and bulbocavernous muscle (LABC), and cowper's glands (CpG) weights were significantly increased. Flutamide inhibited the testosterone-induced re-growth of accessory sex glands (SV, VP and Cp) and organs (GP and LABC) with dose-dependent manner. A rodent 20-day thyroid/pubertal male assay was performed utilizing immature age-matched intact male rats (33 days of age). All rats (10 rats/group) were treated with testosterone (1.0 mg/kg/day, by s.c.) and flutamide (1, 5, and 25 mg/kg/day, by oral) from PND 33 to PND 53, respectively. Testosterone increased significantly the SV and VP weights, with some effect on GP, LABC, and Cp. When flutamide was administered to immature male rats, the accessory sex organs (SV, VP, GP, LABC, and CpG) growth and development was blocked in dose-dependent manner. However, testes weights were significantly increased following flutamide administration (5 and 25 mg/kg/day). In conclusion, 20-day thyroid/pubertal male assay showed similar sensitivity to Hershberger assay for the screening of androgenic/antiandrogenic compounds.

[PA4-24] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

3MC and DPB effects on the expression of drug metabolising enzymes via RT-PCR.

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In order to understand the mechanism of the regulation of drug metabolizing enzyme gene expression, we have studies the induction of CYP1A1 and GSTα, μ, π enzymes in monkey that is treated with 3-methylcholanthrene (3MC) and dibutylphthalate (DBP). The mRNA levels were measured by RT-PCR and enzymatic activity was measured via EROD in brain, intestine and liver. And the copy number of CYP1A1 per 3/20㎍ was measured by competitive PCR. In the case of adult monkey, treatment with 3MC induced CYP1A1 mRNA in brain by 2-fold, in intestine by 11-fold and in liver by 10-fold respectively. And the treatment with DBP induced CYP1A1 mRNA. GST μ was not induced by the treatment with 3MC and DBP. GSTα was not induced by the treatment with 3MC and DBP in liver and brain, but it was induced in intestine (1.5-fold). GSTπ was slightly induced by the treatment with 3MC and DBP in brain, intestine and liver. In the case of fetus monkey, the basal levels of fetus CYP1A1 mRNA and GSTs mRNA were low in comparison to adult monkey and as the age of monkey increased, the basal levels of CYP1A1 mRNA and GSTs mRNA were also increased. The treatment with 3MC induced CYP1A1 mRNA in brain and liver, but it didn't significantly induce CYP1A1 mRNA in intestine. GSTμ and GSTα was not induced by the treatment with 3MC and DBP. GST π was slightly induced by the treatment with 3MC and DBP. The copy number of CYP1A1 per RT product of 3/20㎍ total RNA was about 1×10^6 in the 3MC-treated liver, 5×10^4 in control liver, 5×10^3 in 3MC-treated intestine and 1×10^3 in 3MC-treated brain.

[PA4-25] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

De novo Synthesis Pathway of Ceramide Causes Hypoxia -induced Apoptosis of SH-SY5Y Human Neuroblastoma Cells

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Ceramide has been implicated to be a second messenger in the cell signaling pathway involved in a variety of cellular responses ranging from cell differentiation, cell cycle arrest, cellular senescence, apoptosis to cell survival and cell proliferation in a number of cells. However, there is little information of a role of ceramide in apoptosis in hypoxic injury known to induce necrotic cell death. Ceramide generation was measured in SH-SY5Y cells metabolically labeled with [3H]serine after exposure to chemical hypoxia induced by cobalt chloride. Chemical hypoxia resulted in a

rapid increase in ceramide production prior to any evidence of cell death in SH-SY5Y cells. The inhibitor of ceramide synthase, fumonisin B1, inhibited against chemical hypoxia-induced enhancement of ceramide and cell death. Cobalt chloride also upregulated hypoxia-inducible factor 1a (HIF-1a) known to stimulate the transcription of several genes during hypoxic injury. SH-SY5Y cells exposed to cobalt chloride provoked apoptosis preceded by elevation of ceramide levels, but did not induce a concurrent decrease in sphingomyelin. Addition of exogenous C6-ceramide also induced apoptosis in SH-SY5Y cells in a similar kinetic frame. These results suggest that hypoxia may induce neuronal apoptosis through de novo synthesis pathway of ceramide, not sphingomyelinase pathway.

[PB1-1] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Diabetes-induced cardiac dysfunction is enhanced by an oxazolidine derivative KST221148

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Myocardial dysfunction including coronary dysfunction is known as a common complication of diabetes mellitus. Therefore, the strategy for novel antidiabetics seems to develop a drug which have beneficial effect on complications such as cardiac dysfunction, as well as antibiabetic effect. A well known antidiabetic troglitazone has been reported to have additional cardioprotective effect. KST221148, (2RS, 5SR) 3-(2-chloro- benzoyl)-5-(4-chlorophenoxymethyl)-2-(3,4-dichlorophenyl), is a newly synthesized thirty-five oxazolidine derivative which has been demonstrated to have a good antidiabetic effect.
In the present study, we observed the effect of KST221148 on cardiovascular dysfunctions in streptozotocin-induced diabetic rats.
Diabetes was induced by streptozotocin (50 mg/kg i.p.) 4 weeks before experiment.
Isolated heart from diabetes showed a significant depression in the left ventricular developed pressure (LVDP) and heart rate (HR), and a remarkable decrease in coronary flow rate (CFR) compared with those of age-matched controls, indicating contractile and coronary dysfunctions in diabetes. The treatment of diabetic heart with 10 μM KST221148 significantly improved the decreased LVDP and CFR up to the level of control heart, with no effect on decreased HR. In conclusion, these findings suggest that KST221148 may be a beneficial candidate for the development of antidiabetic.

[PB1-2] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Differential involvement of Ca2+ mobilization and protein kinases in histamine release of rat peritoneal mast cells induced by ATP and compound 48/80

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To investigate the different mechanism between ATP and compound 48/80(C48/80)-induced histamine release, we observed effects of calcium antagonists and protein kinase inhibitors in histamine release of rat peritoneal mast cells. Verapamil (voltage-dependent calcium channel blocker) and TMB-8 (a blocker of intracellular calcium release) significantly inhibited ATP-induced histamine release, but did not inhibit C48/80-induced histamine release. Econazole (a blocker of receptor-operated calcium channel) dose-dependently inhibited both ATP and C48/80-induced histamine release, but inhibitory effect of econazole in ATP-induced histamine release was more