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