As2O3 treatment, and preceded changes in cellular H2O2, ΔΨm, and caspase-3 activation. Moreover, addition of a JNK inhibitor reduced the percentage of apoptotic cells after the As2O3 treatment. Taken together, in the M2 cell line NKM-1, 1 μM of As2O3 induced sustained activation of JNK and apoptosis. This finding may provide a basis to select a subgroup other than acute promyelocytic leukemia, which can benefit from As2O3 treatment.


Cellular and systemic O2 concentrations are tightly regulated to maintain delicate oxygen homeostasis. Although the roles of hypoxia in solid tumors have been widely studied, few studies were reported regarding the possible effects of hypoxia on malignant cells. Here, we showed for the first time that low concentrations of cobalt chloride (CoCl2) a hypoxia-mimicking agent, and 2-3% O2 triggered differentiation of various subtypes of human acute myeloid leukemia (AML) cell lines, including NB4, U937 and Kasumi-1 cells, respectively, from M3, M5 and M2-type AML, but CoCl2 did not modulate AML subtype-specific fusion proteins promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) and AML1-ETO. Treatment with CoCl2 also induced primary leukemic cells from some AML patients to undergo differentiation. Similar to what occurs in solid tumor cells, CoCl2-mimicked hypoxia also increased the level of hypoxia-inducible factor (HIF)-1α protein and its DNA-binding activity in leukemic cells. These results provide an insight into a possible link of hypoxia or HIF-1α and leukemia cell differentiation, and are possibly of significance to explore clinical potentials of hypoxia or hypoxia-mimicking agents and novel target-based drugs for differentiation therapy of leukemia.

624. Transferrin receptor ligand-targeted toxin conjugate (TF-CRM107) therapy of malignant gliomas - D.W. Laske, D.W. Laske, D.W. Laske et al. [Dr. D.W. Laske, Department of Neurosurgery, Temple University, School of Medicine, 3401 N. Broad St., Philadelphia, PA 19140-5103, United States] - J. NEURO-ONCOL. 2003 65/1 (3-13) - sum in ENG

The authors review the preclinical and clinical results of the ligand-targeted toxin conjugate Transferrin-CRM107 (TF-CRM107), for the treatment of malignant gliomas. TF-CRM107 is a conjugate protein of diphtheria toxin with a point mutation (CRM107)-linked to a thioester bond to human transferrin (Tf). This conjugate exhibits potent cytotoxicity in vitro against malignant cells expressing the transferrin receptor with activity at picomolar concentrations. Phase II trial results demonstrated that TF-CRM107, delivered via a high-flow convection method utilizing stereotactically placed catheters, produced tumor response in patients with malignant brain tumors refractory to conventional therapies. Results of a Phase II study are also summarized. TF-CRM107 treatment results in complete and partial tumor response without severe toxicity in 35% of the evaluable patients. These data warrant a Phase III study as well as targeted research in the field of targeted toxins for the treatment of gliomas.
delivery to targeted brain regions, and improving the treatment efficacy by combining with other toxins conjugates targeted to different receptors.


Central nervous system malignant neoplasias, in particular, glioblastoma multiforme (GBM) have defied all current therapeutic modalities. New therapies involving tumor targeting approach are being explored. This approach relies on the identification of unique or over-expressed cell surface receptors or antigens on tumor cells. In that regard, we have identified receptor for an immune regula-ry cytokine, interleukin-13 (IL-13), which is over-expressed on human malignant glioma cell lines and primary tumor cell cultures. To target IL-13 receptors (IL-13R) for cancer therapy, we have developed a recombinant fusion protein composed of IL-13 and a mutated form of Pseudomonas exotoxin (IL-13-PE38QQR or IL-13 cytotoxin). The IL-13 cytotoxin was found to be highly selective and potent in killing human GBM cells in vitro while normal cells including fat cells, endothelial cells, and normal brain cells were generally spared the cytotoxic effect of IL-13 cytotoxin. This is because these cells either expressed none or expressed low levels of IL-13R. Consistent with in vitro cytotoxic activity, IL-13 cy-otoxin mediated remarkable anti-tumor activity to human glioma in animal xenograft models. The direct injection of IL-13 cyto-toxin into subcutaneous human GBM tumors grown in nude mice produced complete and durable regression of established tumors. Intravenous and intraperitoneal administration of IL-13 cytotoxin also reduced tumor burden significantly with fewer complete re-sponders. All animals tolerated therapy well with minimal toxicity to vital organs. Pre-clinical safety and toxicity studies were per-formed in mice, rats and monkeys. Systemic administration of IL-13 cytotoxin appeared to be well tolerated at high doses (up to 50 μg/kg). Intrabrain parenchyma administration of IL-13 cyto-toxin at doses up to 100 μg/ml was very well tolerated without any evidence of gross or microscopic necrosis, whereas at 500 μg/ml dose, localized necrosis was observed in normal rat brain. Based on these encouraging pre-clinical studies, three Phase I/II clinical trials in adults with malignant glioma have been initiated. The first clinical trial involves convection-enhanced delivery (CED) of IL-13 cytotoxin into recurrent malignant glioma. This route of IL-13 cytotoxin administration appears to be fairly well tolerated with no neurotoxicity. The second clinical trial involves infusion of IL-13 cytotoxin by CED following tumor resection. The initial stage of the second study assessed histologic effect of drug administered prior to resection. In third one, IL-13 cytotoxin is infused by CED followed by tumor resection. All three clinical trials are currently ongoing.


We have investigated the inhibitory effect of salmosin on integ- rin-mediated human tumour cell proliferation. SK-Mel-2 homo human melanoma cell adhesion to denatured collagen or vitronectin was found to be significantly and statistically inhibited by salmosin in a dose-dependent manner (P<0.05). Moreover, the binding of SK-Mel-2 cells to salmosin-coated plates was significantly and statistically inhibited by salmosin induced apoptosis in a dose-dependent manner (P<0.05). Anti-integrin αv, monoclonal antibody, anti-integrin αv,β3, monoclonal antibody, and synthetic RGD peptide also suppressed SK-Mel-2 cell proliferation. Several lines of experimental evidence strongly suggested that the inhibition of SK-Mel-2 cell proliferation by salmosin was due to the induction of apoptosis via the blocking of integrin αv-mediated cell survival.

627. Yeast recombination pathways triggered by topoisomerase II-mediated DNA breaks - Sabourin M., Nittis J.L., Nittis K.C. et al. [N. Nittis, Department of Biochemistry, Vanderbilt Univ. School of Medicine, Nashville, TN 37232-0146, United States] - NUCLEIC ACIDS RES. 2003 31/15 (4573-4584) - sum in ENGL.

Topoisomerase II is a ubiquitous enzyme that removes knots and tangles from the genetic material by generating transient double-strand DNA breaks. While the enzyme cannot perform its essential cellular functions without cleaving DNA, this scission activity is inherently dangerous to chromosomal integrity. In fact, etoposide and other clinically important anticancer drugs kill cells by increas-ing levels of topoisomerase II-mediated DNA breaks. Cells rely heavily on recombination to repair double-strand DNA breaks, but the specific pathways used to repair topoisomerase II-generated DNA damage have not been defined. Therefore, Saccharomyces cerevisiae was used as a model system to delineate the recombination pathways that repair DNA breaks generated by topoisomerase II. Yeast cells that expressed wild-type or a drug-hypersensitive mutant topoisomerase II or over-expressed the wild-type enzyme were examined. Based on cytotoxicity and recombination induced by etoposide in different repair-deficient genetic backgrounds, double-strand DNA breaks generated by topoisomerase II appear to be repaired primarily by the single-strand invasion pathway of ho-mologous recombination. Non-homologous end joining also was triggered by etoposide treatment, but this pathway was consider-ably less active than single-strand invasion and did not con tribute significantly to cell survival in S. cerevisiae.

628. Hydropathic analysis of the free energy differences in anthacycline antibiotic binding to DNA - Castan D.J., Scardale J.N. and Kellogg G.E. [G.E. Kellogg, Department of Medicinal Chemistry, Virginia Commonwealth University, 800 East Leigh Street, Richmond, VA 23219-1540, United States] - NUCLEIC ACIDS RES. 2003 31/15 (4410-4416) - sum in ENGL.

Molecular models of six anthacycline antibiotics and their complexes with 32 distinct DNA octamer sequences were created and analyzed using HINT (Hydropathic INTERactions) to describe bind-ing. The averaged binding scores were then used to calculate the free energies of binding for comparison with experimentally determined values. In parsing our results based on specific functional groups of doxorubicin, our calculations predict a free energy contribution of -3.6 ± 1.1 kcal mol-1 (experimental -2.5 ± 0.5 kcal mol-1) from the groove binding daunosamine sugar. The net energetic contribution of removing the hydroxyl at position C9 is -0.7 ± 0.7 kcal mol-1 (-1.1 ± 0.5 kcal mol-1). The energetic contribution of the V amine group in the daunosamine sugar (when replaced with a hydroxyl group) is -3.7 ± 1.1 kcal mol-1 (0.7 ± 0.5 kcal mol-1). We propose that this large discrepancy may be due to uncertainty in the exact protonation state of the amine. The energetic contribution of the hydroxyl group at C14 is +0.4 ± 0.6 kcal mol-1 (+0.9 ± 0.5 kcal mol-1), largely due to unfavorable hydrophobic interactions between the hydroxyl oxygen and the methylene groups of the phosphate backbone of the DNA. Also, there appears to be considerable conformational uncertainty in this region. This computational procedure calibrates our methodology for future analyses where experimental data are unavailable.

629. Vanillin - A novel family of DNA-PK inhibitors - Durant S. and Karran P. [S. Durant, Mammalian DNA Repair, Cancer Research UK, Clare Hall Laboratories, Blanche Lane, South Mimms, Potters Bar, Herts EN6 3LD, United Kingdom] - NUCLEIC ACIDS RES. 2003 31/19 (5501-5512) - sum in ENGL.

Non-homologous DNd end-joining (NHEJ) is a major pathway of double strand break (DSB) repair in human cells. Here we show that vanillin (3-methoxy-4-hydroxybenzaldehyde) - a natu rally occurring food component and an acknowledged antimutagen, anticlastogen and anticarcinogen-is an inhibitor of NHEJ. Vanillin blocked DNA end-joining by human cell extracts by directly inhibiting the activity of DNA-PK, a crucial NHEJ component. Inhibition was selective and vanillin had no detectable effect on other steps of yeast recombination pathways triggered by topoisomerase II-mediated DNA breaks.
the NHEJ process, on an unrelated protein kinase or on DNA mismatch repair by cell extracts. Subtoxic concentrations of vanillin did not affect the ATM/ATR-dependent phosphorylation of Chk2 or the S-phase checkpoint response after ionising radiation. They significantly potentiated the cytotoxicity of cisplatin, but did not affect sensitivity to UVC. A limited screen of structurally related compounds identified two substituted vanillin derivatives that were 100- and 50-fold more potent than vanillin as DNA-PK inhibitors. These compounds also sensitised cells to cisplatin. The inhibition of NHEJ is consistent with the antmitogentic and other biological properties of vanillin, possibly altering the balance between DSB repair by NHEJ and homologous recombination.


Unmethylated Cpg dinucleotides present within certain specific sequence contexts in bacterial and synthetic DNA stimulate innate immune responses and induce cytokine secretion. Recently, we reported that a small but not irrelevant fraction of MBC patients can ported that a small but not irrelevant fraction of MBC patients can...

631. Advanced breast cancer: An update and controversies on diagnosis and therapy - Nicolini A. and Carpi A. [A. Nicolini, Department of Internal Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy] - BIOMED. PHARMACOTHER. 2003 57/10 (439-446) - sum in ENGL

This review on advanced breast cancer considered important differences in the actual definition of this condition. Advanced breast cancer includes locally advanced, locoregionally recurrent and metastatic disease, which have different diagnosis, prognosis and therapy; their actual definitions are relatively uncertain. Differently from the common opinion that metastatic breast cancer (MBC) is a very severe incurable disease, recently it has been reported that a small but not irrelevant fraction of MBC patients can be cured or remain in long-term survival with complete remission. The type of metastases of the population studied in these reports was analysed and the authors hypothesised that the particularly high DFS reported mainly was attributable to the high proportion of patients with locoregional metastases only. Furthermore, the options and therapy; their actual de...


In the therapy of estrogen receptor (ER) positive human mammary carcinomas, the treatment with the antiestrogen tamoxifen has been well established. However, the development of hormone resistance is an important factor in breast cancer progression against endocrine therapy. The presence of the receptor for EGF (EGFR) correlates with lack of response towards antiestrogen therapy. The EGFR is not only involved in tumor cell growth, survival signaling, cell migration and apoptosis, but also serves to confer reduced responses of tumor cells towards anti-hormones. Concomitant inhibition of both, the receptors for estrogen and EGF may be necessary to improve breast cancer therapy. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

633. Intracellular mechanism of estrogen synthesis in breast cancer - Suzuki T., Moriya T., Ishida T. et al. [T. Suzuki, Departement of Pathology, Tohoku University, School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan] - BIOMED. PHARMACOTHER. 2003 57/10 (460-462) - sum in ENGL

It has been demonstrated that biologically active estrogens are locally produced from circulating inactive steroids in an intracellular mechanism in the breast carcinoma. The in situ production of estrogens is considered to play an important role in the proliferation of breast cancer cells, especially in the postmenopausal women. Therefore, the total blockade of this pathway may lead to an improvement in the prognosis in breast cancer patients due to the inhibition of estrogenic actions. In this review, we describe the recent studies of enzymes related to intracellular mechanism of estrogen synthesis, including aromatase, steroid sulfatase (STS), and 17β-hydroxysteroid dehydrogenase, in human breast carcinoma tissues, and discuss the biological significance of local production of estrogens in human breast cancer. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.


Breast cancer is a worldwide epidemic among women, and one of the most rapidly increasing cancers. Not only the incidence rate but also the death rate is increasing. Despite enthusiastic efforts in early diagnosis, aggressive surgical treatment and application of additional non-operative modalities, its prognosis is still dismal. This emphasizes the necessity to develop new measures and strategies for its prevention. The understanding of the biology of angiogenesis is improving rapidly, offering the hope for more specific vascular targeting of tumor neovascularization. Anti-angiogenic therapy is a promising, relatively new form of cancer treatment using drugs called angiogenesis inhibitors that specifically inhibit new blood vessel growth. Extensive studies conducted over the past few years have recognized that overexpression of COX-2. VEGF in the breast cancer might be the leading factors, can induce angiogenesis via induction of multiple pro-angiogenic regulators. Breast tumor growth and metastasization are both hormone-sensitive and angiogenesis-dependent. A single angiogenic inhibitor is not capable to inhibit angiogenesis. Therefore, we should select a combination of angiogenesis inhibitors targeting COX-2, VEGF, and bFGF pathway. This article reviews the background and implementation of the current use of angiogenesis inhibitors and discusses the likely therapeutic roles in the early and advanced breast cancer together with its potential for chemoprevention. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

635. How does interleukin-6 affect the membrane expressions of interleukin-6 receptor and gp130 and the proliferation of the human myeloma cell line OPM-2? - Kovacs E. [E. Kovacs, Socie...

Interleukin-6 (IL-6) is a potent growth factor for the proliferation of multiple myelomas (MM), which accounts for 1-2% of all human cancers. In this study we investigated the effects of IL-6 in various doses on the following parameters in the human myeloma cell line OPM-2: membrane expression of IL-6 receptor (IL-6R) and gp130, proliferation of the tumor cells and the amount of the soluble IL-6 receptor (sIL-6R) in the supernatant. Additionally, we tested the
same parameters with the immunomodulator Viscum album (VA)-
extract. The expression of surface IL-6R and gp130 was analysed by FACS, the measurements of proliferation using the BrdU incor-
poration during DNA synthesis, and the determination of sIL-6R in the supernatant by ELISA. OPM-2 cells proliferate spontaneously (doubling time: 48 h), IL-6-production was not detectable. The exogenous IL-6 upregulated its own receptor up to a mean of 180% of controls at 5 ng/ml (P < 0.001), higher or lower doses were less effective. The membrane expression of gp130 was downregulated to 1-2%.
IL-6 led to increase of the sIL-6R in the supernatant (P < 0.001) and raised the proliferation of the myeloma cells up to a mean of 124% (P < 0.001). These results indicate that the human myeloma cell line OPM-2 has an autocrine IL-6 regulation mechanism, with an additional paracrine signalling by exogenous IL-6. This is the first report that IL-6 inhibits the membrane expres-
sion of gp130, although the proliferation of the myeloma cells increases. VA extract did not affect survival, the expression of surface receptors IL-6 and gp130 or the amount of sIL-6R in the supernatant. However, the proliferation of the tumour cells was inhibited significantly (P < 0.05) suggesting a possible arrest in the cell cycle. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.


Previously, we have described a novel series of low molecular weight cancer-specific antigen tumour antibodies with ammin N-[1,1-dioxide-1,4,2-benzodithiazin-3-yl]methanides (6-19) has been synthesized by the reactions of 3-methylthio-1,4,2-benzodithiazine-1,1-dioxides with 4-DMAP and some active methylene compounds. The in vitro antitumor activity of these compounds has been tested in the National Cancer Institute (NCI), and relationships between structure and antitumor activity are discussed. Among the amimium salts 4-dimethylamino- pyridinium 4-chlorobenzoyl cyano (6-chloro-7-methyl-1,1-dioxide-1,4,2-benzodithiazin-3-yl)methanide (9) was superior to other pyri-
idinium salts in terms of both remarkable activity (logGI50 and logTGI<8.00) and high selectivity for the lung HOP-92 and melanoma UACC-257 cell lines. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.


