Presenilins, neuronal calcium signaling and Alzheimer's disease

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Neuronal calcium (Ca^{2+}) signaling

Amyloid cascade hypothesis of AD

Question

How do PS-FAD mutations cause excessive Ca^{2+} release from the neuronal ER?
Hypothesis
Presenilins support passive ER Ca\(^{2+}\) leak
PS-FAD mutations disrupt ER Ca\(^{2+}\) leak function and result in overfilled Ca\(^{2+}\) stores.
Loss-of-function for presenilins ER Ca\(^{2+}\) leak becomes gain-of-function for InsP\(_3\)R- and RyanR-mediated Ca\(^{2+}\) release from the ER.

Structure of presenilins
- 9 transmembrane domains
- Locate in endoplasmic reticulum (ER)
PS1-M146V and PS2-N1411: FAD mutants with deranged Ca\(^{2+}\) signaling
PS1-UB: FAD mutant lacking exon9 with unique AD pathology (CWP16P)
PS1-I227A: γ-secretase catalytic mutant

BLM reconstitution
Presenilins form cation channels in BLM

Ba$^{2+}$ as current carrier

Tu et al. (2006) Cell

Presenilins and ER Ca$^{2+}$ homeostasis

Wild type

PS-DKO, PS1-M146V, PS2-N141I

Tu et al. (2006) Cell

Question

Correlation of PS1 ER Ca$^{2+}$ leak function with PS1-FAD clinical phenotypes?
PS1-FAD/FTD mutants and Ca^{2+} leak function


ER Ca^{2+} and PSEN1 FAD clinical phenotypes


Two causes of FAD pathology

Massive increase in A\beta_{42}/A\beta ratio (PS1/E9, APP mutations)

Defect in ER calcium leak pathway and ER calcium overload (PS1-M146V mutation)

Sporadic AD?
Dantrolene trial in APPPS1 mice: amyloid load

100 µg of dantrolene in PBS fed twice a week orally between 2 and 12 months of age to 6 APPPS1 and 6 WT mice

Vehicle  Dantrolene

Zhang at al. (2010), J. Neurosci

Presenilins and RyanRs in neuronal ER Ca²⁺ homeostasis

Zhang at al. (2010), J. Neurosci

Presenilins, ER Ca²⁺ and synaptic loss in AD

Calcium and amyloid pathways in AD

I. Bezprozvanny, Trends in Molecular Medicine, 2009

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