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Presenilin Modulates Calcium-permeant, Magnesium-Nucleotide regulated channel, I(MgNUM)

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The presenilin 1 (PS1) or PS2 is an essential component of the γ-secretase complex, which mediates the intramembrane proteolysis of selected type-I membrane, including the β-amyloid precursor protein (APP) to yield Aβ. Familial Alzheimer's disease (FAD)-associated mutations in presenilins give rise to an increased production of a highly amyloidogenic Aβ42. In addition to their well-documented proteolytic function, the presenilins play a role in calcium signaling. We have previously reported that presenilin FAD mutations cause highly consistent alterations in intracellular calcium signaling pathways, which include deficits in capacitative calcium entry (CCE), the refilling mechanism for depleted internal calcium stores. However, molecular basis for the presenilin-mediated modulation of CCE remains to be elucidated. In the present study, whole-cell patch clamp method was used to identify a specific calcium-permeable ion channel current(s) that is responsible for the CCE deficits associated with FAD-linked PS1 mutants. Unexpectedly, both voltage-activated and conventional store depletion-activated calcium currents I(CRAC), were absent in HEK293 cells, which were stably transfected either with wild-type or FAD mutant (L286V, M146L, and delta E9) forms of PS1. Recently, magnesium-nucleotide-regulated metal cation current, or I(MagNum), has been described and appears to share many common properties with I(CRAC) including calcium permeability and inhibitor sensitivity (e.g. 2-APB). We have detected I(MagNum) in all 293 cells tested. Interestingly, FAD mutant 293 cells developed only about half of currents compared to PS1 wild type cells. Conversely, the 293 cells expressing dominant-negative forms of the presenilins exhibited constitutively active I(MagNum), indicating that the presenilins negatively regulate calcium permeant MagNum current. Our studies suggest that aberrant activity or targeting of the I(MagNum) channel may be responsible for the CCE deficits associated with FAD-linked presenilin mutants.