A steroidal oxime ether derivatives and estrone and estrane series have been synthesized and evaluated for the antineo-
plastic activity at National Cancer Institute, Bethesda, Maryland, USA. O-Alkylation of the oximes by various alkylaminoethyl halides gave the oxime ether derivatives. The 17α-ethylendrostan-
edione derivatives 29 (DPJ-684), 30 (DPJ-685), 31 (DPJ-686) and estrane derivatives 35 (DPJ-531) and 36 (DPJ-532) were among the small percentage of compounds, which have been screened by NCI for in vivo hollow fiber assay by virtue of their activity against one or more human tumour cell lines in 60 cell line in vitro prescreen. The preliminary in vivo reports of hollow fiber assays have been referred to the Biological Evaluation Committee for Cancer Drugs for considering these compounds for further detailed in vivo testing. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

638. Phase II trial combining docetaxel and doxorubicin as neo-
adjuvant chemotherapy in patients with operable breast cancer - Ganem G., Tabibina-Hulin M., Fumoleau P. et al. [Dr. G. Ganem, Centre Jean Bernard, 9 Rue Beaunierger, 72000 Le Mans, France] - ANN. ONCOL. 2003 14/11 (1623-1628) - summ in ENGL

The study was conducted to assess the antitumour activity of docetaxel in combination with doxorubicin in neoadju-
vant therapy of patients with breast cancer. Patients and methods: Forty-eight women were treated with intravenous doxorubicin 50 mg/m² over 15 min followed by a 1-h infusion of docetaxel 75 mg/m² every 3 weeks for six cycles. Dexamethasone or prednisol-
one premedication was allowed. Granulocyte colony-stimulating factor was not allowed as primary prophylaxis. The primary end point was the pathologically documented complete response rate (pathological response). Results: The mean relative dose intensity calculated for four or more cycles was 99% for doxorubicin and 99% for docetaxel. Overall, the pathological response rate was 13%. There were 11 complete and 29 partial clinical responses for an overall response rate of 85% (95% confidence interval (CI) 75% to 95%) in the evaluable population (n = 47). Disease-free and overall survival rates were 85% (95% CI 71% to 94%) and 96% (95% CI 85% to 99%), respectively, after a median follow-up of 36.6 months. Grade 3/4 neutropenia was observed in 65% of patients and 17% reported grade 4 febrile neutropenia. Conclusions: Docetaxel and doxorubicin is an effective and well-tolerated combination in the neoadjuvant therapy of breast cancer. Future controlled trials are warranted to investigate the best schedules and to correlate response with biological factors.

639. Apoptotic action of 17β-estradiol in raloxifene-resistant MCF-7 cells in vitro and in vivo - Liu H., Lee E. S., Gajdos C. et al. [Dr. V.C. Jordan, R. H. Lurie Comprehen. Cancer Ctr., Feinberg School of Medicine, Northwestern University, 303 E. Chicago Ave., Chicago, IL 60611, United States] - J. NATL. CANCER INST. 2003 95/21 (1586-1597) - summ in ENGL

Background: Resistance to tamoxifen, a selective estrogen receptor modulator (SERM), involves changes that prevent apoptosis and enhance cell proliferation and survival. Paradoxically, estrogen treatment inhibits the growth of long-term tamoxifen-treated breast tumors. Because of the increasing use of raloxifene, another SERM, to prevent osteoporosis and potentially reduce breast cancer risk, some women will develop raloxifene-resistant breast cancer. We de-
developed a raloxifene-resistant MCF-7 cell model (MCF-7/Ral) and investigated the nature of raloxifene-resistant breast cancer and its response to estradiol. Methods: Raloxifene resistance and hormone responsiveness were assessed by proliferation assays and cell cycle analysis in parental MCF-7 and MCF-7/Ral cells. Nuclear factor κB (NF-κB) activity was investigated with a transient transfection assay. Apoptosis was investigated by annexin V staining, mRNA was measured by real-time polymerase chain reaction, and protein was measured by western blotting. Tumorigenesis was studied by injecting MCF-7 or MCF-7/Ral cells into ovariectomized athymic mice (10 per group) and monitoring tumor size weekly. All statisti-
cal tests were two-sided. Results: Basal NF-κB activity was higher in MCF-7/Ral cells (1.6 U, 95% confidence interval [CI] = 1.2 to 2.0 U) than in MCF-7 cells (0.8 U, 95% CI = 0.4 to 1.1 U; P < .004). When cultured with 1 μM raloxifene, MCF-7/Ral cells grew sta-
tistically significantly (P < .001) faster than MCF-7 cells. Estradiol treatment of MCF-7/Ral cells arrested cells in G2/M phase of the cell cycle, decreased NF-κB activity (0.2 U, 95% CI = 0.2 to 0.3 U; P < .001), increased expression of Fas protein and mRNA (4.5-fold, 95% CI = 2.8- to 6.3-fold versus 0.5-fold, 95% CI = 0.3- to 0.8-fold for control treatment; P < .001), and induced apoptosis. Treatment with either raloxifene or tamoxifen stimulated MCF-7/Ral tumor growth, suggesting that such tumors were resistant to both drugs. When a 9-week raloxifene or tamoxifen treatment was followed by a 5-week estradiol treatment, estradiol statistically significantly reduced the size of tumors stimulated by raloxifene or tamoxifen (at week 14, P = .004 for raloxifene and P < .001 for tamoxifen). Conclusions: Growth of raloxifene-resistant MCF-7/Ral cells in vitro and in vivo is repressed by estradiol treatment by a mecha-
nism involving G2/M-phase arrest, decreased NF-κB activity, and increased Fas expression to induce apoptosis.

640. Paradoxical action of fulvestrant in estradiol-induced re-
gression of tamoxifen-stimulated breast cancer - Gajdos C., Gajdos C., Liu H. et al. [Dr. V.C. Jordan, R. H. Lurie Comprehen. Cancer Ctr., Feinberg School of Medicine, Northwestern University,
Background: Long-term tamoxifen treatment of breast cancer can result in tamoxifen-stimulated breast cancer, in which estrogen inhibits tumor growth after tamoxifen withdrawal. We investigated the molecular mechanisms of reactivation of tamoxifen-resistant breast cancer cells and examined alterations in phospholipid metabolism during 17AAG treatment relative to the pretreatment ratio (P = .02), of HER2/neu mRNA and protein and nuclear factor-κB (NF-κB) protein expression, increased phosphocholine and phosphoethanolamine levels, and a decreased cross-sectional area at week 10 = 0.60 cm², 95% CI = 0.50 to 0.70 cm²; 17AAG treatment leads to alterations in phospholipids that could serve as noninvasive pharmacodynamic markers for analyzing tumor response to treatment with 17AAG or other Hsp90 inhibitors.

Antifolates are the oldest of the antimetabolite class of anticancer agents and were one of the first modern anticancer drugs. The first clinically useful antifolate, described in 1947, was 2,4-diamino-pteroylglutamate (4-amino-folic acid; aminopterin; AMT) which inhibited dihydrofolate reductase (DHFR) and metabolism of MTX to polyglylutamate (Glun). Although several of these analogs have undergone clinical trial, none is proved superior to MTX. Detailed examination of the mechanisms of cytotoxicity and selectivity of MTX showed that inhibition of both dTMP synthesis and de novo purine synthesis, secondary to DHFR inhibition, led to DNA synthesis inhibition and subsequent cell death; inhibition of other folate-dependent pathways did not appear necessary for cell death. Further studies showed that the contribution of inhibition of dTMP or purine synthesis to cell death varied in different cell types. These data suggested that inhibition of one of these pathways individually might (at least in some cases) be therapeutically superior to the dual inhibition induced by MTX. Thus in rational design and in structure-based design studies, new analogs have improved delivery, or that inhibit other targets in folate metabolism. These new analogs are in various stages of preclinical and clinical development.

Antifolate treatment leads to alterations in phospholipids that could serve as pharmacodynamic markers for tumor response to 17AAG. Methods: HCT116, HT29, and SW620 colon cancer cells were treated with 17AAG, and extracts were examined by 31P-MRS. Results: 17AAG treatment leads to alterations in phospholipids that could serve as pharmacodynamic markers for tumor response to 17AAG. HT29 xenografts were examined using in vivo 31P-MRS before and after 17AAG treatment; xenograft tumor extracts were examined by 31P-MRS and proton MRS (1H-MRS). Hsp90 client protein expression was determined by using western blots. Two-tailed t-tests were used to compare metabolite concentrations and ratios, and a Mann-Whitney U test was used to compare proportions. All statistical tests were two-sided. Results: 17AAG treatment led to statistically significantly increased phosphocholine levels in all three cell lines (P = .02). 17AAG treatment also increased phospholipid levels in HT29 cells, whereas NOSC68366 had no effect. Further studies showed that the contribution of inhibition of one of these pathways individually might (at least in some cases) be therapeutically superior to the dual inhibition induced by MTX. Thus in rational design and in structure-based design studies, new analogs have improved delivery, or that inhibit other targets in folate metabolism. These new analogs are in various stages of preclinical and clinical development.
464. Thioguanine, mercaptopurine: Their analogs and nucleosides as antimetabolites - Elfgenime G.L. [G.H. Elfgenime, Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt] - CURR. PHARM. DES. 2003 9/51 (2627-2642) - sum in ENGL

6-Mercaptopurine (6MP) and 6-thioguanine (6TG) are analogs of the natural purines: hypoxanthine and guanine. Both mercaptopurine and thioguanine are substrates for hypoxanthine-guanine phosphorribosyltransferase and are converted into the ribonucleotides 6-thioguanosine monophosphate (6-thioGMP) and 6-thioguanosine monophosphate (6-IMP). The accumulation of these monophosphates inhibits several vital metabolic reactions. Today, these thiopurine bases remain valuable agents for the induction and maintenance of remissions in patients with myelogenous and acute lymphocytic leukemia. Despite their proved clinical importance, 6MP and 6TG have certain therapeutic disadvantages, which have continued to stimulate the search for purine derivatives enhancing therapeutic efficacy. Considerable efforts have been made to prepare novel mercaptopurine and thio-guanine analogs and their nucleosides to improve the antitumor efficacy. The effectiveness of these thiopurine bases against certain tumor cell lines suggested that some of these mercaptopurine analogs and their nucleosides would be worth of consideration in order to determine whether they exert a more selective effect against neoplastic cells than against normal cells or they might be useful in patients whose disease has become resistant to 6MP or 6TG. This review will focus on mercaptopurine analogs and their nucleosides as antimetabolite agents.

465. Immunomodulatory activity of resveratrol: Discrepant in vitro and in vivo immunological effects - Gao X., Deeb D., Medina J. et al. [S.C. Gautam, Division of Hematology/Oncology, Department of Medicine, Henry Ford Health System, 2799 West Grand Boulevard, Detroit, MI 48202, United States] - BIOCHEM. PHARMACOL. 2003 66/12 (2381-2395) - sum in ENGL

Resveratrol is a dietary polyphenolic compound present in grapes, which has been shown to exhibit strong anti-inflammation, antioxidant, and chemopreventive activities. In this study we have compared the in vitro and in vivo effects of resveratrol on the development of various cell-mediated immune responses, including mitogen/antigen-induced T cell proliferation, induction of cytotoxic T lymphocytes (CTLs), interleukin-2 (IL-2) induced lymphokine activated killer cells, and cytokine production. We found significant suppression (>90%) of the mitogen/antigen-induced T cell proliferation and development of allo-antigen specific CTLs in vivo with control concentration of 32μM. Intragastric administration of resveratrol (2mg daily) to mice for 4 weeks showed no effect on age-related gain in body weight, peripheral blood cell counts (WBC, RBC, or platelets), or the cellularity of bone marrow. The number of splenic T cells in spleen or colony-forming units-total in the marrow also remained unaffected by treatment with resveratrol. Spleen cells, which were stimulated in vitro after being removed from mice which had been administered resveratrol for 2 or 4 weeks, showed no significant change in IL-2 or concanavalin A induced proliferation of T cells or production of IL-2 induced lymphokine activated killer cells. Further, the induction of interferon-gamma and IL-12 was not affected by administration of resveratrol, but production of tumor necrosis factor-alpha was reduced. Even when conducted entirely in vivo, treatment with resveratrol was found to only marginally reduce allo-antigen induced T cell proliferation and the generation of CTLs in the draining lymph nodes. Thus, even though resveratrol strongly inhibits T cell proliferation and production of cytolytic cells in vitro, oral administration of resveratrol for 4 weeks does not induce hematologic or hematopoietic toxicity, and only marginally reduces the T cell-mediated immune responses. © 2003 Elsevier Inc. All rights reserved.

466. Induction of the mitochondrial permeability transition by selenium compounds mediated by oxidation of the protein thiol groups and generation of the superoxide - Kim T.-S., Yun B.Y. and Kim I.Y. [I.Y. Kim, Lab. of Cell/Molecular Biochemistry, Sch. of Life Sci. and Biotechnology, Korea University, 15-Ka, Anam-Dong, Sungbuk-ku, Seoul 136-701, South Korea] - BIOCHEM. PHARMACOL. 2003 66/12 (2381-2395) - sum in ENGL

The cancer chemopreventive effect of selenium compounds cannot be fully explained by the role of selenium as a component of antioxidant enzymes, suggesting that other mechanisms, such as thiol oxidation or free radical generation, also underlie this effect. The toxicities of six different selenium compounds (selenite, selenate, selenocystine, selenocysteamine, selenodioxide, and selenu-metionine) have now been compared in HepG2 human hepatoma cells and isolated rat liver mitochondria. Selenite, selenocystine, and selenodioxide induced apoptosis in HepG2 cells and mediated oxidation of protein thiol groups in both HepG2 cells and isolated mitochondria. Selenocysteamine oxidized protein thiol groups in isolated mitochondria and crude extracts of HepG2 cells but not in intact HepG2 cells, suggesting that this compound is not able to cross the cell membrane. The selenium compounds capable of oxidizing thiol groups also induced the mitochondrial permeability transition (MPT) in isolated mitochondria. Furthermore, they generated the superoxide (O2·−) on reaction with glutathione in the presence of mitochondria, and an O2·− scavenger inhibited their induction of the MPT. These results suggest that the pro-apoptotic action of selenium compounds is mediated by both thiol oxidation and the generation of O2·−, both of which contribute to opening of the MPT pore. © 2003 Elsevier Inc. All rights reserved.

467. Ecteinascidin-743 drug resistance in sarcoma cells: Transcriptional and cellular alterations - Shao L., Kasanov J., Hornick E.J. et al. [L. Weissbach, Orthopaedic Research Laboratories, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, United States] - BIOCHEM. PHARMACOL. 2003 66/12 (2381-2395) - sum in ENGL

A human chondrosarcoma cell line, CS-1, was treated successively with increasing concentrations of the marine chemotherapeutic Ecteinascidin-743 (ET-743), yielding a variant cell line displaying a significant degree of resistance to the cytotoxic action of this drug. Various experiments were performed to discern molecular aberrations between the parent and resistant cell line, and also identify potential molecular markers indicative of drug resistance. Although no significant differences in the levels of membrane transporters such as P-glycoprotein or multidrug resistance protein 1 (MRP1) were detected, the cell migratory ability of the ET-743-resistant cell variant was reduced, as was its attachment capability to gelatin-coated cell culture dishes. Staining of the actin-containing cytoskeleton with fluorescent-labeled phalloidin revealed marked differences in the cytoskeleton architecture between the parent and ET-743-resistant CS-1 cell lines. Comparison of serum-free conditioned medium from both cell lines showed conspicuous differences in the levels of several proteins, including a quartet of high molecular weight proteins (>140kDa). The protein sequences of two of these high molecular weight proteins, present at significantly higher concentrations in conditioned medium obtained from the parent cell line, corresponded to subunits of type I and IV collagen. Analysis of type I collagen α1 chain mRNA revealed a significantly
lower level in the ET-743-resistant CS-1 cell line. Thus, prolonged exposure to ET-743 may cause changes in cell function through cytokoskeleton rearrangement and/or modulation of collagen levels. © 2003 Elsevier Inc. All rights reserved.

648. Serum from rabbit orally administered cobra venom inhibits growth of implanted hepatocellular carcinoma cells in mice - Sun P., Ren X.-D., Zhang H.-W. et al. [X.-K. Li, Biopharmaceutical R and D Center, Jinan University, Guangzhou 510632, Guangdong Province, China] - WORLD J. GASTROENTEROL. 2003 9/11 (2441-2444) - sum in ENGL

Aim: To investigate the inhibitory effect of serum preparation from the cobra venom on implanted hepatocellular carcinoma (HCC) cells in mice. Methods: An HCC cell line, HepA, was injected into mice to prepare implanted tumors. The animals (n=30) were divided randomly into SRCV, 5-fluorouracil (5-FU), and distilled water (control) groups. From the second day after transplantation, 20 mg/kg 5-FU was administered intra-peritoneally once a day for 9 days. SRCV (1 000 mg/kg) or distilled water (0.2 ml) was given by gastrogavage. Tumor growth inhibition was calculated by the inhibitory rate (IR). Apoptosis was detected by transmission electron microscopy (TEM), flow cytometry (FCM), and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL). Student’s t-test was performed for statisti-cal analysis. Results: The tumor growth was inhibited markedly by SRCV compared to that in the control group (P<0.01). The treatment resulted in a significant increase in the apoptotic rate of cancer cells by the factors of 10.5±2.4 % and 20.65±3.2 % as demonstrated through TUNEL and FCM assays, respectively (P<0.01). The apoptotic cells were also identified by characteristic ultrastructural features. Conclusion: SRCV can inhibit the growth of implanted HepA cells in mice, and the apoptosis rate appears to elevate during the process.


Pdc4d is a novel gene first identified as a differentially expressed protein during apoptosis. In the meantime not only the impact of Pdc4d in programmed cell death but also an implication in transformation suppression by inhibition of protein translation is discussed. These features implicate a potential value of Pdc4d as a molecu-lar target in cancer therapy. This review summarizes the current knowledge about expression, structure and function of Pdc4d. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.

650. In children and adolescents, the pharmacodynamics of high-dose busulfan is dependent on the second alkylating agent used in the combined regimen (melphalan or thiotepa) - Bouli-gand J., Boland I., Valteau-Couanet D. et al. [Prof. G. Vassal, UPRES EA5335, Pharmaco/Neu Treatments of Cancers, Insti-tut Gustave Roussy, 39 rue Camille Desmoulins, Villejuif 94800, France] - BONE MARROW TRANSPLANT. 2003 32/10 (979-986) - sum in ENGL

A strong relationship has been demonstrated between high systemic exposure to busulfan and the occurrence of hepatic veno-occlusive disease (HVOD) after a busulfan-cyclophospha-mide regimen (BU CY). We report a prospective study aimed at exploring the pharmacodynamics of high-dose busulfan combined with either melphalan (BU MEL) or thiopeta (BU TTP) followed by autologous stem cell transplantation in children and adolescents with a malignant solid tumor. Busulfan was given orally at a total dose of 600 mg m⁻². In all, 45 patients with a median age of 6.3 years were included in the study: 25 received BU MEL and 20 received BU TTP. The incidence of HVOD was 44% (CI 95% [23- 65%]) in the BU MEL group and 25% (CI 95% [9-49%]) in the BU TTP group. In the BU TTP group, patients who developed HVOD had a significantly higher AUC 0-6 h after the 13th dose (6201±670 ng ml⁻¹) than those who did not (5024±978 ng ml⁻¹) (P<0.05). In the BU MEL group, there was no difference in terms of systemic exposure to busulfan between patients who devel-oped HVOD and those who did not. In conclusion, the guidelines established for monitoring BU CY cannot be extrapolated when busulfan is combined with another drug.


