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Presenilin-2 mutation perturbs ryanodine receptor-mediated calcium homeostasis, caspase-3 activation and increases vulnerability of PC12 cells

In Young Hwang, Im Chul Shin, Dae Youn Hwang[1], Young Kyu Kim[1], Ki Hwa Yang[1], Tae Yeol Ha[2], Jin Tae Hong*

College of Phamacy, Chungbuk National University, [1]NITR, Korea Food and Drug Administration, [2]Korea Food Research Institute

Familial form of Alzheimer's disease (FAD) is caused by mutations in presenilin-1 and presenilin-2 (PS2). PS1 and PS2 mutation are known to similar effects on the production of amyloid β peptide (Aβ) and cause of cell death in the Alzheimer's brain. The importance of the alternation of calcium homeostasis in the neuronal cell death by PS1 mutation in a variety of experimental system has been demonstrated. However, no studies on the effect of PS2 on calcium signaling and the relevance to neuronal cell vulnerability against neurotoxins have been reported. Previous study showed that mice expressing mutant PS2 (N1411) increased Aβ production and caspase-3 activity, and caused memorial dysfunction. In the present study, we investigated whether PS2 mutation increased vulnerability of neuronal cells against oxidative and excitotoxic insults through perturbation of calcium homeostasis. Stable transfected PC12 cells with mutant (N1411) PS2 showed a significant increased cytotoxicity and induction of apoptosis by Aβ and L-glutamate compared to those in PC12 cells, PC12 cells expressing vector alone or expressing wild type of PS2. Consistent with the increased cytotoxicity and induction of apoptosis, relatively much greater enhanced intracellular calcium level and activation of caspase-3 were found in PC12 cells expressing mutant PS2 compared to those in PC12 cells, PC12

expressing vector alone or expressing wild type of PS2. Immunostaining and co-immunoprecipitation analysis show that RyR and PS2 are colocalized. The expression of RyR was much higher in PC12 cell expressing mutant PS2, and expression was increased by the treatment of Aβ and L-glutamate. Moreover, pretreatment of dantrolene, an inhibitor of ryanodine receptor of calcium release channel in ER, abolished Aβ and L-glutamate-induced increased intracellular calcium level, apoptosis, caspase-3 activation and altered RyR (and PS2) expression in PC12 cell expressing mutant PS2. The present data suggest that PS2 mutation may increase vulnerability neuronal cell to Aβ and L-glutamate, and this effect may be related to disruption of RyR-mediated calcium homeostasis in the ER.