responses induced by intravenous norepinephrine. Moreover, the perfusion of pinacidil (100 μM) 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 μM), McN-A-343 (100 μM). 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-iduced 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 bioavalability 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 propodium 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 manoalide, phospholipasde 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