induced in SCI-injured rabbits models after oral and IV administration of DA-8159(0.3mg/kg-10mg/kg). Furthermore, the efficacy was potentiated by administration of sodium nitroprusside. These results demonstrate that DA-8159 has a reliable and reproducible effect on penile erection in spinal cord injured rabbits.

[PA1-23] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Pharmacology of novel vanilloid receptor antagonists

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Capsaicin and analogues are valuable analgesic agents when administered to mammals, including humans. However, their pungency, hypothermia and the effects on the cardiovascular and respiratory systems through their general activation of primary afferents severely limit their use. So competitive antagonists have been pursued as a novel pharmacological agent for analgesics, rather than agonists. We have identified a new class of potent and selective vanilloid receptor (VR) antagonists. These antagonists exhibit highly potent antagonistic activities in both $^{45}Ca^{2+}$-uptake and single channel patch clamp assays as well as analgesia in capsaicin test and PBQ writhing test. Furthermore, these compounds are devoid of the important shortcomings of capsaicin, such as hypothermia and pungency. These results suggest that VR blockade could be a novel therapeutic approach to analgesia.

[PA1-24] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

IN VIVO METABOLISM OF 2-METHYLAMINOETHYL-4,4'-DIMETHOXY-5,6,5',6'-DIMETHYLENEDIOXYBIPHENYL-2'-CARBOXY-2-CARBOXYLATE (DDB-S) BY LC/ESI TANDEM MASS SPECTROMETRY

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2-Methylaminoethyl-4,4'-dimethoxy-5,5',6,6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S) is a synthetic compound derived from DDB, which is protects liver against carbon tetrachloride-, D-galactosamine-, thioacetamine-, and prednisolone- induced hepatic injury in experimental animals. We assessed the use of liquid chromatography/electrospray iontrap tandem mass spectrometry (LC/MS/MS) method to identify and quantify in vivo metabolites and to measure excretion. DDB-S was administered intravenous to rats, and samples of urine, and feces were collected and analyzed by LC/MS. This method identified twelve metabolites in urine and feces. The major metabolic pathways of DDB-S in rats were identified as demethylenation of the methylenedioxyphenyl group and demethylation of the carboxymethyl moiety. The others were identified as demethylenation and demethylation, and glucuronidation.

[PA1-25] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Selectivity of the optical isomers of KR30031 on MDR reversal activity and cardiotoxicity

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The present study was performed to compare the cardiovascular adverse effects of verapamil, KR30031 and their each optical isomers, and also to measure their ability to overcome multidrug resistance (MDR). R-isomer of KR30031 (R-KR30031) was equipotent with S-isomer of KR30031 (S-KR30031) and 25 fold less potent than R-isomer of verapamil (R-verapamil) in relaxing the aorta isolated from rat (EC50: 11.8, 10.2 and 0.46 μM, respectively). The effect of R-KR30031 in decreasing left ventricular pressure of heart isolated from rat was 2 and 267 fold smaller than those of S-KR30031 and R-verapamil, respectively (EC50: 23.9, 9.4 and 0.089 mM, respectively). The hypotensive effect of R-KR30031 in rat was about 2 and 23 fold smaller than those of S-KR30031 and R-verapamil, respectively (ED20: 1.15, 0.60 and 0.05 mg/kg, respectively). On the other hand, R-KR30031 elicited potency similar to those of S-KR30031 and R-verapamil in enhancing the paclitaxel-induced cytotoxicity to HCT15/CL02 and MES-SA/DX5 cells that reveal high level of PGP expression (IC50: 3.11, 3.04 and 2.58 μM, respectively). In addition, the intrinsic cytotoxicity of R-KR30031 in HCT15/CL02 and MES-SA/DX5 cells was observed only at the very high concentration of 100 μM. All these results suggest that R- and racemic KR30031 are active modulators of MDR with potentially minimal cardiovascular adverse activity.

[PA1-26] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

DA-7911, rhenium-188 (Re^{188}) tin colloid, as a strong candidate agent for radiation synovectomy

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Radiation synovectomy is an useful alternative treatment to rheumatoid arthritis and Re^{188} is suggested as an ideal radiopharmaceutical agents because beta ray (2.1 MeV) emitted from Re^{188} is appropriate for synovial cell ablation and gamma ray (155 KeV) is ideal for dosimetry. Its' ideal particle size (2-5 mm) was achieved by conjugation with tin-colloid. In this study, we investigated the toxicity, stability and biodistribution to evaluate the suitability of DA-7911 as a synovectomy agent. In acute toxicity of DA-7911 in ICR mice (i.v.), the value of LD_{50} was 60.9 mCi/kg. In vitro stability tests, DA-7911 remained as a colloid form without critical size variation over a 2-day period. In the normal rats, the leakage test from the intraarticular injection site with gamma counting showed that the mean retention percentage of DA-7911 was 98.7% at 1 day. In biodistribution study, the liver produced the highest radioactivity (0.0427% ID/organ) except for the injected knees. After animal experiments, we performed radiation synovectomy in 22 knees from 21 rheumatoid arthritis patients who were refractory to local corticosteroid injection. We evaluated the efficacy and safety of DA-7911 from 3 months up to 23 months after the injection of 10-30 mCi of Re^{188}-tin colloid. In visual analogue scale, pain (86.3 %), joint tenderness (63.6 %), swelling (86.3 %) and range of motion (72.7 %) were improved. In blood, activity of Re^{188} was 0.009 %/injection dose. There were no abnormalities in complete blood count, liver function test and urine analysis in any patients, although transient reactive synovitis was observed in 18 cases (81.8 %).
In conclusion, DA-7911 is a strong candidate agent for radiation synovectomy with its superior efficacy and safety.

[PA1-27] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]