The chemotherapy agent L-asparaginase has been an important part of acute lymphoblastic leukemia therapy for over 30 years. Two of the main disadvantages of the drug are (1) the need for frequent intramuscular injection and (2) a very high rate of allergic reac-tions. Because of this, L-asparaginase seemed like an ideal target for pegylation and PEG-L-asparaginase was developed in the 1970s and 1980s. The drug has undergone extensive testing and appears to retain its antileukemic effectiveness while allowing less frequent administration than the native compound. While the actual cost to patients for PEG-L-asparaginase is greater than that of multiple injections of other L-asparaginas, the reduced need for physician visits and treatment of complications of therapy may make overall treatment costs considerably less than that of the conventional L-asparaginas. In the review below, we outline the history of therapy with L-asparaginase, the development of PEG-L-asparaginase, and clinical trials in which it has been administered. © 2003 Elsevier B.V. All rights reserved.

652. Effect of the antidepressant desipramine on cytosolic Ca²⁺ movements in human esophageal carcinoma cells - Jan C.-R., Lu Y.-C., Tseng L.-L. et al. [J.-K. Huang, Depart-ment of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan] - PHARMACOLOGY 2003 69/4 (190-196) - sum in ENGL

In human esophageal carcinoma MG63 cells, the effect of desipramine, an antidepressant, on intracellular Ca²⁺ concentration ([Ca²⁺]i) was measured by using fura-2. Desipramine (> 10 µmol/l) caused a rapid and sustained rise of [Ca²⁺]i ([Ca²⁺]i was prevented by 80% by removal of extracellular Ca²⁺ but was not altered by voltage-gated Ca²⁺ channel blockers. In Ca²⁺-free medium, thapsigargin, an inhibitor of the endoplasmic reticulum (ER) Ca²⁺-ATPase, caused a monophasic [Ca²⁺]i rise, after which the increasing effect of desipramine on [Ca²⁺]i was abolished; also, pretreatment with desipramine partly reduced thapsigargin-induced [Ca²⁺]i rise. U73122, an inhibitor of phosphodiesterase C, did not affect desipramine-induced [Ca²⁺]i rise. Overnight incubation with 10 µmol/dl desipramine did not alter cell proliferation, but killed 32 % and 89% of cells at concentrations of 100 and 200 µmol/l, respec-tively. These findings suggest that desipramine rapidly increases [Ca²⁺]i in osteoblasts by stimulating both extracellular Ca²⁺ influx and intracellular Ca²⁺ release, and is cytotoxic at high concentra-tions. Copyright © 2003 S. Karger AG, Basel.


AIM: To investigate the inhibition of p27kip1 gene on the growth of esophageal carcinoma cell strain (EC9706). METHODS: Recombinant adenosin Ad-p27kip1 was constructed and transfected into esophageal carcinoma cell EC-9706, and its effect on p27kip1 expression, the growth of esophageal carcinoma cell, DNA repli-cation, protein synthesis, cell multiplication and apoptosis were explored by means of cell growth count, DNA content, DNA fragment analysis and TUNEL. RESULTS: Recombinant adenosin Ad-p27kip1 was successfully constructed with a virus titer of 1.24×10⁷ pfu/ml. p27kip protein expression increased markedly after EC-9706 transfection, while incorporation quantity of 3H-TdR and 3H-Leucine decreased significantly. The growth of esophageal carcinoma cell was inhibited obviously. Testing of flow cytometry displayed a typical apopto-sis peak, and DNA gel electrophoresis showed a typical apoptosis ladder. TUNEL showed the apoptosis rate of Ad-p27kip1 group and control group to be 3.7 % and 1.26 % (P<0.001) respectively.

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CONCLUSION: Ad-p27kip1 can inhibit the growth and multiplication of esophageal carcinoma cells and induce apoptosis. Therefore, enhanced p27kip1 expression may be a new way to treat esophageal carcinoma.

See also: 697, 704, 712, 735, 737, 748.

6.5. Antiinfective agents

654. Cyrmennis, new β-methoxycarbonyl inhibitors of the electron transport. Production, isolation, physico-chemical and biological properties - Sasse F., Leibold T., Kunze B. et al. [F. Sasse, GBE, German Research Center Biotechnology, Dept. of Natural Product Biology, Mascheroder Weg 1, D-38124 Braunschweig, Germany] - J. ANTIMICROB. CHEMOTHER. 2003 56/10 (836-847) - sum in ENGL

New antibiotic compounds, named cyrmennis, were isolated from the culture broth of strains of the myxobacteria Cystobacter armeniaca and Archangium gephyra. The compounds belong to the group of β-methoxycarbonyl (MOA) inhibitors and are the first naturally occurring nitrogen-linked MOAs. The cyrmennins show nearly the same antifungal activity as streptomycin A, but are less toxic in a growth inhibition assay with L929 mouse cells. Cyrmennins inhibit NADH oxidation by submitochondrial particles from beef heart. Investigations by difference spectroscopy showed that cyrmennin B2 blocks the electron transport within the cytochrome bc1-segment (complex III) of the respiratory chain.


Thirty five oxapenem analogues substituted with a range of tertiary groups of C-2 have been synthesised and evaluated as broad-spectrum β-lactamase inhibitors. All analogues enhanced the activity of ceftazidime against bacterial isolates producing Class A and Class B β-lactamases. Compounds with cyclic substituents at C-1′ (attached to C-6) were associated with enhanced antibacterial activity against Staphylococcus aureus. (R) Stereochemistry at C-1′ led to synergistic activity against β-lactamase negative enterococci. (S) Stereochemistry at C-1′ was associated with enhanced inhibition of Class A β-lactamases and lack of synergistic activity against enterococci. AM-113 was unstable in serum and not detectable following subcutaneous or oral dosing in mice. AM-112 and AM-115 achieved good serum levels following subcutaneous dosing. AM-114 exhibited 30% bioavailability following oral dosing. AM-112 [(R,S)-6′-[(2-amino-1,1-dimethylbutyl)-6′-(1′-hydroxyethyl) oxapenem-3-carboxylate] achieved the greatest protection of ceftazidime against Gram-negative producing Class A or Class β-lactamases.

656. Antimycobacterial activity of 2-methyl-adenosine - Barrow E.W., Westbrook L., Bansal N. et al. [W.W. Barrow, Mycobacteriology Research Unit, Dept. of Veterinary Pathobiology, Oklahoma State University, 250 McElroy Hall, Stillwater, OK 74078, United States] - J. ANTIMICROB. CHEMOTHER. 2003 52/5 (801-808) - sum in ENGL

Objectives: The aims of this study were to assess the in vitro activity of 2-methyl-adenosine against Mycobacterium tuberculosis and examine its potential mechanism of action. Methods: In vitro activity was determined by means of a colorimetric microdilution broth assay. Intracellular activity was assessed with a Mono Mac 6 human monocytic cell line. A hypoxic shift-down model was used to evaluate the intracellular activity of 2-methyl-adenosine on M. tuberculosis in a persistent state. Mechanism-of-action studies were conducted by examining the effect of 2-methyl-adenosine on the uptake of appropriate radiolabelled precursors into respective mycobacterial macromolecular components. Results: Studies confirmed the in vitro activity of 2-methyl-adenosine against M. tuberculosis and demonstrated intracellular efficacy against M. tuberculosis within macrophages. 2-Methyladenosine was able to significantly affect the viability of M. tuberculosis in a hypoxic shift-down model previously described to simulate the persistent state that results during tuberculosis. Mechanism-of-action studies revealed that the immediate inhibitory effects of 2-methyl-adenosine were associated with protein and DNA synthesis and not RNA synthesis. Conclusions: Results indicate that 2-methyl-adenosine, or similar derivatives, might be effective against M. tuberculosis infections during latency. This information should be helpful in understanding purne metabolism of M. tuberculosis and also the metabolic activity of this important human pathogen in the persistent state.

657. Hypertrophy of Vascularized Bone Iso graft in Rats Treated with Cyclosporine A - Tsubone T., Shigetomi M., Ibara K. et al. [M. Shigetomi, Department of Orthopedic Surgery, Yamaguchi Univ. School of Medicine, 1-1-1 Minamikogushi, Yamaguchi 755-8505, Japan] - CALCIUM TISSUE INT. 2003 73/4 (393-399) - sum in ENGL

The aim of this study was to investigate the effects of cyclosporine A (CsA) on vascularized tibiofibula isograft between 12-week-old male Lewis rats. After transplantation, 45 rats were randomly allocated to one of the following 7 treatment groups: (1) 4-week vehicle (n = 5), (2) 4-week CsA (n = 5), (3) 8-week vehicle (n = 10), (4) 8-week CsA (n = 10), (5) 4-week CsA followed by 4-week vehicle (n = 5), (6) 16-week vehicle (n = 5), or (7) 4-week CsA followed by 12-week vehicle (n = 5). In soft X-ray and micro-computed tomography examination, hypertrophic change of the grafted bones was apparent in the 4-and 8-week CsA groups. Mineral apposition rate and bone formation rate of the grafted bones in the 4-week CsA group were markedly higher than those in the 4-week vehicle group. In the 4- and 8-week CsA groups, however, bone mineral density (BMD) of the grafted bones was lower and strength of the reconstructed bones was weaker than the 4- and 8-week vehicle groups. Urinary deoxypyridinoline (DPD) level was higher in the 4- and 8-week CsA groups than in the 4- and 8-week vehicle groups. The group of 4-week CsA followed by 4-week vehicle had a level of urinary DPD equal to the 8-week vehicle group, but their BMD of the grafted bones was lower and strength of the reconstructed bones was weaker than the 8-week vehicle group. By contrast, the group of 4-week CsA followed by 12-week vehicle had BMD of the grafted bones and strength of the reconstructed bones similar to the 16-week vehicle group. These findings demonstrate that short-term CsA treatment induces hypertrophic change of vascularized bone graft with high-turnover bone loss, and strength of the reconstructed bone is gradually restored after the cessation of CsA treatment.

658. Semi-synthetic glycopeptide antibacterials - Judice J.K. and Pace J.L. [J.L. Pace, 35 Indian Rock Court, San Anselmo, CA 94960, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (1415-1416) - sum in ENGL

Studies leading to the discovery of TD-6424 and their relevance to other hydrophilically-substituted glycopeptides are reviewed along with a brief comparison of properties for related agents currently undergoing clinical evaluation. © 2003 Elsevier Ltd. All rights reserved.


The influence of an ethylene-oxide spacer element between the bicyclic and the aromatic ring in linezolid is reported. The introduction of such spacer group generated compounds with inferior antibacterial activity. However, the conversion of the thiacarbitone group present in the linezolid analogues to either thio carbamate or thioacetamide functionality restored the activity. The synthesis of linezolid analogues possessing the ethylene-oxide spacer group along with SAR studies with different heterocycles and preparation of some thio carbonyl compounds possessing potent antibacterial property are presented. © 2003 Elsevier Ltd. All rights reserved.

protein binding by the introduction of polar groups are discussed. Animal models, and efforts to improve solubility and reduce serum 

P. aeruginosa is described. Synthesis and in vitro structure-activity relationships have yielded new, potent series of compounds of which the first examples, the O-linked isoaxazoles are described in detail, leading to the selection of the pre-clinical candidate AZD2563. © 2003 Elsevier Ltd. All rights reserved.

661. New classes of antibacterial oxazolidinones with C-5, methylene O-linked heterocyclic side chains - Gravestock M.B., Acton D.G., Betts M.J. et al. [M.B. Gravestock, AstraZeneca R and D Boston, Infection Discovery, 35 Gatehouse Park, Waltham, MA 02451, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4179-4186) - sum in ENGL


663. The synthesis and antibacterial activity of 1,3,4-thiadiazole phenyl oxazolidinone analogues - Thomsen L.M., Gadwood R.C., Weaver E.A. et al. [L.M. Thomsen, Discov. Chem./Discov.-Infect. Dis., Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4193-4196) - sum in ENGL

664. Synthesis and biological evaluation of benzazepine oxazolidinone antibacterials - Johnson P.D., Alizadeh R., Zurenko G.E. et al. [P.D. Johnson, Discovery-Chemistry, Pharmacia Corpora-
tion, 7000 Portage Road, Kalamazoo, MI 49001, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4197-4200) - sum in ENGL


Problems of low solubility, high serum protein binding, and lack of efficacy in vivo in first generation MoxAB-OpM specific efflux pump inhibitors were addressed. Through the use of pharmacophore modelling, the key structural elements for pump inhibition were defined. Use of alternative scaffolds upon which the key elements were arrayed gave second generation leads with greatly improved physical properties and activity in the potentialization of antibacterial quinolones (levofloxacin and sitafloxacin) versus Pseudomonas aerugi-

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668. Combinatorial libraries of N-acylated 5-(S)-aminothiophenoxazolidinone derivatives of S-oxide and S,S-dioxide tetrahydro-4(2H)-thiadiazole phenyl oxazolidinone series have been synthesized on a solid phase and evaluated for antibacterial activity. Representative analogues 2, 5, and 6 display an improved potency versus linezolid against gram-positive and fastidious gram-negative pathogens. The compounds are also active against linezolid- and ciprofloxacin-resistant Staphylococcus au-

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669. N-Acylated ornithine analogues of daptomycin were synthesized and tested for their antibacterial efficacy in vivo in different C-5 acetamidomethyl side chain of the oxazolidonone antibacterials. © 2003 Elsevier Ltd. All rights reserved.

670. New antibacterial tetrahydro-4(2H)-thiophyran and thio-
morpholine S-oxide and S,S-dioxide phenylloxazolidinones - Singh U., Raju L., Lam S. et al. [M.F. Gordeev, Vicuron Pharmaceuticals Inc., 34790 Ardentech Court, Fremont, CA 94555, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4209-4212) - sum in ENGL

Combinatorial libraries of N-acylated 5-(S)-aminothiophenoxazolidinone derivatives of S-oxide and S,S-dioxide tetrahydro-4(2H)-thiophyran and thiomorpholine phenylloxazolidinone series have been synthesized on a solid phase and evaluated for antibacterial activity. Representative analogues 2, 5, and 6 display an improved potency versus linezolid against gram-positive and fastidious gram-negative pathogens. The compounds are also active against linezolid- and ciprofloxacin-resistant Staphylococcus au-

The MOA for these new antimicrobials is consistent with a combination of protein synthesis and gyrase A/topoisomerase IV inhibition, with a structure-dependen-
ted degree of the contribution from each inhibitory mechanism. © 2003 Elsevier Ltd. All rights reserved.

671. The synthesis and in vitro structure-activity relationships of various chelator groups, alpha substituents, P2 substituents in order to achieve optimal antibacterial activity with minimal toxicity liability. © 2003 Elsevier Ltd. All rights reserved.

672. The identifi-
cation of a series of compounds that specifically in-
hibit efflux by the MexAB-OpM pump system in Pseudomonas aeruginosa is described. Synthesis and in vitro structure-activity relationships (SARs) are outlined. Early leads lacked activity in animal models, and efforts to improve solubility and reduce serum protein binding by the introduction of polar groups are discussed. © 2003 Elsevier Ltd. All rights reserved.

673. Novel efflux pump inhibitors in Pseudo-

We report the synthesis and biological activity of analogues of (S)-1-(3-[(2'-S-(tert-butoxycarbonyl)-N-hydroxy-3-R-butyl-3-

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674. Novel efflux pump inhibitors in Pseudo-
monas aeruginosa. Part 1: Discovery and early strategies for lead optimization - Nakayama K., Ishida Y., Ohtsuka M. et al. [K. Nakayama, Med. Chemistry Research Laboratory, Daichi Pharma-
aceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4201-4204) - sum in ENGL

We report the synthesis and biological activity of analogues of (S)-1-(3-[(2'-S-(tert-butoxycarbonyl)-N-hydroxy-3-R-butyl-3-

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675. Combinatorial libraries of N-acylated 5-(S)-aminothiophenoxazolidinone derivatives of S-oxide and S,S-dioxide tetrahydro-4(2H)-thiophyran and thiomorpholine phenylloxazolidinone series have been synthesized on a solid phase and evaluated for antibacterial activity. Representative analogues 2, 5, and 6 display an improved potency versus linezolid against gram-positive and fastidious gram-negative pathogens. The compounds are also active against linezolid- and ciprofloxacin-resistant Staphylococcus au-

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676. Novel efflux pump inhibitors in Pseudo-

We report the synthesis and biological activity of analogues of (S)-1-(3-[(2'-S-(tert-butoxycarbonyl)-N-hydroxy-3-R-butyl-3-

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677. Structure-activity relationship in the oxazolidinone-quin-
olone hybrid series: Influence of the central spacer on the

Oxazolidinone-quinolone hybrids, which combine the pharma-coptrophores of a quinolone and an oxazolidinone, were synthesised and shown to be active against a variety of susceptible and resistant Gram-positive and Gram-negative bacteria. The nature of the spacer greatly influences the antibacterial activity by directing the mode of action, that is quinolone- and/or oxazolidinone-like activity. The best compounds in this series have a balanced dual mode of action and overcome all types of resistance, including resistance to quinol-one and linezolid, in clinically relevant Gram-positive pathogens. © 2003 Elsevier Ltd. All rights reserved.

672. The effect of remote chirality on the antibacterial activity of indolinyl, tetrahydroquinolyl and dihydrobenzoxazinyl oxazolidinones - Ciske F.L., Barbachyn M.R., Genin M.J. et al. [M.R. Barbachyn, Pfizer, 7000 Portage Road, Kalamazoo, MI 49001, United States] - BIOORG. MED. CHEM. LETT. 2003 13/23 (4235-4239) - summ in ENGL

The oxazolidinones are promising agents for the treatment of infections caused by gram-positive bacteria, including multidrug-resistant strains. In ongoing studies we have discovered that a strategically placed chiral center of appropriate absolute configuration improves the antibacterial activity of indolinyl oxazolidinone analogues (gram-positive MIC’s of 0.5 µg/mL for the most potent compounds). The design, synthesis, antibacterial activity and phar-macokinetic profile of a selected series of α-methylated indoline derivatives and a related set of tetrahydroquinolyl and dihydrobenzen-oxazinyl analogues are discussed. © 2003 Published by Elsevier Ltd.


Following the optimization of diamine-containing efflux pump inhibitors with respect to in vitro potentiation activity, in vivo stability and acute toxicity, we addressed the question of how to control the pharmacokinetic properties of the series. Upon intravenous administration in the rat, tissue levels of MC-04,124 (the lead compound) were high and prolonged compared to those in the serum. The lipophilicity and basicity of analogues of this compound were systematically varied, and effects on potency and pharmacokinetics explored. The ratio of drug levels in tissue versus serum was not significantly reduced in any of the active analogues examined. © 2003 Published by Elsevier Ltd.


