Presenilins in Alzheimer’s disease and frontotemporal dementia

Jie Shen

From 2011 International Conference on Molecular Neurodegeneration
Shanghai, China. 22-24 September 2011

Background
Synaptic dysfunction is widely thought to be an important pathogenic event in Alzheimer’s disease (AD). Presenilins, which harbor large numbers of mutations for familial AD and frontotemporal dementia (FTD), are important for neurotransmitter release and synaptic plasticity as well as memory and age-related neuronal survival.

Results
Our recent report showed that presenilins regulate synaptic function by modulating ryanodine receptor-mediated calcium release from the ER. To determine how presenilins regulate intracellular calcium signaling in neurons, we performed Ca$^{2+}$ imaging coupled with electrophysiological and molecular analyses using both acute hippocampal slices of unique presenilin conditional mutant mice and cultured hippocampal neurons, in which presenilins are acutely inactivated with a lentivirus expressing Cre recombinase.

Conclusion
Our results reveal a selective interaction between presenilins and ryanodine receptors in the regulation of calcium homeostasis and synaptic function, and suggest that disruption of calcium homeostasis may be an early pathogenic event leading to synaptic dysfunction in AD. We also generated two presenilin-1 knockin mice, in which either an AD- (L435F) or FTD (G183V) -causing mutation is introduced into the respective presenilin-1 endogenous genomic locus, to investigate the mechanisms by which presenilin mutations cause AD or FTD. The analysis of these mutant mice will also be presented.

Published: 7 February 2012

doi:10.1186/1750-1326-7-S1-L8

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