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15-DEOXY-Δ12,14-PROSTAGLANDIN J2 DECREASED ACTIVATION OF TRANSCRIPTION FACTOR NF-κB BY BETA-AMYLOID IN MUTANT PS-2 TRANSFECTED PC12 CELLS

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Mutations in the presenilin genes (PS-1 and PS-2) are linked to early onset familial Alzheimer's disease(AD), but its underlying cellular mechanisms have not been clear. 15-Deoxy-Δ12,14-prostaglandin J2 (15-deoxy-PGJ2) is know as a naturally occurring ligand of the peroxisome proliferator-activated receptor-γ (PPAR-γ). In this study, we investigated whether N141I PS-2 mutation can be in a favor of production of beta-amyloid (Aβ), and thereby increase the induction of apoptosis. We also examined the expression of inflammatory mediators to test whether inflammation may be a causing factor of the induction of apoptosis, and also investigated whether or not 15-deoxy-PGJ2 inhibits apoptosis by Aβ in mutant N141I PS-2 transfected PC12 cells. Aβ prominently enhanced expression of caspase 3, caspase 9, p21 and transcription factor NF-κB activation, however, did not induce PPAR-γ expression. We observed significant increase of Aβ production, the expression of genes involved in inflammation (TNF-α, COX-2, IκB), and Aβ-induced apoptosis in PC12 cell transfected with mutant PS-2 compared to control PC12 cells. And 15-deoxy-PGJ2 increased cell proliferation rate and cell viability of mutant N141I PS-2 transfected PC12 cells that were decreased by toxicity of Aβ, and inhibited activation of transcription factor NF-κB by Aβ on dose-dependent manners. These results demonstrate that PS-2 mutations may significantly contribute to the production of Aβ causing apoptosis through induction of inflammation, and 15-deoxy-PGJ2 could be suggested as a potent AD therapeutic drug through decrease the activation of NF-κB signal pathway.

keyword : Apoptosis, Cell viability, Inflammation