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Calcium Signal Dependent Cell Death by Presenilin-2 Mutation in PC12 Cells and in Cortical Neuron from Presenilin-2 Mutation Transgenic Mice

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Familial form of Alzheimer's disease (FAD) is caused by mutations in presenilin-1 (PS-1) and presenilin-2 (PS-2). PS1 and PS2 mutation are known to similar effects on the production of amyloid β peptide (Aβ) and cause of neuronal cell death in the brain of patient of AD. The importance of the alternation of cellular calcium homeostasis in the neuronal cell death by PS1 mutation in a variety of experimental systems has been demonstrated. However, no studies on the effect of PS2 or mutant PS2 on cellular calcium homeostasis, and relevance of its change to neuronal cell vulnerability against neurotoxins have been reported. In the present study, we investigated whether PS2 mutation increased vulnerability of PC12 cells and cortical neuronal cells against neurotoxic insults through perturbation of calcium homeostasis. Stable transfected PC12 cells with mutant (N141I) showed a significant increased vulnerability of cells determined by cell viability and induction of apoptosis after treatment of L-glutamate and Aβ compared to those in PC12 cells, PC12 cells expressing vector alone or expressing wild type of PS2. Consistent with the increased cell vulnerability, much greater enhanced intracellular calcium level were found in PC12 cells expressing mutant PS2 after treatment of L-glutamate and Aβ. Double-labeling confocal micrograph analysis shows that ryanodine receptor (RyR) and PS2 are colocalized in endoplasmic reticulum (ER) of PC12 cells and cortical neurons from transgenic mice. PS2 and RyR expression was increased by the treatment of Aβ and L-glutamate. Moreover, pretreatment of dantrolene, an agent that block calcium release though RyR sensitive store protected against PS2 mutation-enhanced neuronal cell death. The present data suggest that PS2 mutation promotes neuronal degeneration in AD through perturbation of RyR sensitive calcium homeostasis in ER.

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