

responses induced by intravenous norepinephrine. Moreover, the perfusion of pinacidil (100 μ M) into an adrenal vein of the rat for 20 min inhibited the CA secretory responses evoked by ACh (5.32 mM), high K^+ (56 mM), DMPP (100 μ M), McN-A-343 (100 μ M). Collectively, these results obtained from the present study demonstrate that intravenous pinacidil causes a dose-dependent depressor action in the anesthetized rat at least partly through the blockade of adrenergic α_1 -receptors. Pinacidil also causes vascular relaxation in the isolated aortic strips of the rat via the blockade of adrenergic α_1 -receptors, in addition to the known potassium channel opening-induced vasorelaxation. It seems that pinacidil has the inhibitory effects on CA secretion in the perfused rat adrenal gland.

[PA1-33] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

CJ-11668, a new selective and potent cox-2 inhibitor, has long-acting pharmacokinetic profiles

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CJ-11668 is a new potent and selective COX-2 inhibitor (IC_{50} COX-2 65nM; COX-1/COX-2 ratio 770). The pharmacokinetic profile of CJ-11668 (20 mg/kg, p.o.) in the rat was characterized by high bioavailability (90%) and long plasma half-life (11.7 hr) with low clearance (0.4 L/hr/kg). In the dog, the PK profiles (2 mg/kg, p.o.) also showed long plasma half-life (17.9hr) with low clearance (0.5 L/hr/kg), and the bioavailability of 60%. The inhibition of CJ-11668 in five different cytochrome P450 isozymes (1A2, 2C9, 2C19, 2D6 and 3A4) was determined in vitro and had observed no significant effect. When CJ-11668 was incubated with liver microsomes for 1hr, the parent drug was remained 68%. The protein binding in human and rat serum exhibited 98% and 96%, respectively. In conclusion, these results suggest that CJ-11668 have a good therapeutic potential for inflammation and pain in human arthritis owing to its long acting pharmacokinetic profiles.

[PA1-34] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Intracellular Ca^{2+} release mediates apoptosis induced by ascorbic acid (vitamin C) in HepG2 human hepatoma cells

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Ascorbic acid (vitamin C) has been shown to have anti-cancer actions. However, the exact mechanism of this action is not fully understood. In this study we investigated the possible mechanism of anti-cancer action of ascorbic acid in HepG2 human hepatoblastoma cells. Ascorbic acid induced apoptotic cell death in a dose-dependent manner in the HepG2 cells, assessed by the flow cytometric analysis of hypodiploid nuclei stained with propidium iodide. In addition, ascorbic acid increased intracellular Ca^{2+} concentration, whereas the level of reactive oxygen species was not significantly changed, suggesting that ascorbic acid may not alter cellular redox potential in the cells. Ascorbic acid-induced increased intracellular Ca^{2+} was not significantly altered by EGTA, an extracellular Ca^{2+} chelator, whereas dantrolene, an intracellular Ca^{2+} release blocker, completely blocked the action of ascorbic acid. Furthermore, U-73122 and manojalide, phospholipase C (PLC) inhibitors, effectively prevented the ascorbic acid-induced intracellular Ca^{2+} increase. Furthermore, Ascorbic acid-induced apoptosis was also significantly suppressed by treatment with dantrolene and these PLC inhibitors. Collectively, these results suggest that ascorbic acid induced apoptosis in HepG2 cells and that PLC- IP_3 -intracellular Ca^{2+} signal may mediate the apoptotic action of ascorbic acid.

[PA1-35] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Acanthoic acid blocks production of pro-inflammatory mediators by inhibiting the ERK activation in trypsin-stimulated human leukemic mast cells