Synthetic array technology was utilized to rapidly synthesize and analyze a diverse set of reductive alklylation analogues of daptycmin. Analysis of the array suggested the use of polar functionality such as sulfonamides or amide or polar spaces such as piperazine would beneficially affect activity. © 2003 Elsevier Ltd. All rights reserved.

675. Square wave adsorptive stripping voltammetric determi-nation of piromidic acid. Application in urine - Guiberteau Cabanillas A., Ortiz Burguillo J.M., Martínez Cañas M.A. et al. [A. Guiberteau Cabanillas, Department of Analytical Chemistry, Faculty of Sciences, University of Extremadura, Avda. Elvas s/n, 06071 Badajoz, Spain] - J. PHARM. BIOMED. ANAL. 2003 33/4 (553-562) - summ in ENGL

A simple procedure for the determination of piromidic acid by square wave adsorptive stripping voltammetry (SW-AASV) at a hanging mercury drop electrode has been developed. The variables affecting to accumulation process such as concentration of perchloric acid, accumulation potential and accumulation time have been optimised (0.025 mol L-1, -0.25 V and 140 s, respectively) by using response surface methodology. A linear relationship between concentration of piromidic acid and peak intensity has been found in the range 2.22×10-9 to 3.33×10-6 mol L-1. The detection limit (1.65×10-9 mol L-1) has been calculated by the method proposed by Clayton et al. so that protection against both false positive and false negative errors is assured. The procedure was successfully applied to determine piromidic acid in spiked urine samples. The obtained recovery values were in the range 97.3-103.3% at different levels of concentration of piromidic acid. © 2003 Elsevier B.V. All rights reserved.


To obtain molecular insights into the action mode of antimicrobial activity of pediocin PA-1, the interactions between this bacteriocin and dimyristoylphosphatidyicholine (DMPC) or dimyristoylphospho-tidylglycerol (DMPG) model membranes have been investigated in D2O at pH 6 by Fourier transform infrared spectroscopy. The interactions were monitored with respect to reflection of the sec-ondary structure of pediocin, as registered by the amide I’ band, and phospholipid conformation, as revealed by the methylene v(CH2) and carbonyl v(C=O) stretching vibrations. The results show that no interaction between pediocin and DMPC occurs. By contrast, pediocin undergoes a structural reorganization in the presence of DMPG. Upon heating, pediocin self-aggregates, which is not ob-served for this p3D in aqueous solution. The gel-to-crystalline phase transition of DMPG shifts to higher temperatures with a concomi-tant dehydration of the interfacial region. Our results indicate that pediocin is an extrinsic peptide and that its action mechanism may lie in a destabilization of the cell membrane.

677. The effects of fruit juices on drug disposition: A new model for drug interactions - Dresser G.K. and Bailey D.G. [Dr. G.K. Dresser, Department of Medicine, London Health Sciences Centre, Victoria Campus, 370 South Street, London, Ont., Canada] - EUR. J. CLIN. INVEST. SUPPL. 2003 33/2 (10-16) - summ in ENGL

Grapefruit juice produces mechanism-based inhibition of intesti-nal drug metabolism when consumed in normal quantities. This can produce clinically important increases in oral drug bioavailabil-it y when coadministered with substrates of cytochrome P450 3A4 (CYP3A4) that undergo high presystemic metabolism. Furamocou-maris such as bergamottin and 6,7,9′- dihydroxybergamottin have been identified as probable active constituents. Grapefruit juice may also inhibit intestinal P-glycoprotein-mediated efflux transport of drugs such as cyclosporine to increase its oral bioavailability. However, grapefruit juice does not enhance the absorption of di-goxin, a prototypical P-glycoprotein substrate, likely because it has high inherent oral bioavailability. Grapefruit and other fruit juices have recently been shown to be potent in vitro inhibitors of a number of organic anion-transporting polypeptides (OATPs). These juices were also found to decrease the absorption of the nonmetabolized OATP substrate, lexofenadine. Taken together, the data support in-hibition of intestinal uptake transporters by fruit juices to decrease drug bioavailability. This would represent a new mechanism for food-drug interactions. These findings with grapefruit and other fruit juices continue to enhance our understanding of the complex nature of food-drug interactions, and their possible influence on the clinical effects of medications.

678. Pharmacokinetic characterization of a human immuno-deficiency virus protease inhibitor, saquinavir, during ethanol intake in rats - Shibata N., Kageyama M., Kishida T. et al. [N. Shibata, Department of Pharmacokinetics, Kyoto Pharmaceutical University, 5 Nakauchi-cho Missasagi, Yamashina-ku, Kyoto 607-8414, Japan] - BIOPHARM. DRUG DISPOS. 2003 24/8 (335-344) - summ in ENGL

Throughout therapeutic drug monitoring of human immuno-deficiency virus (HIV) protease inhibitors in HIV-infected patients,
it was found that plasma concentrations of saquinavir (SQV) were reduced in patients who had a habit of alcohol intake during double protease therapy with SQV and ritonavir (RTV). This study confirmed the pharmacokinetic profiles of SQV during ethanol intake in rats.

After oral administration of SQV alone (20mg/kg) in rats prepared for free access to 15% ethanol solution for 14 days (day 14 rats), the area under the concentration vs time curves (AUC) showed a significant decrease (p<0.01) in comparison with control rats from 0.78 ± 0.10 to 0.38 ± 0.03 μg/mL. For intravenous administration of SQV alone (5mg/kg) to day 14 rats, the total body clearance increased significantly by 1.4-fold (p < 0.05), whereas for intracolonic administration of SQV alone, no significant differences in the values of pharmacokinetic parameters were found between control and day 14 rats. With RTV, which has the strongest inhibitory effect on the CYP3A enzyme of the current HIV protease inhibitors, the AUC values of SQV at RTV doses of 2 and 20mg/kg in day 14 rats also decreased significantly (p<0.05) from 0.06 to 0.57 ± 0.05 μg/mL and from 17.63 ± 1.66 to 4.18 ± 0.94 μg/mL respectively, indicating that the degree of the decrease of AUC values after oral administration with RTV after ethanol intake was larger than the mono-therapy with SQV. This study showed that ethanol-intake decreases the bioavailability of SQV after oral administration alone or with RTV. These observations provide useful information on the treatment of HIV-infected patients when they receive a combination therapy with SQV and RTV, and arouse the attention for the effects of alcohol intake. Copyright © 2003 John Wiley & Sons, Ltd.

679. A simple and sensitive assay for cefepime in human plasma using high performance liquid chromatography - Kim Y.-S., Yim D.-S., Lee D.-G. and Lee S.-B. [D.-S. Yim, Department of Pharmacology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Soncho-gu, Seoul 137-701, South Korea] - KOREAN J. PHYSIOL. PHARMACOL. 2003/74 (247-250) - sum in ENGL. A simple and sensitive assay method was developed for cefepime in human plasma using high performance liquid chromatography (HPLC). Cefepime and cefadroxil (the internal standard) were extracted from heparinized human plasma by simple deproteination with perchloric acid. The extract was injected into an Atlantis dC18 column (250 x 4.6 mm; particle size 5 μm, Waters) and the column was eluted with methanol and 0.01 M dihydrogen phosphate at pH 3.0 (15 : 85 v : v) as a mobile phase at a flow rate of 0.7 mL/min. Linearity was confirmed for the range 0.25 to 200 μg/mL and the limit of quantitation was 0.25 μg/mL. The retention times were 10.2 min and 13.4 min for cefepime and cefadroxil, respectively. This method was successfully applied to a pharmacokinetic study of cefepime in plasma from bone marrow transplant patients.


The continuing rise of resistance rates among bacteria today has led to the need for the development of new antibiotics with the ability to circumvent current resistance mechanisms. Daptomycin (Cubicin, Cubist Pharmaceuticals) is an injectable novel lipopeptide antibiotic shown to have excellent in vitro bactericidal activity against gram-positive organisms, including resistant isolates. First in this class of lipopeptide antibiotics, daptomycin possesses a unique mechanism of action. Clinical studies in patients with complicated skin and skin structure infections have shown daptomycin to be similar in clinical cure rates compared to standard therapy, Daptomycin was recently approved by FDA for the treatment of complicated skin and skin structure infections caused by susceptible strains of specific gram-positive microorganisms. Daptomycin may offer an alternative in the treatment of gram-positive infections, especially when resistance is suspected.


The primary objective was to determine whether rifampicin influences the pharmacokinetics of enfuvirtide in HIV-1-infected patients. In a single-center, open-label, one-sequence crossover, clinical pharmacology study, 12 HIV-1-infected adults received enfuvirtide (90 mg, twice daily) on days 1 to 3 and days 11 to 13 (morning dose only on days 3 and 13) and rifampicin (600 mg, once daily) from days 4 to 13. Plasma concentrations were measured for enfuvirtide and its metabolite (days 3 and 13) and rifampicin (day 13 only). The ratios of least squares means (LSM) and 90% confidence intervals for enfuvirtide and enfuvirtide metabolite pharmacokinetic parameters (AUC12h, Cmax, Cmax/CL) were estimated in the presence and absence of rifampicin. Treatments were compared using an analysis of variance for natural log-transformed variables, with factors patient and treatment. Efficacy and safety were also monitored. Steady-state rifampicin had no appreciable effect on any of the pharmacokinetic parameters assessed for either enfuvirtide or its metabolite. The ratio of LSM for AUC12h, Cmax, Cmax/CL for enfuvirtide was 97.5%, 103%, and 98.9%, respectively, and 108%, 112%, and 92.9%, for the enfuvirtide metabolite. Rifampicin did not affect the t1/2 of enfuvirtide or its metabolite. There were no unexpected effects of rifampicin on the short-term antiviral effect or safety of the administered antiretroviral treatment. The pharmacokinetics of enfuvirtide are not induced by a 10-day pretreatment with rifampicin.

682. Synthesis and anti-measles virus activity of new isoquinol-1-one derivatives - Santagati N.A., Bousquet E., Garozzo A. et al. [N.A. Santagati, Dptto. di Scienze Farmaceutiche, Facolta di Farmacia, Univ. degli Studi di Catania, Viale Andrea Doria, 6, 95125 Catania, Italy] - J. PHARMACO 2003 58/12 (1217-1225) - sum in ENGL.

Despite intense efforts to increase vaccine coverage, measles virus (MV) still causes significant morbidity and mortality in the world sometimes as a results of severe, chronic and lethal diseases. In an effort to develop therapies to supplement immunization strategies a number of 1-oxo-2-[1(E)-phenylmethylene]amino]-1,2-dihydrosoxiquinoline-4-carboxylic acid derivatives were synthesized and evaluated for anti-measles activity. The substrates on the aromatic ring were chosen in order to evaluate the influence of electron-withdrawing or electron-donating effects on the electronic density of the aromatic moiety. We also evaluated the introduction of a vinyl chain between the exocyclic nitrogen and phenyl moiety. The biological results allow to outline some preliminary considerations on structure-activity relationship. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.


The different dialkyl and diaryl diselenides with carbamoyl and sulfonyl moieties 2, 3, 5 and other substituents in the ortho position of benzene ring 4, 7, 8 as well as derivatives of 1,2,4-benzoxadiazine (6) were designed as antiviral and antimicrobial agents and synthesized. Some of them, particularly 8a and 8b, were found in the antiviral assay in vitro to be strong inhibitors of cytopathic activity encephalomyocarditis virus (EMCV). The compound 4a and 8a were found to have a broad spectrum of activity against bacteria, yeasts and pathogenic fungi in vitro. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

684. Synthesis of styrlybenzofuran derivatives as styrlyquinone analogues for HIV-1 integrase inhibitor - Yoo H., Lee J.Y., Park J.H. et al. [Y.S. Lee, Medicinal Chemistry Research Center, Life Sciences Division, Korea Inst. of Sci. and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, South Korea] - J. PHARMACO 2003 58/12 (1243-1250) - sum in ENGL.

A series of styrlybenzofuran derivatives (8a-i) as styrlyquinone isoformers were efficiently prepared by Wittig reaction and evaluated for inhibitory activity against HIV-1 integrase. In this series compounds 8g, 8h and 8i containing a free catechol ring showed

A new series of 3-alkyl-, 3-trifluoromethyl-, 3-carboxyethyl- and 3-bromomethylquinoloxin-2-ones and 2,3-bis(carboxyethyl)quinoloxines bearing Cl, CF3, morpholine on the benzo-moity, were synthesised and submitted to a preliminary in vitro evaluation for antibacterial and antifungal activities. Results of the screening showed that compounds 9b, 14b and 19b (MIC=62.5 µg/ml) and 10b (MIC=15.6 µg/ml) were the most active against Vibrio alginolyticus. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.

686. Synthesis and antimicrobial activities of some new benzimidazole derivatives - Ayhan-Kilcigil G. and Altanar N. [G. Ayhan-Kilcigil, Dept. of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, 06100 Tando{g}an, Ankara, Turkey] - FARMACO 2003 58/12 (1345-1350) - summ in ENGL

Some benzimidazolylbenzamides were synthesized and their antimicrobial activities against Staphylococcus aureus, Streptococcus faecalis, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans evaluated. It was shown that the compound 14 exhibited the best activity against B. subtilis, P. aeruginosa and C. albicans. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.


From ether extracts of the tunicate Cynthia savignyi, collected in Morocco, a new alkaloid-cynthichlorine-has been isolated. The structure of cynthichlorine was determined to be a natural product of unusual chemical composition. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.

688. Effect of polyamines on the inhibition of peptidyltransferase by antibiotics: Revisiting the mechanism of chloramphenicol action. Here, we examine further the inhibition effect of chloramphenicol (I) on the peptidyltransferase activity and increases the chloramphenicol potency, without affecting the isomerization step. As indicated by photoaffinity labeling, the peptidyltransferase center at which chloramphenicol binds, is one of the preferred cross-linking sites for polyamines. This fact may explain the effect of spermine on chloramphenicol binding to ribosomes.


We have performed solid-state 31P-19F REDOR nuclear magnetic resonance (NMR) experiments to monitor changes in minor groove width of the oligo-nucleotide d(CGCAAA)3/UTGCC-d(GCCATGpT)TGGCG (A3T2) upon binding of the drug distamycin A at different stoichiometries. In the hydrated solid-state sample, the minor groove width for the unbound DNA, measured as the 2±UT-p819 inter-label distance, was 9.4 ± 0.7 Å, comparable to that found for similar A-T-rich DNAs. Binding of a single drug molecule is observed to cause a 2.4 Å decrease in groove width. Subsequent addition of a second drug molecule results in a larger conformational change, expanding this minor groove width to 13.6 Å, consistent with the results of a previous solution NMR study of the 2:1 complex. These 31P-19F REDOR results demonstrate the ability of solid-state NMR to measure distances of 7-14 Å in DNA-drug complexes and provide the first example of a direct spectroscopic measurement of minor groove width in nucleic acids.


A potential means to improve the efficacy of steric-blocking anti-sense oligonucleotides (ON) is to increase their affinity for a target RNA. The grafting of cationic amino groups to the backbone of the ON is one way to achieve this, as it reduces the electrostatic repulsion between the ON and its target. We have examined the duplex stabilising effects of introducing cationic phosphoramidate internucleoside linkages into ON with a non-natural α-anomeric configuration. Cationic α-ON bound with high affinity to single-stranded DNA and RNA targets. Duplex stabilisation was proportional to the number of cationic modifications, with fully cationic ON having particularly high thermal stability. The average stabilisation was greatly increased at low ionic strength. The duplex formed between cationic α-ON and their RNA targets were not substrates for RNase H. The penalty in Tm in an RNA target, reflected by a single mismatch, however, was high; suggesting that they are well suited as sequence-specific, sterically-blocking, antisense agents. Using a well-described target sequence in the internal ribosome entry site of the human hepatitis C virus, we have confirmed this potential in a cell-free translation assay as well as in a whole cell assay. Interestingly, no vectorisation was necessary for the cationic α-ON in cell culture.

691. Functional dissection of the C-terminal domain of type II DNA topoisomerase from the kinetoplastid hemoflagellate Leishmania donovani - Sengupta T., Mukherjee M., Mandal C. et al. [H.K. Majumder, Department of Molecular Parasitology, Development and Molecular Modeling, Indian Institute of Chemical Biology, Kolkata 700032, India] - NUCLÉIC ACIDS RES. 2003 31/18 (5305-5316) - summ in ENGL

The amino acid sequences of the C-terminal domain of type II DNA topoisomerase from the kinetoplastid hemoflagellate Leishmania donovani contained two divergent C-terminal domains. A set of C-terminal deletion mutants of Leishmania donovani topoisomerase II was constructed. Removal of more than 178 amino acids out of 1236 amino acid residues from the C-termius inactivates the enzyme, whereas removal of 118 amino acids or less has no apparent effect on the ability of the enzyme to complement a temperature-sensitive mutation of the Saccharomyces cerevisiae.
cerevisiae topoisomerase II gene. Deletion analysis revealed a po-
tent nuclear localization signal (NLS) within the amino acid residues
998-1058. Immunomicroscopy results suggest that the removal of
an NLS in the CTD is likely to contribute to the physiological
dysfunction of these proteins. Modeling of the LiTF2 based on
the crystal structure of the yeast type II DNA topoisomerase showed
that the parasite protein assumes a structure similar to its yeast coun-
terpars harboring all the conserved residues in a structurally similar
position. However, a marked difference in electrostatic potential
was found in a span of 60 amino acid residues (998-1058), which also
do not have any homology with topoisomerase II sequences. Such
significant differences can be exploited by the structure-based
design of selective inhibitors using the structure of the Leishmania
enzyme as a template.

692. Antifungal therapy - State of the art at the beginning of
the 21st century - Polak A. [Dr. A. Polak, Spitzenzrainweg 45,
CH-4147 Aesch, Switzerland] - PROG. DRUG RES. 2003 2/SPEC.
ISS. (59-190) - sumin in ENGL

The most relevant information on the present state of the art of
antifungal chemotherapy is reviewed in this chapter. For dermato-
orelated infections, a wide variety of topical antifungals are available, and safe and
efficacious systemic treatment, especially with the fungicidal drug
terbinfine, is possible. The duration of treatment can be drastically
shortened. Substantial progress in the armamentarium of drugs for
invasive fungal infections has been made, and a new class of anti-
fungals, echinocandins, is now in clinical use. The following drugs
in oral and/or intravenous formulations are available: the broad
spectrum polyene amphotericin B with its new "clothes"; the sterol
biosynthesis inhibitors flucanazole, itraconazole, and voriconazole;
the glucon synthase inhibitor caspofungin; and the combination
partner flucytosine. New therapy schedules have been studied;
combination therapy has found a significant place in the treatment of
severely compromised patients, and the field of prevention and
empiric therapy is fast moving. Guidelines exist nowadays for the
treatment of various fungal diseases and maintenance therapy. New
approaches interfering with host defenses or pathogenicity of fungal
cells are being investigated, and molecular biologists are looking
for new targets studying the genomics of pathogenic fungi.

