mechanism on rat aortic VSMCs by luteolin was investigated. Luteolin significantly inhibited the platelet-derived growth factor(PDGF)-BB-induced proliferation of rat aortic VSMCs in a concentration-dependent manner evaluated by cell count and [3H]-thymidine incorporation assay. Luteolin did not show any cellular toxicity or apoptosis as determined by flow cytometric analysis and MTT assay at the concentration used in this study. Luteolin showed an arrest of PDGF-BB-induced VSMC cycle progression by flow cytometry. In order to elucidate the anti-proliferative mechanism, we examined the effects of luteolin on the PDGF-BB-induced activation of PDGF-β receptor(PDGF-Rβ) by western blot in cultured VSMCs. Pre-treatment of VSMCs with luteolin resulted in a significant inhibition of the PDGF-BB-induced phosphorylation of PDGF-Rβ. Downstream of PDGF-Rβ such as extracellular signal-regulated kinase 1/2 (ERK1/2), phospholipase C-γ1 (PLC-γ1) and Akt cascade were also inhibited by luteolin. Taken together, these results suggest that the inhibition of vascular smooth muscle cell proliferation by luteolin may be mediated mainly by inhibition of PDGF-β receptor, which leads to the inhibition of downstream such as ERK1/2, PLC-γ1 and Akt cascade.

[PA1-25] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

ROLES OF HUMAN LIVER CYTOCHROMES P450 3A4 AND 1A2 IN THE OXIDATION OF MYRISTICIN

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Myristicin, 1-allyl-3,4-methylenedioxy-5-methoxybenzene, is a naturally occurring alkenylbenzene compound. It is found in nutmag, mace, parsley, carrot, black pepper, many natural oils, and flavoring agents. The aim of this work was to identify the form(s) of human liver cytochrome P450 (P450) involved in the hepatic transformation of myristicin to its major metabolite, 5-allyl-1-methoxy-2,3-dihydroxybenzene (M1). When several human liver microsomes were compared, the M1 formation activity was well correlated (r=0.87) with nifedipine oxidation (a marker of P4503A4). When a microsomal sample having high P4503A4 activity was used, microsomal oxidation of myristicin to M1 was markedly inhibited by ketoconazole, a selective inhibitor of P4503A enzymes, but not by any of several other P450 inhibitors. Antibodies raised against P4503A4 could also inhibit most of the myristicin oxidation, but antibodies recognizing other P450s had no effect. The oxidation of myristicin to M1 was catalyzed by purified recombinant P4503A4 and P4501A2. These results provide evidence that P450s 3A(4) and P4501A2 play in the formation of major metabolite, M1. [supported by grant No. R01-2001-00209 from the Korea Science & Engineering Foundation].

[PA1-26] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Antiplatelet Constituent Isolated from Thujopsis dolabrata var. hondai

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The steam distillate obtained from sawdust of *Thujopsis dolabrata* var. *hondai* was fractionated by centrifugal thin-film evaporation, and then the fractions were investigated against antiplatelet

activity using washed rabbit platelets *in vitro*. The biologically active constituent of *T. dolabrata* sawdust was isolated by silica gel column chromatography and HPLC and characterized as carvacrol by various spectral analyses (^{1}H-, ^{13}C-NMR and GC/MS studies). The inhibition values of carvacrol at the concentration of 1.0 μg/mL for collagen, arachidonic acid, or PAF-induced platelet aggregations were 21, 92, and 2%, respectively. However, carvacrol at the same concentration no affected thrombin (0.1 unit/mL)-, calcium ionophore A23187 (2 μM)-, or PMA (20 μM)-induced platelet aggregation. These results suggest that carvacrol isolated from *T. dolabrata* sawdust may be useful as a lead compound and new agents for inhibiting platelet aggregation induced by arachidonic acid.

[PA1-27] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

β-EUDESMOL CAUSES VASODILATORY EFFECT IN THE NORMOTENSIVE RAT

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β-Eudesmol is one of various compounds derived from the bark of Magnolia obovata Thunberg, a medicinal plant. It has been shown that β-eudesmol also markedly alleviated muscle fasciculation, tremor and convulsion induced by diisopropylfluorophosphate and prolonged the time to death in mice (Chiou et al., 1995). Actually, the extract of magnolia bark has been shown to have depressant actions on the central nervous system (Watanabe et al., 1973). Recently, it has been reported that the crude extract of magnolia bark, an herbal drug, inhibited the secretion of catecholamines from bovine adrenal chromaffin cells stimulated by acetylcholine in a concentration-dependent manner (Tachikawa et al., 2000). Therefore, the present study was conducted to investigate the effects of β-eudesmol on arterial blood pressure and vascular contractile responses in the normotensve rats and to establish the mechanism of action. Phenylephrine (an adrenergiα1-receptor agonist) and high potassium (a membrane-depolarizing agent) caused greatly contractile responses in the isolated aortic strips, respectively. These phenylephrine (10-5 M)-induced contractile responses were depressed in the presence of high concentrations of bornyl acetate (10 ~ 20 μg/ml), but not affected in low concentration of bornyl acetate (2.5 ~ 5 μg/ml). Also, high potassium (5.6 x 10-2 M)-induced contractile responses were greatly inhibited in the presence of β-eudesmol (2.5 ~ 20 μg/ml) in a dose-dependent fashion. β-eudesmol (1 ~ 10 mg/kg) given into a femoral vein of the normotensive rat produced a dose-dependent depressor response, which is transient (data not shown). Interestingly, the infusion of a moderate dose of β-eudesmol (3 mg/kg/30 min) made a significant reduction in pressor responses induced by intravenous norepinephrine. Collectively, these results obtained from the present study demonstrate that intravenous β-eudesmol causes a dose-dependent depressor action in the anesthetized rat at least partly through the blockade of adrenergic α1-receptors. β-Eudesmol also causes vascular relaxation in the isolated aortic strips of the rat via the blockade of adrenergic α1-receptors, in addition to the unknown direct mechanism.

[PA1-28] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Enantio-Selective Inhibition of (1R,9S)- and (1S,9R)-β-Hydrastines on Dopamine Biosynthesis in PC12 Cells

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