Inhibition of C2-ceramide induced contraction in cat esophageal smooth muscle cell by newly synthesized Ceramide analogues

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It has been shown that C2-ceramide (C2), short chain ceramide, plays a role in mediating contraction of cat esophageal smooth muscle cells. We examined the effect of newly synthesized ceramide analogues on the C2-ceramide induced contraction in esophageal smooth muscle cells isolated with collagenase.
C2-ceramide produced contraction of smooth muscle cells in a dose dependent manner. CY 3523, CY3525, or CY 3723 (a ceramide analogue) inhibited C2-ceramide induced contraction in a dose dependent manner, which inhibition produced maximally at 10^{-5} M of each analogue. CY 3523 showed the 35~40% inhibition, and CY3525, CY3723 showed 25~35% inhibition. The inhibition of C2-ceramide induced contraction by ceramide analogues was recovered by treatment with PMA (100 nmol, PKC activator) for each analogue. These result suggest that ceramide analogues can inhibit C2-ceramide induced contraction via PKC-dependent pathway.

[PA1-17] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Inhibitory Effects of 1,3-Selenazol-4-one Derivatives on Mushroom Tyrosinase

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This study reports depigmenting potency of 1,3-selenazol-4-one derivatives, which would be based upon the finding of direct inhibition to mushroom tyrosinase. 1,3-Selenazol-4-one derivatives exhibited inhibitory effect on dopa oxidase activity of mushroom tyrosinase. In this study, inhibitory effects of six kinds of 1,3-selenazol-4-one derivatives (3a, 3c, 3d, 3e, 3g and 3i) on mushroom tyrosinase were investigated. Compounds at a concentration of 500 mM exhibited 33.4 - 62.1 % of inhibition on dopa oxidase activity of mushroom tyrosinase. Their inhibitory effects were higher than that of kojic acid (31.7 %), a well known tyrosinase inhibitor. 2-(4-Methylphenyl)-1,3-selenazol-4-one (3a) exhibited the strongest inhibitory effect among them dose-dependently and in competitive inhibition manner.

[PA1-18] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Inhibitory effects of new quinone compounds on eNOS activity in rat aorta and nNOS activity in rat brain

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Nitric oxide (NO) has been shown to play an important role in the regulation of vascular tone, platelet function, neurotransmission, and immune function. NO is synthesized from the L-arginine by NO synthase (NOS). Three distinct isoforms of NOS have been identified: calcium/calmodulin-dependent

endothelial (eNOS) and neuronal (nNOS) isoforms which are constitutive and produce small quantities of NO, and an inducible isoform (iNOS) which is markedly induced in response to lipopolysaccharide (LPS) or inflammatory cytokines. Newly synthesized quinone derivatives were tested for their inhibitory effects on endothelial NOS (eNOS) by investigating the effect on endothelium-dependent relaxation of isolated rat aorta, and also tested for their inhibitory effects on neuronal NOS (nNOS) by measuring NOx (nitrate/nitrite) produced by NOS in rat forebrain homogenates. Among the tested compounds including twelve 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones (HPBIQ1-12), six 7-arylamino-5,8- quinazolinediones (SKH3, SKH5, SKH13, SKH15, SKH21, and SKH28), and two 6-arylamino-5,8-quinazolinediones (DQZ18 and DQZ21), SKH3, SKH5 and DQZ4 produced strong inhibitory effects on the acetylcholine-induced vasorelaxation of phenylephrine-precontracted aorta with the intact endothelium indicating their possession of inhibitory effect on eNOS, and also decreased nNOS activity by about 50% in rat brain at a tested concentration. Compounds SKH13, SKH15 and SKH21 produced moderate inhibitory effects on both eNOS and nNOS. None of HPBIQs showed inhibitory effects on eNOS, on the other hand, most of HPBIQs (except HPBIQ1 & 3) exhibited relatively strong inhibitory effects on nNOS. SKH28 and DQZ18 showed relatively weak inhibition of eNOS in rat aorta, but inhibited nNOS activity by about 50% in rat brain. This study found new quinone compounds which might be developed as NOS inhibitors with different selectivity.

[PA1-19] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

Attenuation of monocrotaline-induced pulmonary hypertension with DA-8159, a potent PDE 5 inhibitor

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This study was carried out to demonstrate the effects of oral administration of DA-8159, a selective phosphodiesterase 5 inhibitor, on development of pulmonary hypertension induced by monocrotaline (MCT). MCT-treated rats(60mg/kg) were divided into three groups and orally administered vehicle, 1mg/kg or 5mg/kg of DA-8159 twice a day for 3 weeks. Increased right ventricular weights, medial wall thickening in pulmonary arteries, myocardial fibrosis, decrease of plasma cyclic guanosine monophosphate (cGMP) level and body weight gains were shown in MCT group. However, DA-8159 markedly and dose-dependently reduced the development of right ventricular hypertrophy and medial wall thickening. Furthermore, DA-8159 amplified the increase in plasma cGMP level and significantly increased the level of lung cGMP compared with MCT group. Although body weight gain was still lower from the saline-treated control group, DA-8159 demonstrated a significant increase in body weight gains both in 1mg/kg and 5mg/kg groups when compared with MCT group. In myocardial morphology, MCT-induced myocardial fibrosis was markedly prevented by DA-8159. These results suggest that DA-8159 may be useful oral treatment option for pulmonary hypertension.

[PA1-20] [10/18/2002 (Fri) 09:30 - 12:30 / Hall C]

TOLERANCE AND PHARMACOKINETICS OF SINGLE-DOSE DA-8159, A SELECTIVE PDE5 INHIBITOR, IN HEALTHY MALES

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Tolerance and pharmacokinetics after single-dose administration of DA-8159, a new selective PDE5 inhibitor under phase I study, were examined in 42 healthy male volunteers in a six-period, double-