693. Single-Dose Azithromycin for Acute Otitis Media: A Phar-
macokinetic/ Pharmacodynamic Rationale - Rothermel C.D. [Dr.
C.D. Rothermel, Clinical Research, Anti-Infectives, Pfizer Inc., 235
East 42nd Street, New York, NY 10017, United States] - CURR.
THER. RES. CLIN. EXP. 2003 64/SUPPL. A (A4-A15) - sumin in
ENGL

The pharmacokinetic (PK) and pharmacodynamic (PD) proper-
ties of the azalide azithromycin distinguish it from other antibiotics.
The PK profile of azithromycin features high tissue-to-serum ratios,
including high concentrations in the middle ear, and a prolonged
elimination half-life. These characteristics result from the accumu-
lation of drug within cells and its subsequent slow, sustained release
from cells and tissues into the bloodstream. The PD properties of
azithromycin include bactericidal activity against key respira-
tory tract pathogens and a prolonged postantibiotic, or persistent,
effect. In addition, white blood cells deliver the drug to infected
foci, thereby enhancing local tissue concentrations and improving in
vivo efficacy. Recent PK studies in mice suggest that a single, large
dose of azithromycin achieves higher tissue concentrations than do
multidose regimens. Other studies in animal infection models, in
particular, a gerbil model of acute otitis media, have demonstrated
improved bacterial eradication when azithromycin is administered
as a single dose rather than divided over 2 or 3 days. Taken together,
the results from the preclinical studies provide a PK/PD rationale
for the use of single-dose azithromycin in the treatment of acute
otitis media. Clinical data on the efficacy and safety of single-dose
azithromycin for the treatment of acute otitis media in children are
presented in 2 accompanying articles in this supplement. Copyright
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694. A Pilot Study of Single-Dose Azithromycin Versus
Three-Day Azithromycin or Single-Dose Ceftriaxone for Un-
complicated Acute Otitis Media in Children - Arguedas A.,
Louza C., Perez A. et al. [Dr. A. Arguedas, Inst. de Atencion
Pediat., San José, Costa Rica] - CURR. THER. RES. CLIN. EXP.
2003 64/SUPPL. A (A16-A29) - sumin in ENGL

Background: The pharmacokinetic profile of azithromycin sup-
ports its use as single-dose therapy for uncomplicated acute otitis
media (AOM) in children. Objective: This study was designed to
to clinically evaluate the safety of single-dose oral azithromycin, 3 daily
doses of oral azithromycin, and a single dose of intramuscular ce-
fraxone for the treatment of uncomplicated AOM in children, and
(2) to provide preliminary efficacy data to support the initiation of a larger,
comparative trial of single-dose azithromycin for the treatment of
uncomplicated AOM in children. Methods: In this single-center
pilot study, children with uncomplicated AOM were randomly as-
signed to receive single-dose oral azithromycin (30 mg/kg), 3-day
oral azithromycin (10 mg/kg once daily), or single-dose intramuscu-
lar ceftraxone (50 mg/kg). Tympanocentesis was performed before
administration of the first dose, and clinical response was assessed
on days 1, 4, 15 and 28-30. Results: Between September 1999 and
May 1997, 198 children (mean age, 2.5 years) were enrolled. All
of the patients were evaluable for the safety and clinical intent-to-
treat (ITT) analyses, and 98 were evaluable for the microbiologic
ITT analysis. On day 14-15, rates of clinical success (cure or
improvement) for the 3 treatment groups were: 62/64 (97%) for
single-dose azithromycin, 60/63 (95%) for 3-day azithromycin, and
61/62 (98%) for single-dose ceftraxone. On day 28-30, the correspond-
ing clinical success rates were 61/65 (94%), 61/66 (92%), and
62/64 (97%). For the 98 microbiologically evaluable patients,
clinical success rates at day 14-15 were 26/30 (87%) for single-
dose azithromycin, 31/35 (89%) for 3-day azithromycin, and 33/33
(100%) for single-dose ceftraxone. On day 28-30, the correspond-
ing clinical success rates were 27/30 (90%), 30/35 (86%), and 32/33
(97%). Treatment-related adverse event rates for single-dose azi-
thromycin, 3-day azithromycin, and single-dose ceftraxone were
10.6%, 9.1%, and 9.1%, respectfully. Conclusion: In this pilot study
comparing single-dose azithromycin, 3-day azithromycin, and
single-dose ceftraxone for the treatment of uncomplicated AOM
in children, no differences were detected among the 3 regimens.
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695. Single-Dose (30 mg/kg) Azithromycin Compared with
10-Day Amoxicillin/Clavulanate (45 mg/kg per day) for the
Treatment of Uncomplicated Acute Otitis Media - Block S.L.,
Arrieta A., Seibel M. et al. [Dr. S.L. Block, Kentucky Pediatric
Research, 201 South Fifth Street, Bardstown, KY 40004, United
States] - CURR. THER. RES. CLIN. EXP. 2003 64/SUPPL. A (A30-
A42) - sumin in ENGL

Background: The long half-life of azithromycin allows for single-
dose oral therapy for acute otitis media (AOM). Objective: This
study was designed to compare the efficacy and safety of single-
dose azithromycin with 10-day, twice-daily amoxicillin/clavulanate
for the treatment of new-onset, uncomplicated AOM in children.
Methods: Children aged 6 months to 12 years with new-onset AOM
were randomly assigned to receive either a single 30-mg/kg dose
of azithromycin or standard-dose amoxicillin/clavulanate (45 mg/kg
day divided BID for 10 days) in a double-blind, double-placebo,
multicenter clinical trial. The diagnosis of AOM was based on
cific clinical signs and symptoms, and was confirmed by pneumatic
otoscope and acoustic reflectometer (level ≥ 3). Clinical response
was assessed on days 12-16 and 28-32. Results: Mean (SD) age of
children receiving azithromycin (n = 173) or amoxicillin/clavula-
nate (n = 173) was 2.7 (2.3) years and 3.4 (2.8) years, respectively,
with 43% and 36% ≤ 2 years of age. Clinical success rates (intent-
to-treat) for azithromycin and amoxicillin/clavulanate, respectively,
were 87% and 88% (95% CI, 92.2 to 6.5) on day 12-16 and 75%
and 75% (95% CI, 1.2 to 10.5) on day 28-32. The incidences of
treatment-related adverse events for azithromycin and amoxicillin/
clavulanate were 16.8% and 22.5%, respectively. Clinical success
rates of diarrhea were 6.4% and 12.7%, respectively. Vomiting,
which was generally mild, occurred in 7 children in each group.
One azithromycin patient and 5 amoxicillin/clavulanate patients
discontinued treatment because of adverse events. The compli-
ance rate for azithromycin was significantly higher than that for
amoxicillin/clavulanate (99% vs 83%; P < 0.001). Conclusions:
In this trial comparing the efficacy of single-dose azithromycin
(30 mg/kg) with amoxicillin/clavulanate (45 mg/kg per day) for the
treatment of new-onset, uncomplicated AOM, no differences were

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detected between the 2 regimens. Single-dose azithromycin was generally well tolerated and provides an alternative to conventional oral regimens for AOM. Copyright © 2003 Excerpta Medica, Inc.


The preparation and evaluation as potential anti-protozoal agents of molecules bearing an endocyclic hydrazine moiety is presented. The synthetic route to this new series of compounds is straightforward, involving a hetero Diels-Alder reaction between different benzotropolone esters and diethyl azodicarboxylate (DEAD). While they show limited or no in vitro activity against Leishmania donovani, Plasmodium falciparum and Trypanosoma brucei rhodesiense, several of the compounds have activities against Trypanosoma cruzi in the 15.8-41.0 \( \mu \)M range. These activities are comparable to that of benznidazole (IC50 6.0 \( \mu \)M), the main chemotherapy employed in the treatment of T. cruzi infections. In addition, all but one of the new bicyclic hydrazine esters are virtually non-toxic, one of the most important drawbacks of currently available trypanocidal drugs. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

697. Polysubstituted pyrazoles, part 5. Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems. A novel class of potential antimicrobial and anti-HCV agents - Rostom S.A.F., Shalaby M.A. and El-Demellawy M.A. [S.A.F. Rostom, Department of Medicinal Chemistry, Fac. of Medicine and Allied Sciences, King Abdul-Aziz University, P.O. Box 80205, Jeddah 21589, Saudi Arabia] - EUR. J. MED. CHEM. 2003 38/11-12 (959-974) - sum in ENGL.

A novel series of 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems are reported. A new class of potential antimicrobial and anti-HCV agents has been identified. The synthetic route to this new series of compounds is straightforward, involving a hetero Diels-Alder reaction between different benzotropolone esters and diethyl azodicarboxylate (DEAD). While they show limited or no in vitro activity against Leishmania donovani, Plasmodium falciparum and Trypanosoma brucei rhodesiense, several of the compounds have activities against Trypanosoma cruzi in the 15.8-41.0 \( \mu \)M range. These activities are comparable to that of benznidazole (IC50 6.0 \( \mu \)M), the main chemotherapy employed in the treatment of T. cruzi infections. In addition, all but one of the new bicyclic hydrazine esters are virtually non-toxic, one of the most important drawbacks of currently available trypanocidal drugs. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.


Several diflunisal hydrazide-hydrazone derivatives namely 2\(\cdot\)4-difluoro-4-hydroxyphenyl-3-carboxylic acid [5-nitro-2-furyl substituted phenylimethylene] hydrazide (3a) have been synthesised. Methyl 2\(\cdot\)4-difluoro-4-hydroxyphenyl-3-carboxylic acid hydrazide (2) were also synthesised and used as intermediates. All synthesised compounds were screened for their anticytotoxicity and anti-HCV activity against Mycobacterium tuberculosis H37Rv, antimalarial activities against Plasmodium falciparum and Trypanosoma brucei rhodesiense, and anti-HCV activity and wide anti-bacterial spectra, similar to the activity of N. vani, Plasmodium falciparum and Trypanosoma brucei rhodesiense, several of the compounds have activities against Trypanosoma cruzi in the 15.8-41.0 \( \mu \)M range. These activities are comparable to that of benznidazole (IC50 6.0 \( \mu \)M), the main chemotherapy employed in the treatment of T. cruzi infections. In addition, all but one of the new bicyclic hydrazine esters are virtually non-toxic, one of the most important drawbacks of currently available trypanocidal drugs. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

700. Synthesis and anti-microbial activities of choline-like quaternary ammonium chlorides - Pernak J. and Chwałkowska H. - EUR. J. MED. CHEM. 2003 38/11-12 (1035-1042) - sum in ENGL.

New choline-like quaternary ammonium chlorides were obtained. The work-up procedure of synthesis was quick and efficient. The obtained chlorides showed anti-microbial activities. Quaternary ammonium chlorides derivatives of deamin esters exhibited strong activity and wide anti-bacterial spectra, similar to the activity of benzalkonium chloride. The relationship between chemical structure and anti-microbial activity was analyzed by the QSAR method. © 2003 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

701. A quantum chemical and statistical study of flavonoid compounds (flavones) with anti-HIV activity - Souza J. J., De Almeida Santos R.H., Ferreira M.M.C. et al. - EUR. J. MED. CHEM. 2003 38/11-12 (929-938) - sum in ENGL.
The molecular orbital semi-empirical method AM1 was employed to calculate a set of molecular properties (variables) of 22 flavonoid compounds (flavones) with anti-HIV-1 activity and nine new compounds were proposed for anti-HIV-1 activity prediction. Pattern recognition techniques, principal component analysis (PCA), hierarchical cluster analysis (HCA), stepwise discriminant analysis (SDA), and K-nearest neighbor (KNN) were used to create patterns of flavones kNN methods and only one of them was predicted as active against HIV-1. © 2003 Editions scientifiques et médicales Elsevier SAS. All rights reserved.


Recently, heteroarylpirimidines (HAP) have been identified as potent inhibitors of capsid maturation. Here we discuss the HAP mode of action comparing the aggregation phenotype of wild-type and mutant core proteins with the respective phenotype imposed by HAP or other agents interacting with core protein. Pertinent tests include core fusion protein-mediated transactivation in a two-hybrid system and capsid formation. The finding that transactivation appeared to be unaffected by HAP or by mutations preventing assembly, is surprising and raises the question for the structure of the interacting hybrid core proteins: Are they monomers, dimers or even oligomers? A direct activity of core fusion monomers is not excluded but considered to be highly unlikely due to rapid homodimerisation. A role of core fusion dimers in transactivation would indicate distinct interactions with a differential sensitivity to HAP. Regarding significance of data gained in two-hybrid systems, caution is necessary, since the site of transactivation is the nucleus, whereas the real site of the core protein interactions during replication is the cytoplasm. Apparently, HAP leave the monomer-monomer interface of HBV core protein unaffected but prevent capsid maturation by interacting with a region known to be crucial for dimer multimerisation and formation of stable capsids. It is suggested to use antivirals as tools for the elucidation of early steps in genome replication and capsid assembly. A frame for this could be the hypothesis that the virus uses soluble core protein, namely intracellular maturation intermediates of HbeAg for a core targeted self-restriction of replication. © 2003 Elsevier Inc. All rights reserved.

703. Involvement of tumor suppressor protein p53 and p38 MAPK in caffeic acid phenethyl ester-induced apoptosis of C6 glioma cells - Lee Y.-J., Kuo H.-C., Chu C.-Y., et al. [T.-H. Tseng, Department of Applied Chemistry, Chung Shan Medical University, No. 110, Sect. 1, Chien Kuo N. Road, Taichung, Taiwan] - BIOCHEM. PHARMACOL. 2003 66/12 (2281-2289) - sum in ENGL

Caffeic acid phenethyl ester (CAPE), an active component of propolis, has many biological and pharmacological activities including antioxidant, anti-inflammatory, antiviral action, and anticancer effect. Our previous studies showed that CAPE exhibited significant cytotoxicity in oral cancer cells. Herein we further investigated the cytotoxicity potential of CAPE and the mechanism of its action in C6 glioma cells. The data exhibited that C6 glioma cells underwent internucleosomal DNA fragmentation 24hr after the treatment of CAPE (50µM). The proportion of C6 glioma cells with hypodiploid nuclei was increased to 24% at 3hr after the exposure. Further results showed that CAPE induced the release of cytochrome c from mitochondria into cytosol, and the activation of CPP32. CAPE application also enhanced the expression of p53, Bax, and Bak. Finally, the potential signaling components underlying CAPE induction of apoptosis were elucidated. We found that CAPE activated extracellular signal-regulated kinase (ERKs) and p38 mitogen-activated protein kinase (p38 MAPK) in C6 glioma cells. More importantly, p38 kinase formed a complex with p53 after the conjugation and thiol groups. The exposure for p53-phospho-serine 15 of p53, and Bax, and inactivate form of CPP32 was suppressed by a pretreatment of a specific p38 MAPK inhibitor, SB203580. The resultant data suggest that p38 MAPK mediated the CAPE-induced p53-dependent apoptosis in C6 glioma cells. © 2003 Elsevier Inc. All rights reserved.

704. Mechanism underlying cytotoxicity of thialysine, lysine analog, toward human acute leukemia Jurkat T cells - Jun Y.D., Rue S.W., Han K.H. et al. [Y.H. Kim, Department of Microbiology, College of Natural Sciences, Kyungpook National University, Taegu 702-701, South Korea] - BIOCHEM. PHARMACOL. 2003 66/12 (2291-2300) - sum in ENGL

We first report the mechanism for the inhibitory effect of the lysine analog, thialysine on human acute leukemia Jurkat T cells. When Jurkat T cells were treated with thialysine (0.32-2.5µM), apoptotic cell death along with several biochemical events such as mitochondrial cytochrome c release, caspase-9 activation, caspase-3 activation, degradation of poly (ADP-ribose) polymerase, and DNA fragmentation was induced in a dose- and time-dependent manner. However, these thialysine-induced apoptotic events were significantly abrogated by an ectopic expression of Bcl-xL, which is known to block mitochondrial cytochrome c release. Deyclubi- quanine, a mitochondrial permeability transition pore inhibitor, also suppressed thialysine-induced apoptotic events. Comparison of the thialysine-induced alterations in the cell cycle distribution between Jurkat T cells transfected with Bcl-xL gene (J/Bcl-xL) and Jurkat T cells transfected with vector (J/Neo) revealed that the apoptotic cells were mainly derived from the cells accumulated in S and G2/M phases following thialysine treatment. The interruption of cell cycle progression in the presence of thialysine was accompanied by a significant decline in the protein level of cdk4, cdk6, edc2, cyclin A, cyclin B1, and cyclin E. These results demonstrate that the cytotoxic activity of thialysine toward Jurkat T cells is attributable to not only apoptotic cell death mediated by a mitochondria-dependent death signaling pathway, but also interruption of cell cycle progression by a massive down-regulation in the level of cdks and cyclins. © 2003 Elsevier Inc. All rights reserved.

705. Highly active antiretroviral therapy and the cardiovascular system: The heart of the matter - Barbaro G. [Dr. G. Barbaro, Viale Anicio Gallo 63, IT-00174 Rome, Italy] - PHARMACOLOGY 2003 69/4 (177-179) - sum in ENGL

Highly active antiretroviral therapy (HAART) has prolonged many patients’ lives, but many cardiac sequelae of HIV are not affected by HAART and continue to develop even with treatment. In addition, HAART itself causes in a high proportion of patients a metabolic syndrome, characterized by lipodystrophy/ lipatrophy, dyslipidemia and insulin resistance that may be associated with an increase in coronary artery disease and stroke. Careful cardiovascular evaluation in the course of HIV disease can identify cardiac complications early enough to treat. All HIV-infected patients are candidates for antiretroviral therapy and patients already under treatment should undergo an assessment that includes the evaluation of the cardiovascular risk according to the available guidelines. Copyright © 2003 S. Karger AG, Basel.


