aporphine alkaloids.

[PB3-3] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

β-Hydrastine derivatives inhibit dopamine biosynthesis in PC12 cells

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The effects of (+)-β-hydrastine hydrochloride and (-)-β-hydrastine on dopamine biosynthesis in PC12 cells were investigated. (+)-β-Hydrastine hydrochloride and (-)-β-hydrastine significantly decreased the intracellular dopamine content in dose- and time-dependent manner, and the IC50 values were 9.3 μM and 20.7 μM, respectively. Dopamine content was lowered at 6 h and reached a minimal level at 18 h and 12 h after the exposure to 10 μM (+)-β-hydrastine hydrochloride and 20 μM (-)-β-hydrastine. The decreased dopamine content was maintained for up to 48 h, and then dopamine content completely recovered to the control level at about 72 h. Intracellular tyrosine hydroxylase (TH) activity was also inhibited by these compounds and reached the minimal level at about 6 h and 12 h, respectively. Intracellular cAMP and Ca++ concentrations were also decreased by β-hydrastine derivatives. These results indicate that β-hydrastine derivatives contributes partially to the decrease in dopamine content by the inhibition of TH activity in PC12 cells.

[PB3-4] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

EVALUATION OF ABUSE LIABILITY OF EPHEDRINE IN RATS.

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Ephedrine is a main component of ma huang, Ephedra sinica, which has been used as a medicinal agent to treat hay fever or asthma. Nowadays, this sympathomimetic drug is abused in many countries. In this study, we investigated the abuse liability of ephedrine by measuring locomotor activities (LA) and self-administration (SA) profiles in Sprague-Dawley rats. LA was determined in rats treated i.p. with 3, 10 and 30 mg/kg ephedrine once a day for 14 days. Intravenous SA by ephedrine (0.23, 1 and 2.3 mg/kg) was examined in food-trained rats, and the changes of ephedrine-induced SA by treating dopamine receptor antagonist, spiperone (30 μg/kg, s.c. 1 hr before testing) were examined. We also tested the reinforcing effect of ephedrine in rats maintained to self-administer 0.1 mg/kg/inj. Methamphetamine (METH, i.v.). Body weight was not changed, but LA was dose-dependently increased in ephedrine-treated group. Saline substitution for ephedrine increased SA rates. The SA of ephedrine was decreased by spiperone. And SA rates of 1.15, 2.3 and 4.6 mg/kg/inj. ephedrine were similar to that of saline in rats trained SA by METH. These findings suggested that ephedrine may have abuse liability, partially related to dopaminergic system, but it may not substituted for METH self-administration.

[PB3-5] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Activation of p38 MAP kinase and AP-1 during the promotion of neurite extension of PC-12 cells by 15-deoxy-Δ12,14-prostaglandin J2

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15-Deoxy-Δ12,14-prostaglandin J2 (15-deoxy-PGJ2), a naturally occurring ligand activates the peroxisome proliferator-activated receptor-γ(PPAR-γ). It was known to have promoting ability of nerve growth factor(NGF)-induced neurite extension. However, it is not clear yet as to what signaling pathway is involved in its promoting ability of neurite extension. Since MAP kinase classes as well as transcription factors have been known to be implicated in neuronal cell differentiation, we investigated whether 15-deoxy-PGJ2 exert its ability to promote cell differentiation through up-regulation of MAP kinase classes and the activation of transcription factors. PC 12 cells treated with 15-deoxy-PGJ2 (0.2 to 1.6 μM) alone showed measurable neurite extension and expression of neurofilament, markers of cell differentiation. However much greater extent of neurite extension and expression of neurofilament was observed in the presence of NGF (50 ng/ml). In parallel with its increasing effect on the neurite extension and expression of neurofilament, 15-deoxy-PGJ2 enhanced NGF-induced p38 MAP kinase expression and its phosphorylation in addition to the activation of transcription factor AP-1 in a dose dependent manner. Moreover, pretreatment of SD 203580, a specific inhibitor of p38 MAP kinase inhibited the promoting effect of 15-deoxy-PGJ2 (0.8 μM) on NGF (50 ng/ml)-induced neurite extension. This inhibition correlated well with the ability of SB203580 to inhibit the enhancing effect of 15-deoxy-PGJ2 on NGF-induced the expression of p38 MAP kinase and activation of AP-1. These data demonstrate that activation of p38 MAP kinase in conjunction with AP-1 signal pathway may play an important role in the promoting activity of 15-deoxy-PGJ2 on the NGF-induced differentiation of PC12 cells.

[PB3-6] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

PRESENILIN-2 MUTATION ALTERS NEURITE EXTENTION, APOPTOSIS AND TRANSCRIPTION FACTOR(NF-KB) ACTIVATION.

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Alzheimer's disease (AD) is characterized by β-amyloid deposition and associated with loss of neuron cells in brain regions involved in learning and memory process. Many cases of early onset autosomal dominant inherited forms of AD are caused by mutation in the genes encoding presenilin-2 (PS-2). However, its pathogenic mechanisms in AD are not known. Here we report that expression of an AD-liked human PS-2 mutation (N141I) in PC12 cells resulted in aberrant differentiation responses to nerve growth factor (NGF) and β-amyloid. NGF-induce neurite extension was significantly reduced in cells stably expressing mutant PS-2. Induction of apoptosis and apoptosis-associated gene expression by β-amyloid was markedly increased in cells carrying mutant PS-2. The DNA binding activity of the transcription factor NF-kB by β-amyloid was decreased in the cells carrying mutant PS-2. These finding shows that altered responsibility to neurotrophic (or neurotoxic) factors could a role in the pathogenesis of AD carrying PS-2 mutations.

[PB3-7] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

L-DOPA-Induced Neurotoxicity Is Enhanced by Tetrahydropapaveroline in PC12 Cells

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Tetrahydropapaveroline (THP) is formed in Parkinsonian patients receiving L-DOPA therapy and is detected in plasma and urine of the patients. THP and its derivatives were proposed to be candidates of dopaminergic neurotoxins related to the pathogenesis of Parkinsonism. In this study, we have investigated the effects of THP on dopamine content and L-DOPA-induced neurotoxicity in cultured rat pheochromocytoma (PC12) cells. PC12 cells were exposed to THP, L-DOPA, or a combination of the two for 24h or 48 h. THP at concentration range of 5-15 μM decreased dopamine content in a concentration-dependent manner. L-DOPA at 20-100 μM increased dopamine content in PC12 cells, but the increase in dopamine levels by L-DOPA was in part inhibited when L-DOPA was associated with 5-15 μM THP. Exposure of PC12 cells up to 10 μM THP or 20 μM L-DOPA after 24h or 48h, neither affected cell viability, determined by MTT assay, nor induced apoptosis, by flow cytometry and TUNEL staining. However, at