concentrations higher than 15 μM, THP showed a cytotoxicity through an apoptotic process. In addition, THP at 5-15 μM significantly enhanced L-DOPA-induced neurotoxicity (L-DOPA concentration, 50 μM). Treatment of PC12 cells with 15 μM THP and 50 μM L-DOPA, alone or in combination, also induced cell death via a mechanism which exhibited morphological and biochemical characteristics of apoptosis, including chromatin condensation and membrane blebbing. Exposure of PC12 cells to THP, L-DOPA and THP plus L-DOPA for 48 h resulted in a marked increase in the cell loss and percentage of apoptotic cells compared with exposure for 24 h. These findings indicate that the enhancing effects of THP on L-DOPA-induced neurotoxicity were time and concentration dependent. Furthermore, these results suggest that THP inhibits L-DOPA-induced increase in dopamine content and enhances L-DOPA-induced neurotoxic and apoptotic effects on PC12 cells.

[PB3-8] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Increase of intracellular Ca2+ and cytotoxicity induced by neuro-toxicants in PC12 cells carrying mutant presenilin-2

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Many cases of early onset autosomal dominant inherited forms of Alzheimer's disease (AD) are caused by mutation in the genes encoding presenilin-2 (PS-2) on chromosome 1. It is characterized by amyloid deposition and associated with loss of neuron. However, molecular mechanisms underlying the role of PS-2 mutation in the pathogenic AD are not known. Pathophysiological elevation of intracellular calcium concentration in the neuron has been demonstrated as an important responsible factor in the neuronal cell death. In this study, we compared real-time alteration of intra-cellular calcium concentration and cellular response (cytotoxicity) in the pheochromocytoma cells (PC12) and PC12 cells carrying mutant PS-2 stimulated either by beta-amyloid and glutamate. Prolonged elevation of intra-cellular calcium concentration by glutamate and beta-amyloid was significantly enhanced in cells carrying mutant PS-2. With reverse correlation with the level of intra-cellular calcium concentration, significant decrease of cell viability and increase of the induction of apoptosis was found in the cells carrying mutant PS-2. This results showing that PS-2 mutation elevates intra-cellular calcium concentration and thereby render neurons vulnerable to neuro-toxic stimuli, suggested that perturb of intra-cellular calcium homeostasis could play a important role in the pathogenesis of AD.

[PB3-9] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

15-DEOXY-△12,14-PROSTAGLANDIN J2, A LIGAND OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR-γ INDUCE APOPTOSIS THROUGH PHOSPHORYLATION OF ERK PATHWAY IN NEUROBLASTOMA CELLS

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15-Deoxy-Δ12,14-prostaglandin J2 (15-deoxy-PGJ2), a peroxisome proliferator-activated receptors (PPAR-γ) ligand, has been shown to stimulate the differentiation and induction of apoptosis in the several cancer cells including breast, prostate and lung cancer cells. In the previous our study, it was found that 15-deoxy-PGJ2 inhibit cell growth through induction of apoptosis in neuroblastoma cells (SK-N-MC and SK-N-SH cells). Here we demonstrated possible molecular mechanisms underlying the induction of apoptosis by 15-deoxy-PGJ2. 15-Deoxy-PGJ2 dose (2-16 μM) dependently induced apoptosis. Consistent with the induction of apoptosis,15-deoxy-PGJ2 reduced the expression of anti-apoptotic gene Bcl-2 but increased the expression of pro-apoptotic genes : caspase-3 and 9, and Bax. In parallel with the increasing of apoptosis, 15-deoxy-PGJ2 increased the expression of phosphorylated ERK. Moreover,