Combination therapy with antiretroviral drugs is used for the treatment of patients infected with the human immunodeficiency virus. To achieve optimal drug concentrations for viral suppression and avoidance of drug toxicity, monitoring of drug levels has been considered essential. We set up an analytical procedure for monitoring the plasma concentrations of a total of seven drugs: abacavir,
6.6. Immunologic agents

707. The contralateral effect conferred by intra-articular ade
novirus-mediated gene transfer of viral IL-10 is specific to the
[Dr. P.D. Robbins, Dept. of Molec. Genet./Biochemistry, Univ.
of Pittsburgh Sch. of Medicine, E1240 Biomedical Science Tower,
Pittsburgh, PA 15261, United States] - GENE THER. 2003 10/24
(2029-2035) - sum in ENGL

We have demonstrated previously that local, adenoviral-mediated
gene transfer of vIL-10 to a single joint of rabbits and mice with
experimental arthritis can suppress disease in both the treated and
untreated contralateral joints. These therapeutic effects observed in
distant untreated joints following local intra-articular gene delivery
have been termed the 'contralateral effect'. To begin to understand
the underlying immunologic mechanism that confers this effect, a
dual-antigen model of antigen-induced arthritis (AIA) in rabbit knee
joints was utilized. Rabbits were immunized against two proteins,
ovoalumin and keyhole limpet hemocyanin, and AIA generated by
intra-articular injection of each antigen into contralateral knees.
Intra-articular adenovirus-mediated gene transfer of vIL-10 sig
ificantly reduced intra-articular leukocytosis and cartilage matrix
degradation, while preserving near normal levels of cartilage matrix
synthesis within treated joints. However, no antiarthritic effect was
confessed in the contralateral control joints that received only a
marker gene, in contrast to the results seen in a single-antigen AIA
model. These results suggest that the distant antiarthritic effects
associated with local gene delivery to joints are antigen-specific,
and not due to vIL-10-induced generalized immunosuppression of
the animal.

708. Comparative sequence analysis of the P-, M- and L-cod
ing region of the measles virus CAM-70 live attenuated vaccine
strain - Santos P.R., Azevedo M.L.B., Borges M.B.J. et al. [M.T.B.
Moraes, Bio-Manguinhos, FIOCRUZ, Av. Brasil, 4365 Rio de
Janeiro, RJ, Brazil] - BRAZ. J. MED. BIOL. RES. 2003 36/11 (1475-
1484) - sum in ENGL

Measles virus is a highly contagious agent which causes a major
health problem in developing countries. The viral genomic RNA is
single-stranded, nonsegmented and of negative polarity. Many live
attenuated vaccines for measles virus have been developed using ei
ther the prototype Edmonston strain or other locally isolated measles
strains. Despite the diverse geographic origins of the vaccine viruses
and the different attenuation methods used, there was remarkable
sequence similarity of H, F and N genes among all vaccine strains.
CAM-70 is a Japanese measles attenuated vaccine strain widely
used in Brazilian children and produced by Bio-Manguinhos since
1982. Previous studies have characterized this vaccine biologically
and genetically. Nevertheless, only the F and N genes have been
sequenced in the present study. We have sequenced the remaining P,
M and L genes (approximately 1.6, 1.4 and 6.5 kb, respectively) to
complete the genomic characterization of CAM-70 and to assess the
extent of genetic relationship between CAM-70 and other cur
rent vaccines. These genes were amplified using long-range or
standard RT-PCR techniques, and the cDNA was cloned and auto-
matically sequenced using the dideoxy chain-termination method.
The sequence analysis comparing previously sequenced genotype
A strains with the CAM-70 Bio-Manguinhos strain showed a low
diversity among them. However, the CAM-70 strains (CAM-70
Bio-Manguinhos and a recently sequenced CAM-70 submaster seed
strain) were assigned to a specific group by phylogenetic analysis
using the neighbor-joining method. Information about our prod
uct at the genomic level is important for monitoring vaccination
campaigns and for future studies of measles virus attenuation.

709. Effects of the Anti-ICAM-1 Monoclonal Antibody, Allo
purinol, and Methylene Blue on Intestinal Reperfusion Injury
- Ilhan H., Alatar O., Tokar B. et al. [Dr. H. Ilhan, Osmangazi
University, Cucuk Cerrahii AD, Meselik. 26480-TR, Eskişehir,
Turkey] - J. PEDiatR. SURG. 2003 38/11 (1591-1595) - sum in
ENGL

Purpose: The aim of this study was to evaluate the effect of
allopurinol, methylene blue, and a monoclonal antibody to the
adhension molecule ICAM-1 in intestinal ischemia and reperfusion
injury. Methods: The rats were divided into 5 groups. CG (n =
8) was untreated controls, SISG (n = 11) received sterile isotonic
saline solution, ICAMG (n = 12) received a monoclonal antibody
to rat ICAM-1, ALLOG (n = 12) received allopurinol, and MBG (n
= 14) received methylene blue. Intestinal ischemia was performed
for 60 minutes followed by 60 minutes of reperfusion. The agents
were injected 10 minutes before the reperfusion to animals. After
60 minutes of reperfusion, the plasma samples for myeloperoxidase
(MPO) activity, tumor necrosis factor alpha (TNF-α) and uric acid
levels, and the intestinal biopsies of ileum and jejunum for histo
pathologic examination were taken. Results: The mucosal damage
was attenuated, and TNF-α level significantly decreased in ALLOG
and ICAMG compared with SISG. The MPO activity was the lowest
in ICAMG, and uric acid level was significantly decreased in AL
LOG compared with the other groups. Methylene blue decreased
TNF-α response to reperfusion injury but significantly increased the
grade of the mucosal damage and the MPO activity. Conclusions:
This study shows that prereperfusion application of allopurinol and
monoclonal antibody to the adhesion molecule ICAM-1 may at
temuate the damage caused by intestinal ischemia and reperfusion,
but the different time-points for application, the effects observed in
the different ischemia and reperfusion durations, and the long-term
results also should be investigated in the same experimental model
before the final conclusion. Methylene blue was not effective to
prevent or attenuate the intestinal tissue injury, but because this was
the first study examining the effect of methylene blue on intestinal
reperfusion injury, further studies with the different doses, ischemic
duration, and application times will be needed. α 2003 Elsevier
Inc. All rights reserved.

710. Hypotension with intravenous immunoglobulin therapy:
Importance of pH and dimer formation - Kroez E.J., Gronski P.
and Dickneite G. [G. Dickneite, Aventis Behring GmbH, Emil von
Behring Strasse 76, 35041, Marburg, Germany] - BIOLOGICALS
2003 31/4 (277-286) - sum in ENGL

Therapy with intravenous immunoglobulin preparations has been
used effectively in a wide range of conditions. Although generally
well tolerated, intravenous immunoglobulin preparations may be
associated with transient hypotension in some patients. This study
examined the role of different immunoglobulin G fractions in the
development of intravenous immunoglobulin-induced hypotension
in an anaesthetized rat model and assessed the effects of a new
liquid immunoglobulin prepared at a low pH on both the formation
of immunoglobulin G dimers and the development of hypotension.
The effects of this new preparation in an experimental autoimmune
encephalomyelitis model were also evaluated. Results from the
haemodynamic studies indicated that immunoglobulin G dimers in
polyclonal immunoglobulin G are responsible for the hypotensive
effects associated with some immunoglobulin preparations. They
also showed that adjustment to an acidic pH results in the rapid
dissociation of immunoglobulin G dimers and prevents the develop-
ment of hypotension. Additional experiments demonstrated that
only immunoglobulin G dimers with a functional Fc fragment can
bind to Fcγ receptors on macrophages to induce the release of blood
pressure-lowering mediators. Moreover, essentially monomeric Fc-
fragments can block the blood pressure-lowering effects of im-
munoglobulin G dimers. Preparation of a new liquid intravenous
immunoglobulin with the pH adjusted to 4.3 prevents the forma-
tion of immunoglobulin G dimers even over long-term storage and
does not significantly affect blood pressure in a rat model. This
preparation is as effective as other intravenous immunoglobulin
preparations in ameliorating symptoms of experimental autoim-
mune encephalomyelitis. These results, like those from previous
studies, indicate that preparation of intravenous immunoglobulin
at a low pH substantially reduces immunoglobulin G dimerization;
this effect significantly decreases the potential for intravenous im-
munoglobulin to induce hypotension without reducing its clinically
relevant biological activity. © 2003 The International Association
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711. Stability of murine, chimeric and humanized antibodies
against pre-S2 surface antigen of hepatitis B virus - Park S.S.,
of Oncology/Biotechnol., 52 Oun-dong, Yasong, Taegu 305-333,
South Korea] - BIOLOGICALS 2003 3/11 (295-302) - sum in ENGL.
We have constructed a humanized antibody with specificity for
the pre-S2 surface antigen of hepatitis B virus (HBV) by grafting
the complementarity determining regions (CDR) of parental
murine monoclonal antibody (mAb) into human anti-αm antibody
framework regions. The humanized antibody has a substitution
at position 94 in a framework region of the heavy chain variable
region, and exhibits the same antigen binding affinity as the parental
murine monoclonal and chimeric antibodies. In order to assess the
stability of these antibodies, thermal inactivation of the parental,
chimeric and humanized antibodies was analyzed. Fifty percent in-
activation of the chimeric and humanized antibodies was observed
at 63.7°C and 68.7°C, respectively, compared to 55.0°C for murine
antibody. The humanized antibody also exhibited increased stability
against denaturant. Guanidine-induced unfolding monitored by the
changes in fluorescence intensity at 360 nm showed that midpoints
of the transition of the chimeric and humanized antibodies were 2.47
M and 2.56 M, respectively, whereas that of the murine antibody
was 1.36 M. © 2003 The International Association for Biologicals.
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712. The immunopharmacology of paclitaxel (Taxol®), doc-
etaxel (Taxotere®), and related agents - Fitzpatrick P.A. and
Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
84103, United States] - INT. IMMUNOPHARMACOL. 2003 3/13-
14 (1743-1749) - sum in ENGL.
The effects of ferric-sorbitol-citrate and ferric-citrate on the sever-
ity of experimental arthritis, TNF-α secretion and the immune status
were examined in mice. Arthritis was induced by intraperitoneal injec-
tion of methylated BSA and intraperitoneal injection of Bordetella
pertussis. Joint and footpad swelling were measured weekly by a
caliper. TNF-α serum levels were measured by ELISA. The immune
status was determined by the response of mouse lympho-
cytes to ConA in vitro and by the antigen-presenting cell assay.
Experimental arthritis was aggravated by ferric-citrate, whereas
ferric-sorbitol-citrate did not promote it. If applied to normal
(non-arthritic) mice three times a week for 4 weeks, ferric-sorbit-
tol-citrate stimulated isolated splenocytes to increase production of
TNF-α, the function of antigen-presenting cells and lymphocyte
proliferation in response to ConA in vitro. TNF-α production by
cultured splenocytes was also stimulated. In mice with antigen-
induced arthritis, iron compounds did not additionally stimulate
TNF-α production. Thus, we have shown that ferric-sorbitol-cit-
rate stimulated TNF-α production, antigen-presenting cell activity
and cellular immune response. Development of antigen-induced ar-
thritis and TNF-α production in arthritic mice were not stimulated.
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715. Effect of endosulfan and malathion on lipid peroxidation,
nitrite and TNF-α release by rat peritoneal macrophages - Ayub
S., Verna J. and Das N. [N. Das, Department of Biochemistry, All
India Inst. of Medical Sciences, Ansari Nagar, New Delhi 110029,
India] - INT. IMMUNOPHARMACOL. 2003 3/13-14 (1819-1828) -
sum in ENGL.
Endosulfan and malathion are organochlorine and organophos-
phate insecticides, respectively. The toxicity of both the insecticides
are well known on non-target organisms. Both endosulfan and
malathion are reported to suppress humoral as well as cellular im-
munological responses. We investigated the possible effect of these
insecticides on lipid peroxidation, nitrite production and TNF-α
release in rat peritoneal macrophages in vitro conditions. Rat
peritoneal cells were collected and cultured with or without in-
secticides and relevant stimulants for lipid peroxidation, generation
of nitric oxide and TNF-α. FeSO4 was used as an inducer for lipid
peroxidation and LPS was used to induce nitric oxide synthase and
release of TNF-α. Lipid peroxidation was assayed by estimating
MDA; nitric oxide was determined by estimating nitrite and TNF-α
by using an assay kit in culture supernatants. Both endosulfan and
malathion had no effect on lipid peroxidation. Endosulfan did not
have any influence on nitrite production, but suppressed the LPS-
induced TNF-α generation. Malathion, however, showed a direct
suppression on nitrite production and suppression of LPS-induced
TNF-α generation. This study suggests that functional aberrations
of macrophages may contribute significantly to the immunomod-
ulation reported for these insecticides. © 2003 Elsevier B.V. All
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126.2

717. Laser scanning confocal fluorescence microscopy: An over-
Immuno/Immunol. Jean Daoust Lab., Graz University M.S. and Hospital,
Auenbruggerplatz 8, A-8036, Graz, LKH, Austria] - INT. IMMU-
NOPHARMACOL. 2003 3/13-14 (1715-1729) - sum in ENGL.
Innovative and important aspects of laser scanning confocal fluo-
rescence imaging (LSCFI) are presented here as a general overview.
We have described and discussed the technology of the procedure
in some detail. We also report some of our original work with
transmembrane uptake of 5S gamma-globulin on living human
leukocytes as an example of one specific application of LSCFI. These
original data and results are presented, as well as citing other
uses and applications, to show the power of LSCFI technique.
The article will hopefully be useful for those not familiar with
the methodology and utility of laser scanning confocal fluorescence
microscopy. Applications of LSCFI are very diverse, and there
are new applications of this technology constantly being developed.
Interest is growing in LSCFI, particularly in the pharmacologic and
therapeutic areas, as demonstrated in this article. © 2003 Elsevier
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714. Differing effects of two iron compounds on experimen-
tal arthritis, TNF-α levels and immune response in mice -
Poljak-Blazić M., Hrvačić B., Žapatnović Z. et al. [M. Poljak-
Blazić, Division of Molecular Medicine, Radjer Bošković Inst., Bijenička
54, 10002, Zagreb Croatia] - INT. IMMUNOPHARMACOL. 2003
3/13-14 (1743-1749) - sum in ENGL.
Endosulfan and malathion are organochlorine and organophos-
phate insecticides, respectively. The toxicity of both the insecticides
are well known on non-target organisms. Both endosulfan and
malathion are reported to suppress humoral as well as cellular im-
munological responses. We investigated the possible effect of these
insecticides on lipid peroxidation, nitrite production and TNF-α
release in rat peritoneal macrophages in vitro conditions. Rat
peritoneal cells were collected and cultured with or without in-
secticides and relevant stimulants for lipid peroxidation, generation
of nitric oxide and TNF-α. FeSO4 was used as an inducer for lipid
peroxidation and LPS was used to induce nitric oxide synthase and
release of TNF-α. Lipid peroxidation was assayed by estimating
MDA; nitric oxide was determined by estimating nitrite and TNF-α
by using an assay kit in culture supernatants. Both endosulfan and
malathion had no effect on lipid peroxidation. Endosulfan did not
have any influence on nitrite production, but suppressed the LPS-
induced TNF-α generation. Malathion, however, showed a direct
suppression on nitrite production and suppression of LPS-induced
TNF-α generation. This study suggests that functional aberrations
of macrophages may contribute significantly to the immunomod-
ulation reported for these insecticides. © 2003 Elsevier B.V. All
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126.2

716. Polyphenolic antioxidants inhibit peptide presentation by
antigen-presenting cells - Gong J. and Chen S.-S. [S.-S. Chen,
Section 30 vol 126.2
Division of Allergy, La Jolla Inst. for Allerg./Immunol., San Diego, CA, United States] - INT. IMMUNOPHARMACOL. 2003 3/13-14 (1841-1852) - summ in ENGL

Antigen-presenting cells (APC) provide two essential signals, e.g., antigenic peptides as well as costimulatory molecules for T-cell activation. Small molecules of smoke tobacco extracts (SM-STE) inhibited antigen presentation of A20 to OVA-specific T-cell hybridomas. Pretreatment of A20 but not T hybridomas abrogates the APC function. Viability of APC and levels of MHCII, CD40 and B7 of APC were not affected by this treatment. The active principle, inhibiting APC was reproduced with pure tobacco polyphenols, quercetin and its glycoside, rutin. Antioxidant activity of rutin is relevant since rutin downregulated levels of reactive oxygen species (ROS) in phorbol ester-stimulated A20; moreover, another antioxidant, N-acetyl cysteine (NAC) also inhibited antigen presentation, albeit at a higher concentration. Other types of APC, such as bone marrow-derived mast cells (BMMC), MHCI-transfected fibroblast, and splenocytes are affected by tobacco polyphenols. We propose that polyphenols may affect redox-sensitive signal transduction pathway since APC function of PD 98059, MEK inhibitor-pretreated A20 were similarly abrogated. Taken together, we propose that maintaining appropriate intracellular redox of APC is crucial for its antigen-presenting function. © 2003 Elsevier B.V. All rights reserved.


Androgens influence some immunological processes, including alternation of the number and function of the circulating lymphocytes and monocytes. In the present study, the effects of three different doses of testosterone on the numbers and percentages of the peripheral blood cells were investigated: the lymphocyte subsets were determined and the proliferation of lymphocyte was detected. Groups of Sprague-Dawley rats were treated with 0.5, 2.5, 12.5 mg/kg or only vehicle, respectively. Compared with controls, the results of complete blood counts showed that the absolute and relative numbers of monocytes decreased. The lymphocyte subpopulations determined by flow cytometry indicated an increase in CD8+ T cells, whereas the CD3+, CD4+ and CD4+CD8+ T cells remained unchanged. The immunoregulatory index (CD4+/CD8+ ratio) decreased. The proliferative activities determined by MTT assay were down-regulated. In conclusion, the immunosuppressive effects of testosterone may be attributed to a decline in number of monocytes, whereas the CD3+, CD4+ and CD4+CD8+ T cells remained independent. Influence of testosterone on the different doses of APC is crucial for its antigen-presenting function.© 2003 Elsevier B.V. All rights reserved.


Neuropeptides are able to modulate cytokine production by macrophages in response to various stimulators. In this study, the effects of neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) on production of pro-inflammatory cytokines TNF and IL-1β by macrophages were considered. Mouse peritoneal macrophages were infected with herpes simplex virus type-1 (HSV-1), or remained unstimulated, and cytokine assays were performed after 12 h. IL-1β and TNF secretion by unstimulated macrophages have been significantly increased in the presence of SP and CGRP. Each neuropeptide, alone or in combination with the other, caused significant increase in IL-1β and TNF production by HSV-infected mouse peritoneal macrophages. It was concluded that the macrophage-mediated inflammatory response to HSV-1 is enhanced in the presence of these neuropeptides. © 2003 Elsevier B.V. All rights reserved.


