Presenilins Function as ER Calcium Leak Channels: Implications for Alzheimer's Disease

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DOI: 10.1134/S199074780903012X

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder. Mutations in presenilins are responsible for approximately 40% of all early onset familial Alzheimer's disease (FAD) cases in which a genetic cause has been identified. FAD mutations and genetic deletions of presenilins have been linked with calcium signaling abnormalities, but mechanistic basis for these results has not been clearly determined. Presenilins are highly conserved transmembrane proteins that support cleavage of the amyloid precursor protein by gamma-secretase. In our studies we discovered that in addition to acting as a gamma-secretase, presenilins also function as passive endoplasmic reticulum Ca^{2+} -leak channels. We demonstrate that wild type PS1 and PS2 proteins form low conductance divalent cation-permeable ion channels in planar lipid bilayers. In experiments with PS1/2 double knockout (DKO) mouse embryonic fibroblasts (MEFs) we discovered that presenilins account for ~80% of passive Ca^{2+} leak from the endoplasmic reticulum (ER). The ER Ca^{2+} -leak function of presenilins is independent from their gamma-secretase function. In additional experiments we demonstrated that ER Ca^{2+} -leak function of presenilins is impaired by many FAD-causing

mutations in presenilins. Our data uncover a novel Ca^{2+} signaling function of presenilins and provide support to the potential role of disturbed Ca^{2+} homeostasis in AD pathogenesis. Recently we expanded our studies of presenilins and Ca^{2+} signaling to neuronal system. Our latest findings will be discussed.

Supported by McKnight Neuroscience of Brain Disorders Award, Robert A. Welch Foundation, the Institute for the Study of Aging, the NINDS grants R01NS38082 and R01NS056224.

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