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INCREASE OF INTRACELLULAR CA^{2+} 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.

keyword : calcium , PS-2 , neurotoxicity , Alzheimer's disease(AD)