Injury to the liver results in rapid induction of transforming growth factor-beta1 (TGF-β1) consistent with a role for TGF-β1 in repairing damaged tissue. In addition to its ubiquitous role in injury repair, TGF-β1 is also well established as a critical regulator of immune homeostasis; however, its mechanisms of action remain enigmatic. We have previously demonstrated that the hepatotoxic chlorinated hydrocarbon, carbon tetrachloride, suppresses helper T-lymphocyte function in a TGF-β1-dependent manner. Here, we report that, in opposition to its immunosuppressive effects at picomolar concentrations, femtomolar concentrations of TGF-β1 augment T cell-dependent anti-IgM IgM antibody forming cell (APC) and T cell-independent DNP-Picoll-induced APC responses. These data support a concentration-dependent bifunctional effect by TGF-β1 on humoral immune responses in vitro. We further investigated a putative mechanistic role for Smad3, an intracellular mediator of TGF-β1 signal, in propagating the inhibitory effects of TGF-β1 on humoral immune responses. Relative to wild type littermates, splenocytes from mice homologous for a null mutation in the gene encoding the TGF-β1 receptor-activated Smad3 (Smad3<sup>−/−</sup>) were less sensitive to inhibition by TGF-β1 following anti-IgM- and LPS-sensitization in vitro. In agreement, inhibition of IgM protein production by TGF-β1 was also dampened in LPS-sensitized Smad3<sup>−/−</sup> spleen B cells. Moreover, stimulation of IgA by TGF-β1 was abrogated and LPS-sensitized Smad3<sup>−/−</sup> splenocytes suggesting an additional role for Smad3 in regulating IgA production in vitro. Our results suggest that the effects of TGF-β1 on humoral immune responses fundamentally differ in a concentration-dependent manner and are mediated, in part, through Smad3 signaling. © 2003 Elsevier B.V. All rights reserved.


The inflammatory mediator leukotriene B<sub>4</sub> (LTB<sub>4</sub>) binds to and activates a G-protein-coupled receptor named BLT<sub>1</sub>. We have previously produced two monoclonal antibodies, named 7B1 and 14F11, that bind specifically to a subset of OVA-specific LTB<sub>4</sub> binding and calcium release, and activation of a MAP-kinase-sensitive luciferase reporter system. The normal chemotactic movement of polymorphonuclear cells towards higher OVA-specific LTB<sub>4</sub> was also strongly inhibited by both antibodies. Neither antibody was found to activate BLT<sub>1</sub>, and experiments using cyclic peptide fragments of the BLT<sub>1</sub> n-terminal and extracellular loops showed that these antibodies bind only to complex epitopes in the tertiary, membrane bound, conformation of the receptor protein. In ligand binding experiments, 7B1 was found to be a competitive antagonist, while 14F11 was a noncompetitive antagonist that inhibited receptor activation, but not agonist (LTB<sub>4</sub>) binding. 14F11 will be a useful tool for studying the mechanisms of receptor activation. © 2003 Elsevier B.V. All rights reserved.

721. Cholera toxoid elicits dendritic cells through dependence on MG1-ganglioside which is mediated by NF-κB translocation - Kawamura Y.I., Kawashima R., Shirai Y. et al. [T. Dohi, Department of Gastroenterological Research Institute, International Medical Ctr. of Japan, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655, Japan] - EUR. J. IMMUNOL. 2003 33/11 (3205-3212) - summ in ENGL

Cholera toxin (CT) is a potent adjuvant; however, the mechanism for its ability to enhance mucosal immunity has not been fully elucidated. We report here that CT exerts its adjuvant properties by signaling through the GM1 ganglioside receptor. When ganglioside-defective mice were given the antigen (Ag) ovalbumin (OVA) with CT by the oral route, CT failed to support either OVA-specific antibody or CD4<sup>+</sup> T cell responses. In vitro treatment of murine bone
matured dendritic cells (DC) with CT induced full maturation as evidenced by upregulation of the costimulatory molecules, as well as by an enhanced ability to effectively present OVA for Ag-specific T cell responses. On the other hand, ganglioide-negative DC failed to differentiate to full function as Ag-presenting cells in response to CT. Since ganglioide-negative DC showed a mature phenotype after stimulation with lipopolysaccharide (LPS), the effects of CT on DC was independent of signal transduction through adjuvant receptor for LPS, the Toll-like receptor 4. Furthermore, CT also induced nuclear translocation of nuclear factor (NF)-κB in DC in a GM1-dependent fashion. These results highlight ganglioide expressed by DC for recognition of the non-self protein bacterial enterotoxin, which employ a unique signaling pathway to induce both innate and adaptive immunity.


The direct and indirect healthcare costs associated with multiple sclerosis is high. In the managed care setting, before treatment is initiated, these costs must be reconciled with other factors such as the epidemiological and clinical features of MS and current recommendations for pharmacologic management. Managed care organizations (MCOs) have the opportunity to improve the outcomes of MS through a system of care. MCOs can also manage the costs of the 2 first-line therapies (glatramer and agents from the interferon class) used to treat MS by using stepped care and preferred formulary designations. In addition, improved outcomes can be achieved by establishing a disease management approach to treat MS.


This study sought to investigate the effects of nadroparine on an in vivo experimental model of type I hypersensitivity response in the rat conjunctiva. Following drug application onto the eye, either before or after challenge with the mast cell degranulator, basic polyanime compound 48/80, the conjunctival histamine content and the nitrile levels in the conjunctival lavage fluid were quantified fluorometrically and spectrophotometrically, respectively. Instillation into the eye of nadroparine inhibited the C48/80-induced decreases in conjunctival histamine and the delayed increases in nitrile levels, without influencing basal mediator levels. Protonide did not induce histamine release and only partially reversed the effects of nadroparine post-challenge, yet it had no effect on the protective action of the drug when administered prior to degranulation. The results showed that nadroparine was equally effective in attenuating the effects of compound 48/80 in the eye when administered topically either before or after challenge. © 2003 Elsevier B.V. All rights reserved.

724. Pharmacokinetics of daclizumab and mycophenolate mofetil with cyclosporin and steroids in renal transplantation - Pescevitz M.D., Bumgardner G., Gaston R.S. et al. [Dr. M.D. Pescevitz, Dept. Surgery/Microbiology/Immunol., Indiana University, 550 N. University Blvd., Indianapolis, IN 46202, United States] - CLIN TRANSPLANT 2003 176 (511-517) - sum in ENGL

Daclizumab and mycophenolate mofetil (MMF) decrease the incidence of acute allograft rejection. This double-blind, randomised, placebo-controlled trial was performed primarily to assess the pharmacokinetics of MMF in an immunosuppressive regimen incorporating daclizumab. At five centers, 75 renal transplant recipients were randomized to: 1) receive either daclizumab 1 mg/kg or placebo pre-transplantation and every other week, for a total of five doses. All patients received cyclosporine, steroids, and MMF; Levels of mycophenolic acid (MPA), its glucuronide metabolite, and daclizumab were measured after dosing on days 28 and 56. Safety parameters evaluated included: adverse events, laboratory abnormalities, infections, patient/grant survival, incidence of lymphoproliferative disorders, and incidence of acute rejection at 12 months. The concomitant administration of daclizumab and MMF had no effect on the pharmacokinetics of MPA: AUC<sub>0-56</sub> values (μg h/mL ± SD) on day 28 were 30.1 ± 13.3 for daclizumab-treat patients and 37.7 ± 18.2 for daclizumab-treated patients vs. 35.7 ± 14.0 for placebo. Adverse events were similar between the two groups. Acute rejection at 12 months occurred in 14% of patients receiving daclizumab and 20% of patients receiving placebo. The coadministration of daclizumab did not result in a pharmacokinetic interaction with MPA, the active metabolite of MMF.


Background/Purpose: Cutaneous cis-urocanic acid (cUCA) or ultraviolet B exposure has been shown to cause diminished cutaneous contact hypersensitivity (CH) and to induce systemic tolerance (increased regulatory T lymphocytes) in mice. Permethrin is also a known CH inhibitor, but the molecular mechanisms are currently poorly understood. In this study, CH was evaluated in four strains of mice: an immunosensitive strain (C57BL/6N), an immunoresistant strain (SvImJ), a strain developed from C57BL/6N mice but genetically altered at both the tumor necrosis factor-alpha receptors (TNF<sub>α</sub> p55R and p75R), and a strain developed from C57BL/6N but genetically deleted at the interferon-gamma (IFN<sub>γ</sub>) locus. Methods: CH was evaluated in each group via oxazolone challenge following a 5-day exposure to intradermal (ID) cUCA or a single exposure to topical permethrin, or co-exposure to both chemicals in 5-week-old female C57BL/6N, SvImJ, and C57BL/6N mice genetically altered at the TNF<sub>α</sub> or IFN<sub>γ</sub> locus. Results: A 5-day exposure to ID cUCA or a single exposure to topical permethrin resulted in diminished CH response in C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals.

7.6. Emetics and antiemetics


Underlying all motivated behavior is the concept of brain arousal, the generalized activation of forebrain and behavior. A concrete expression of this would be sexual arousal and behavior. The genes which are turned on by estrogens and whose products facilitate the behavior are known CH inhibitor, but the molecular mechanisms are currently poorly understood. In this study, CH was evaluated in four strains of mice: an immunosensitive strain (C57BL/6N), an immunoresistant strain (SvImJ), a strain developed from C57BL/6N mice but genetically altered at both the tumor necrosis factor-alpha receptors (TNF<sub>α</sub> p55R and p75R), and a strain developed from C57BL/6N but genetically deleted at the interferon-gamma (IFN<sub>γ</sub>) locus. Methods: CH was evaluated in each group via oxazolone challenge following a 5-day exposure to intradermal (ID) cUCA or a single exposure to topical permethrin, or co-exposure to both chemicals in 5-week-old female C57BL/6N, SvImJ, and C57BL/6N mice genetically altered at the TNF<sub>α</sub> or IFN<sub>γ</sub> locus. Results: A 5-day exposure to ID cUCA or a single exposure to topical permethrin resulted in diminished CH response in C57BL/6N mice, and this effect was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals. CH in SvImJ was both cUCA- and permethrin-resistant relative to C57BL/6N mice, and this result was exacerbated with concurrent exposure to both chemicals.
and even through other preparative behaviors. An unexpected result derived from a microarray study was the estrogenic effect on prostat glandin-D synthetase, important because of the marked actions of prostat glandin-D on arousal and sleep. © 2003 Published by Elsevier B.V.

6.8. Autocoids and prostat glandis


It is currently debated whether the mechanism of action of therapeutic doses of recombinant factor VIIa (rFVIIa, NovoSeven) relies on the tissue factor (TF)-independent activity of the enzyme. The present study was conducted to investigate the in vivo haemostatic effects of rFVIIa and 3 analogs thereof with superior intrinsic activity (FVIIa114K, K337A-FVIIa IIa, and M298Q-FVIIa) in mice with antihemophilic factor (AHF) deficiency. A highly significant dose response was observed for the bleeding time and blood loss for each of the rFVIIa variants. The bleeding time and blood loss were increased after administration of 10 mg/kg rFVIIa, 3 mg/kg K337A-FVIIa IIa, and 3 mg/kg M298Q-FVIIa, indicating a potency of these FVIIa analogs 3-4 times above that of rFVIIa in FVIII-depleted mice. The different in vivo potencies of the various forms of FVIIa could not be explained by the pharmacokinetics. Histopathological evaluation of kidneys revealed no signs of treatment-related pathological changes even after treatment with the superactive variants. The fact that FVIIa analogs with enhanced intrinsic activity are more efficacious in the murine hemophilia A model strongly suggests that the TF-independent procoagulant activity of FVIIa contributes to its clinical hemostatic effect. © 2003 by The American Society of Hematology.

728. Bilirubin and S-nitrosothiols interaction: Evidence for a possible role of bilirubin as a scavenger of nitric oxide - Mancuso C., Bonsignore A., Di Stasio E. et al. [C. Mancuso, Institute of Pharmacology, Catholic University, School of Medicine, Largo Francesco Vito, 1, 00168 Rome, Italy] - BIOCHEM. PHARMACOL. 2003 66/12 (2355-2363) - summ in ENGL.

Bilirubin (BR), the final product of heme catabolism, plays a crucial role in the defense against reactive oxygen species in various cell types. In this study, we addressed the hypothesis that BR can act as a physiological scavenger of nitric oxide (NO), a gaseous mediator involved in many cellular functions and able to trigger the formation of reactive nitrogen species with pro-oxidant activity. We found that S-nitrosocysteine (SNOC) and S-nitrosoglutathione (GSNO), which have a half-life of 0.52±0.07hr and 38±5hr and release NO at a constant rate of 1.42±0.2hr⁻¹ and 0.018±0.002hr⁻¹, respectively, are able to decrease BR half-life in a concentration-dependent manner under physiological conditions. This effect appears to be dependent on NO formation as L-cysteine and GSH did not affect BR consumption and nitrate was four to five times less efficient than SNOC in reducing BR half-life. Oxymegoglobin, a well-known scavenger of NO, protected BR from SNOC-mediated degradation. In addition, the reaction between SNOCSNOC and BR modified the absorption spectrum of the bile pigment showing a gradual increase in the absorbance at 510nm. This change in the bile spectrum indicates that the bile pigment could be a target for N-nitrosation reactions, since it resembles the modifications occurring in some molecules such as di-peptides and uric acid are nitrosated. Taken together, these data suggest that BR should not be considered only as an endogenous antioxidant but also as a molecule with the potential ability to counteract intracellular nitrosative stress reactions. © 2003 Elsevier Inc. All rights reserved.

729. Endogenous glucocorticoids inhibit scratching behavior by the administration of compound 48/80 in mice - Hirayama K., Sudo N., Sueyasu M. et al. [N. Sudo, Hlth. Care Admin. and Management, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi, Fukuoka 812-8582, Japan] - EUR. J. PHARMACOL. 2003 481/1 (59-65) - summ in ENGL.

In this study, we investigated the effects of endogenous glucocorticoids on the compound 48/80 (a condensation product of N-methyl-p- methoxyphenylethylamine with formaldehyde)-induced mouse scratching behavior using either RU-486 (mifepristone), a glucocorticoid receptor antagonist, or a surgical resection of the adrenal glands. Subcutaneous injection of compound 48/80 induced not only a corticosterone elevation in the plasma but also an enhanced expression of corticotropin releasing hormone (CRH)-mRNA in the paraventricular nucleus, which thus suggests that hypothalamic-pituitary-adrenal axis is activated by the compound 48/80-induced cutaneous reaction. Inhibition of such an endogenous glucocorticoid activity by RU-486 significantly increased the degree of scratching behavior at not only the early-phase (<60 min) but also the late-phase (>60 min) time course after the injection of compound 48/80. Since the elevation of the histamine levels in the plasma in the RU-486-treated mice was no longer found in late-phase scratching behavior, these results thus indicate that histamine is a dominant mediator responsible for early-phase scratching behavior, while different mediators other than histamine may be also involved in the induction of late-phase scratching behavior. Moreover, surgical removal of adrenal glands also significantly increased the compound 48/80-induced scratching behavior without affecting anxiety and locomotor parameters, indicating that endogenous glucocorticoids exert their anti-pururitogenic effects independently of changes in behavioral performance. In conclusion, endogenous glucocorticoid activity was found to suppress the compound 48/80-induced scratching behavior in mice. © 2003 Elsevier B.V. All rights reserved.


To examine the effects of reperfusion after short and prolonged ischemia on the coronary action of endothelin-1, left circumflex coronary artery flow was electromagnetically measured, and 15- or 60-min occlusion of this artery followed by reperfusion was induced in anesthetized goats. In non-treated animals, during reperfusion after 15-min occlusion, the duration but not the peak of endothelin-1-induced coronary effects (0.01-0.3 nmol) was increased, and the effects of acetylcholine (3-100 ng) were unchanged. During reperfusion after 60-min occlusion, the peak and duration of endothelin-1-induced effects were increased whereas those of acetylcholine were decreased. N-nitro-L-arginine methyl ester (L-NAME) treatment did not modify the peak and duration of the coronary effects of endothelin-1 during reperfusion after both durations of occlusion. This treatment inhibited the effects of the two higher doses but not those of the two lower doses of acetylcholine during reperfusion after 15-min occlusion, and it did not modify the effects of any dose of this drug during reperfusion after 60-min occlusion. Meclofenamate treatment did not modify the coronary effects of endothelin-1 and acetylcholine during reperfusion after both durations of occlusion. These results suggest that ischemia-reperfusion increases the coronary response to endothelin-1, which is more pronounced during reperfusion after prolonged than after brief ischemia, and that this increased response is probably related to inhibition of nitric oxide release, without involvement of prostanoids. © 2003 Elsevier B.V. All rights reserved.

6.9. Medicinal plants and herbal medicines


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Cissampelos sympodiums Eichl species are used in folk medicine for the treatment of asthma, arthritis and rheumatism. In the present study, we investigated the immunomodulatory effect of an aqueous fraction of a 70% (v/v) ethanol extract of C sympodiums leaves on B lymphocyte function. The hydroalcoholic extract inhibited the in vitro proliferative response of resting B cells induced by LPS (IC_{50} = 17.2 μg/ml, anti-delta-dextran (IC_{50} = 13.9 μg/ml) and anti-IgM (IC_{50} = 24.3 μg/ml) but did not affect the anti-MHC class II antibody-stimulated proliferative response of B cell blasts obtained by stimulation with IL-4 and anti-IgM. Incubation with the hydroalcoholic extract used at 50 μg/ml induced a 700% increase in intracellular cAMP levels. IgM secretion by resting B cells (obtained from normal mice) and polyclonally activated B cells (obtained from Trypanosanza cruzi-infected animals) was inhibited by the hydroalcoholic extract. The latter were more sensitive to the hydroalcoholic extract since 6.5 μg/ml induced a 20% inhibition in the response of cells from normal mice while it inhibited the response of B cells from infected animals by 75%. The present data indicate that the alcoholic extract of C. sympodiums inhibited B cell function through an increase in intracellular cAMP levels. The finding that the hydroalcoholic extract inhibited immunoglobulin secretion suggests a therapeutic use for the extract from C. sympodiums in conditions associated with unregulated B cell function and enhanced immunoglobulin secretion. Finally, the inhibitory effect of the hydroalcoholic extract on B cells may indicate an anti-inflammatory effect of this extract.


In the quality control of liquid herbal drug preparations, i.e. tinctures and liquid extracts, the ethanol content is determined and the test on methanol and 2-propanol is performed. Capillary headspace GC/MS methods for both analyses were developed and fully validated. These specific, selective, accurate and precise methods are a fast and fully automated alternative for the laborious methods of the European Pharmacopoeia, since they need no or only simple sample preparation. © 2003 Elsevier B.V. All rights reserved.

