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