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

potent than that in C48/80-induced histamine release. EGTA dose-dependently inhibited ATP and C48/80-induced histamine release, but C48/80-induced histamine release was slightly inhibited by high concentrations (>2mM) of EGTA. Bisindolylmaleimide (protein kinase C antagonist) dose-dependently inhibited ATP and C48/80-induced histamine release. Calmodulin antagonists (W-7, trifluoperazine) had a little effect in ATP and C48/80-induced histamine release at low concentrations(<3μM), but at high concentration (W-7, >10μM; trifluoperazine, >3μM) they stimulated ATP and C48/80-induced histamine release. Tyrosine kinase inhibitors (methyl 2,5-dihydroxycinnamate, genistein) dose-dependently inhibited ATP and C48/80-induced histamine release. Protein kinases (such as protein kinase C, calmodulin-dependent pathway and tyrosine kinase) seem to be involved in histamine release induced by ATP and C48/80. These results suggest that ATP-induced histamine release is related to both intracellular calcium release and extracellular calcium influx via voltage-dependent calcium channel and receptor-operated calcium channel. C48/80-induced histamine release is related to extracellular calcium influx, especially by receptor-operated calcium channel rather than voltage-dependent calcium channel.

[PB1-3] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

Effect of Four-Week Ethanol Intake on Exocrine Pancreatic Secretion in Rats

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To investigate the effect of long-term ethanol intake on pancreatic exocrine secretion, rats were freely accessed to 5% (w/v) ethanol instead of water for 4 weeks. These rats consumed approximately 2.5-3.0 g of ethanol daily. Pancreatic juice secretion rate was 25.4 2.3 l/hr in normal rats and 23.1 1.5 l/hr in ethanol-fed rats. Amylase activity and phospholipase A2 activity of pancreatic juice in normal rats were similar to those in ethanol-fed rats. However, protein concentration of pancreatic juice in ethanol-fed rats was significantly greater than that in normal rats. In acute pancreatitis induced by CBPD obstruction, water contents, amylase activity and phospholipase A2 activity of pancreatic fragment significantly increased. These increases indicate typical inflammatory response as acute pancreatitis. In ethanol-fed rats, water contents and amylase activity also significantly increased but phospholipase A2 activity did not as compared with that in normal rats. The obstruction of CBPD resulted in the increase of protein concentration, amylase activity and phospholipase A2 activity in serum. In ethanol-fed rats, serum protein concentration was significantly higher than that of normal rats, whereas amylase activity and phospholipase A2 activity were similar to those of normal rats. This result suggests that long-term intake of 5% ethanol like beer may cause the pancreatic inflammation.

[PB1-4] [10/20/2000 (Fri) 15:30 - 16:30 / [Hall B]]

The role of PKC activation on hypoxia-induced cell death in cardiomyocyte and smooth muscle cells

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Protein kinase C (PKC) has been known to play a role in the protective effect of ischemic preconditioning in heart and vascular cells. On the basis of the fact that high glucose can produce PKC activation, in the present study, we investigated whether high glucose (22 mM) can produce protective effect against hypoxia-induced cell death and whether the effect of high glucose is correlated with PKC activation in H9c2 cardiomyocyte and A7r5 smooth muscle cells.
The lactate dehydrogenase(LDH) release is estimated as a parameter of cellular injury. Apoptotic cell death was examined by the method of TUNEL(Terminal Deoxynucleotidyl-transferase Nick-End Labeling) staining.