733. Determination of hamamelitannin, catechins and gallic acid in witch hazel bark, twig and leaf by HPLC - Wang H., Provan G.J. and Hellwell K. [H. Wang, R and D Department, William Ransom and Son plc, Hitchin, Herts SG5 1LY, United Kingdom] - J. PHARM. BIOMED. ANAL. 2003 33/4 (539-544) - sum in ENGL.

An HPLC method for the determination of hamamelitannin, catechins and gallic acid in witch hazel bark, twig and leaf has been developed. The separation system consisted of a C18 reversed-phase column, a gradient elution system of methanol/water and a post-column derivatization system using 2,4,6-trinitrobenzenesulphonic acid as a reagent. The determination system was validated using real samples following the ICH guidelines and compared with the USP reference standard. The assay was linear from 0.1 to 10 μg/ml in witch hazel leaves. The method was applied to the determination of hamamelitannin, catechins and gallic acid in witch hazel leaves from different sources. © 2003 Elsevier B.V. All rights reserved.


Background/Purpose: A continuation of liver fibrosis after undergoing successful Kasai operation has become the important clinical issue in the long-term follow-up of patients with biliary atresia (BA). The aim of this study is to evaluate the efficacy of the herbal medicine Inchinko-to (TJ-135) on the treatment of liver fibrosis in patients with BA without jaundice, especially from the viewpoint of the long-term effects of TJ-135. Methods: Six postoperative patients with BA ranging between 3 and 13 years of age with normal serum total bilirubin levels (total bilirubin < 1.0 mg/dL, 17 μmol/L) received TJ-135 from 2 to 4 years. The liver enzyme (glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], gamma glutamyl transpeptidase) γ-GTP and transpeptidase levels and albumin acid (HA) levels were compared before and after the administration of TJ-135. The monthly collected data were averaged on a 1-year basis. The record of one postoperative patient with BA and a normal serum total bilirubin level was incorporated as a control. This patient showed portal hypertension and did not receive TJ-135. Results: Five of the six patients who showed abnormal values for liver enzymes, exhibited a significant decrease in serum GOT, γ-GTP, GPT levels after 1 to 3-year administration of TJ-135, and the improvement in these parameters persisted thereafter. Furthermore, one patient who had an abnormally high value of HA also showed a significant decrease in the serum level of HA. In the remaining patient with normal liver enzyme values, no significant change was observed during the administration of TJ-135. The control patient exhibited a chronological decrease in the serum GOT and GPT levels by 5 years of age, but the serum γ-GTP and HA levels remained stable throughout the postoperative period. Conclusions: The long-term effectiveness of TJ-135 was only found in those patients with abnormal liver enzyme levels and HA, thereby suggesting that TJ-135 has a protective and antifibrotic effect on the liver. © 2003 Elsevier Inc. All rights reserved.

735. The β(1→6)-branched β(1→3) glucanoxaose and its analogues containing a β(1→3)-linked bond have similar stimulatory effects on the mouse spleen as Lentimann - Yan J., Zong H., Shen A. et al. [J. Gu, Research Center, Shanghai Medical Center, Fudan University, Shanghai 200032, China] - INT. IMMUNOPHARMACOL. 2003 3/13-14 (1861-1871) - sum in ENGL.

The stimulatory effects of the synthetic β(1→6)-branched β(1→3) glucanoxaose and its analogues containing an α(1→3)-linked bond on the mouse spleen were studied for elucidation of the mechanism of their antitumor activity, and their stimulatory effects were compared with Lentimann. The mouse spleen’s weight was increased after the intraperitoneal (i.p.) injection of the oligosaccharides compared with the saline group. In addition, routinely hematocytin and eosin (HE)-stained spleen sections showed that the injection also changed the spleen’s histopathology. RNA samples were isolated from spleens of oligosaccharides, Lentimann or saline-injected mice. Reverse transcription-polymerase chain reaction (RT-PCR) and Northern blot showed that the administration of the oligosaccharides or Lentimann enhanced mouse spleen mRNA production of TNF-α but not IL-2. The injection also enhanced Concansalvin A (Con-A)-induced mouse splenocytes proliferation, but the in vitro administration of the oligosaccharides did not have the proliferation-enhancing effect. Taken together, these results suggest a different β(1→6)-branched β(1→3) glucanoxaose and its analogues containing an α(1→3)-linked bond have similar stimulatory effects as Lentimann. Additionally, they may exert their antitumor effects through the induction of splenocytes mediated immune responses. © 2003 Elsevier B.V. All rights reserved.


Platycodon grandiflorum, a traditional oriental herbal medicine, is known to have immunostimulatory and antitumor effects. PG, a polysaccharide isolated from P. grandiflorum, has been reported to activate macrophages and B cells. Here, we investigated the membrane receptor and intracellular signaling responsible for the activation of macrophages by PG. PG induced the production of nitric oxide (NO) and the mRNA expression of iNOS in RAW 264.7 cells. To investigate the membrane receptor involved in the activation of NO production, we examined the effect of PG on the production of NO in mouse peritoneal macrophages isolated from wild type C3H/HeN and functional Toll-like receptor 4 (TLR4)-deficient C3H/HeN mice. PG induced NO production by macrophages

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isolated from CSH/HeN mice, but had no effect on NO production by macrophages isolated from CSH/HaI mice. Moreover, mono-
clonal antibodies directed to TL4 blocked PG-mediated induction of NO production. In addition, LBP and sCD14 was also found to be involved in the activation of NO production by PG. To further investigate, we examined the effect of PG on the activation of DNA
binding of NF-κB, which is a downstream transcriptional regulator of TL4. PG caused degradation of IκB and activation of DNA binding of NF-κB. In addition, TPCK, a specific NF-κB inhibitor, abolished PG-mediated induction of DNA binding of NF-κB, pro-
duction of NO and mRNA expression of iNOS, demonstrating the involvement of NF-κB in PG-mediated macrophage activation. Taken together, these results suggest that PG-mediated induction of NO production and iNOS mRNA expression in macrophages is mediated, at least in part, by TL4/NF-κB signaling pathway. © 2003 Elsevier B.V. All rights reserved.

737. An extract of Uncaria tomentosa inhibiting cell division and NF-κB activity without inducing cell death - Åkesson C., Lindgren H., Pero R.W. et al. [F. Ivars, Section for Immunology, Dept. of Cell and Molecular Biology, University of Lund, Sweden] - "INT. IMMUNOPHARMACOL. 2003 3/13-14 (1889-1900) - summ in ENGL"

Previous reports have demonstrated that extracts of the plant Uncaria tomentosa inhibit tumor cell proliferation and inflammatory responses. We have confirmed that C-Med 1000®, a hot water extract of this plant, inhibits tumor cell proliferation albeit with variable efficiency. We extend these findings by showing that this extract also inhibits proliferation of normal mononuclear T and B lymphocytes and that the inhibition is not caused by toxicity or by induction of apoptosis. Further, the extract did not interfere with IL-2 production nor IL-2 receptor signaling. Since there was no discrete cell cycle block in C-Med 1000®-treated cells, we proposed that retarded cell cycle progression caused the inhibition of proliferation. Collectively, these data suggested interference with a common pathway controlling cell growth and cell cycle progression. Indeed, we provide direct evidence that C-Med 1000® inhibits nuclear factor κB (NF-κB) activity and propose that this at least partially causes the inhibition of proliferation. © 2003 Elsevier B.V. All rights reserved.

738. The in vivo effects of sho-saiko-to, a traditional Chinese herbal medicine, on two cytotoxic P450 enzymes (1A2 and 3A) and xanthine oxidase in man - Seruwatari J., Nakagawa K., Shinjo J. et al. [T. Iishiaki, Div. of Clinical Pharmacology, Grad. School of Pharmaceut. Sciences, Kumamoto University, Oe-honmachi 5-1, Kumamoto 862-0973, Japan] - "J. PHARM. PHARMACOL. 2003 55/11 (1553-1559) - summ in ENGL"

The traditional Chinese medicine sho-saiko-to is a mixture of seven herbal components (Bupleurum root, Pinellia tuber, Scutellaria root, Paeonia radix, Stem of Glycyrrhiza root, and Zizyphus spina-cristata) and one proprietary formula (Berberis heterophylla bark). We assessed the effects of sho-saiko-to on the activity of cytotoxic P450 (CYP 1A2, CYP3A) and xanthine oxidase (XO) in man. Twenty-six healthy subjects were studied to evaluate their baseline activity of CYP1A2 and XO by the respective enzyme dehydrogenase assay in human liver microsomes of normal volunteers. Based on the results, we concluded that sho-saiko-to reduces CYP1A2 and XO activity in man. Standardized extracts from the Ginkgo biloba tree are purported to exert positive neuroprotective effects and may also be useful in the treatment of a variety of vascular and other disorders. This dietary supplement is among the most commonly used herbal preparations in the world. The objective of this study was to assess in normal volunteers (n = 12) the influence of standardized Ginkgo biloba (GB) (GB) on the activity of cytochrome P-450 (CYP) 2D6 and 3A4 normal volunteers phenotyped as CYP2D6 extensive metabolizers. Probe substrates dextromethorphan (CYP2D6 activity) and dextro-
zolam (CYP 3A4 activity) were co-administered orally at baseline, and following treatment with GB (120 mg twice daily) for 14 days. Urinary concentrations of dextromethorphan and dextrophan were quantified and dextrophan metabolite ratios (DMRs) were determined at baseline and after GB treatment. Likewise, plasma samples were collected (0-60 hrs) for alprazolam pharmacokinetics at baseline and after GB treatment to assess effects on CYP 3A4 activity. Validated HPLC methods were used to quantify all compounds and relevant metabolites. No statistically significant differences were found between baseline and post-GD treatment DMRs indicating a lack of effect on CYP2D6. For alprazolam there was a 17% decrease in the area under the plasma concentra-
tion versus time curve (AUC); (P < 0.05). However, the half-life of elimination was not significantly different after GB administration indicating a lack of pharmacodynamic interaction. We conclude that standardized extracts of GB at recommended doses are unlikely to significantly alter the disposition of co-administered medications primarily dependent on the CYP2D6 or CYP3A4 pathways for elimination.

740. Antiinflammatory activity of the aqueous extract of Ur-
ctica dioica - Brouhah M., Merhoun F.-Z., Ziyat A. et al. [M. Brouhah, Lab. de Physiol./Pharmacologie Cell., UFR de Physi-
ologie et Pharmacologie, Université Mohamed Ier, B.P. 524, Oujda, Morocco] - "FITOTERAPIA 2003 74/7-8 (677-681) - summ in ENGL"

When administered 30 min before glucose loading, the aqueous extract of Urtica dioica (nights) (250 mg/kg) showed a strong glucose lowering effect. The decrease of glycemia has reached to 33±3.4% of the control value 1 h after glucose loading. This effect was persist-
ent during 3 h. In contrast, nettle did not show hypoglycemic effect in allloxan-induced diabetic rats. The amount of glucose absorbed in a segment jejunum in situ was 8.05±0.68 mg in presence of nettle extract vs. 11.1±0.75 mg in control rats during 2 h (P < 0.05). The results indicate that nettle has a significant antiinflammatory effect in OGT T model. This effect may be caused in part by the reduction of intestinal glucose absorption. LPS30 is 3.5 g/kg (i.p.). © 2003 Elsevier B.V. All rights reserved.

section, Bhabha Atomic Research Centre, Mumbai 400 085, India] - "FITOTERAPIA 2003 74/7-8 (699-701) - summ in ENGL"

The ethanolic extract of Gymnema sylvestre leaves demonstrated antimicrobial activity against Bacillus subtilis, Pseudomonas aeruginosa and Staphylococcus aureus and inactivity against Proteus vulgaris and Escherichia coli. © 2003 Elsevier B.V. All rights reserved.

742. Antimicrobial activity of aqueous extracts and of berberine isolated from Berbersis heterophylla - Freile M.L., Giannini F., Pucci G. et al. [R.D. Enriz, Fac. de Quim., Bioquim. y Farmaco-
ica, Universidad Nacional de San Luis, Chacabuco 917, San Luis 5700, Argentina] - "FITOTERAPIA 2003 74/7-8 (702-705) - summ in ENGL"

The antimicrobial activity of Berbersis heterophylla leaves, stem and root aqueous extracts was studied in vitro on Gram-negative and Gram-positive bacteria and fungi. The in vitro antifungal activity of berberine isolated from the same source against different Candida species was also investigated. © 2003 Elsevier B.V. All rights reserved.

743. Antimicrobial and cytotoxicity evaluation of Buchholzia coriacea stem bark - Ajayaeeo E.O., Onoza P.A., Nwozo S.O.
Fractions prepared from the methanol extract of Buchholzizoria coriacea stem bark exhibited a high concentration-dependent antibacterial and antifungal activity compared to the standard antibiotics, ampicillin and toconazole. In the brine shrimp lethality (BSL) assay, the methanol extract was found to be non-toxic with an LC₅₀ of 1031 μg/ml. The two main compounds present in the most active fraction were isolated and identified as lupeol and β-sitosterol. © 2003 Elsevier B.V. All rights reserved.

474. Ethnobotanical knowledge of the Istro-Romanians of Žejane in Croatia - Pieroni A., Giusti M.E., Münz H. et al. [A. Pieroni, Department of Pharmacy, School of Life Sciences, University of Bradford, Richmond Road, Bradford, West Yorkshire BD7 1DP, United Kingdom] - FITOTERAPIA 2003 74/7-8 (710-719) - sumin ENGL

An ethno-pharmacognostic survey was carried out in one of the smallest ethnic and lingusitic groups in Europe: the Istro-Romanians of the village of Žejane (in Croatia), which has a population of approximately 140 persons, mainly elderly. Using an intensive field participant observation methodology, we recorded about 60 remedies of the local folk pharmacopoeia, and mainly derived from plants. Among them, the uncommon traditions to use homemade vinegar from wild apple (Malus sylvestris) and Cornelian cherries (Cornus mas) for diverse medical purposes, and houseleek (Sempervivum tectorium) against ear pains have been briefly discussed. © 2003 Elsevier B.V. All rights reserved.

475. Antinephritis and radical scavenging activity of prenylflavonoids - Fuku T., Satoh K., Nonura T. and Sakagami H. [T. Fuku, School of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan] - FITOTERAPIA 2003 74/7-8 (720-724) - sumin ENGL

Antinephritis activity of 5 prenylflavonoids similar to glabridin (1-5), isolated from Morus alba, Arctocarpus communis, Glycyrrhiza uralensis and G. inflata, was evaluated in mice with glomerular disease (Masugi-nephritis). Oral administrations of artonin E (2) or licochalcone A (4) for 10 days (30 mg kg⁻¹ day⁻¹) reduced the amount of urinary protein excretion compared to nephritic mice. ESR spectroscopy demonstrated that morusin (1) and licoridiflavon A (5) increased the radical intensity of sodium ascorbate by about two times. Morusin, licoricidin (3), licochalcone A and licoridiflavon A showed weak scavenging activity against superoxide anion radical. © 2003 Elsevier B.V. All rights reserved.

476. Spasmolytic activity of several extracts obtained from some Mexican medicinal plants - Rodriguez-Lopez V., Salazar L. and Estrada S. [S. Estrada, Facultad de Farmacia, Univ. Auton. del Estado de Morelos, Ave. Univ. 1001, Colonia Chamult, Cuernavaca Morelos 62210, Mexico] - FITOTERAPIA 2003 74/7-8 (725-728) - sumin ENGL

A total of ten extracts from different parts of eight medicinal plants that are used in the treatment of gastrointestinal disorders, were evaluated to determine their spasmyloytic action on in vitro isolated rat ileum. All extracts were less potent than papaverine, which was used as a positive control. © 2003 Elsevier B.V. All rights reserved.


The ethanol extract and fractions from Coccoloba acrostichoides aerial parts were assayed for in vitro antimicrobial activity. The extract was active against the assayed bacteria while most of the fractions also inhibited fungal growth, especially the n-hexane and EtOAc fractions. The isolated β-sitosterol and betulin were tested, being the last one active against Fusarium oxysporum. © 2003 Elsevier B.V. All rights reserved.

478. Cytotoxic activity of Ozoroa insignis from Zimbabwe - Rea A.I., Schmidt J.M., Setzer W.N. et al. [E.T. Gwebo, Department of Chemistry, Oakwood College Huntsville, Huntsville, AL 35896, United States] - FITOTERAPIA 2003 74/7-8 (732-735) - sumin ENGL

The crude methanol bark extract of the Zimbabwean medicinal plant, Ozoroa insignis, showed in-vitro cytotoxic activity against Hep-G2 (human hepatocellular carcinoma), MDA-MB-231 (human mammary adenocarcinoma), and 5637 (human primary bladder carcinoma). Bioactivity-directed chromatographic separation led to isolation of anacardic acid and ginkgolic acid as the cytotoxic components. © 2003 Elsevier B.V. All rights reserved.


The crude methanolic extracts of the leaves, stem and root barks of Alstonia scholaris and Leea tetramera on partitioning (petrol, dichloromethane, ethyl acetate, butanol) gave fractions exhibiting improved and broader spectrum of antibacterial activity. Especially the butanol fractions of A. scholaris and the root bark of L. tetramera. None of the fractions were active against the fungi tested. © 2003 Elsevier B.V. All rights reserved.

750. Direct inhibitory effect of curcumin on Src and focal adhesion kinase activity - Leu T.-H., Su S.L., Chuang Y.-C. and Maa M.-C. [M.-C. Maa, Institute of Biochemistry, Chung Shan Medical University, Taichung, Taiwan] - BIOCHEM. PHARMACOL. 2003 66/12 (2323-2331) - sumin ENGL

Curcumin (diferuloylmethane) is a well-known agent with anti-inflammatory, antioxidant, and anticarcinogenic properties. In this study, we observed that curcumin inhibited the kinase activity of v-Src, which led to a decrease in tyrosyl substrate phosphorylation of Shc, cortactin, and FAK. Our in vitro kinase experiment revealed that the inhibitory effect of curcumin on Src could be direct. Consistent with the abrogation of Src activity was the reduction of Src-Tyr-416 phosphorylation, Src-mediated Shc-Tyr-317 phosphorylation, decreased ERK activation, and cell proliferation in v-Src transformed cells. Remarkably, curcumin not only exerted its negative effect on FAK via the disappearance of Src-mediated FAK phosphorylation, but also directly inhibited its enzymatic activity. Concurrent to reduced cortactin tyrosyl phosphorylation and FAK kinase activity was the abolishment of v-Src-mediated cell motility. To our knowledge, this is the first report indicating that curcumin can retard cellular growth and migration via downregulation of Src and FAK kinase activity. © 2003 Elsevier Inc. All rights reserved.
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