Presenilins, neuronal calcium signaling and Alzheimer's disease

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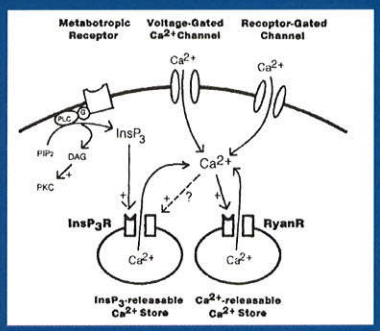
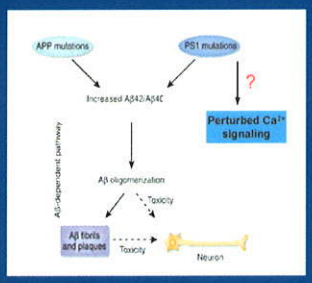
Neuronal calcium (Ca^{2+}) signaling

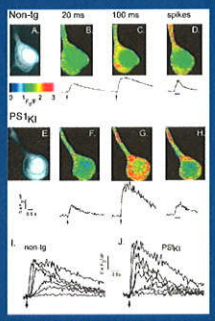


Amyloid cascade hypothesis of AD



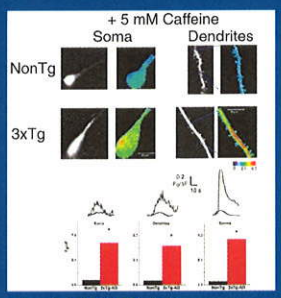
Adapted from Gandy at al (2006) *Nat Med*, v 12, pp. 1121-3.

$InsP_3$-induced Ca^{2+} signals in KI-$PS1_{M146V}$ cortical neurons



Stutzmann et al. (2004) *J. Neurosci.*, v 24, pp 508-13

Caffeine-induced Ca^{2+} signals in 3xTg (KI-$PS1_{M146V}$) hippocampal neurons



Chakroborty et al. (2009) *J. Neurosci.*, v 29, pp 9458-70

Question

How do PS-FAD mutations cause excessive Ca^{2+} release from the neuronal ER?

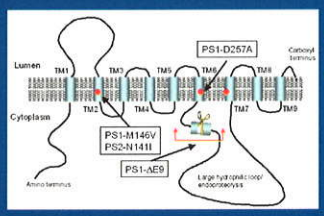
Hypothesis

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 $InsP_3R$- and RyanR-mediated Ca^{2+} release from the ER.

Structure of presenilins



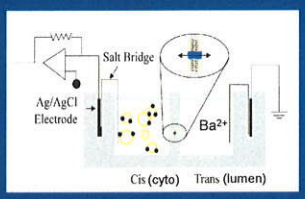
- 9 transmembrane domains
- Locate in endoplasmic Recticulum (ER)

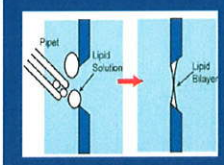
PS1-M146V and PS2-N141I: FAD mutants with deranged Ca^{2+} signaling

PS1-ΔE9: FAD mutant lacking exon9 with unique AD pathology (CWP/SP)

PS1-D257A: γ-secretase catalytic mutant

BLM reconstitution



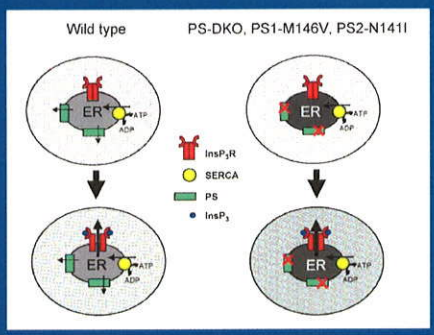


Presenilins form cation channels in BLM

Ba^{2+} as current carrier

Tu at al (2006) *Cell*

Presenilins and ER Ca^{2+} homeostasis

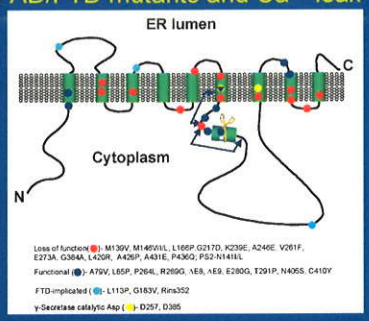


Tu at al. (2006) *Cell*

Question

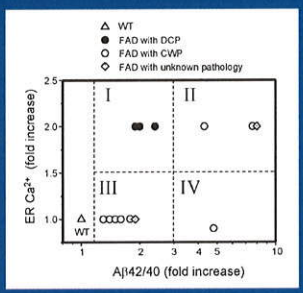
Correlation of PS1 ER Ca^{2+} leak function with PS1-FAD clinical phenotypes?

PS1-FAD/FTD mutants and Ca^{2+} leak function



Tu at al (2006) *Cell*; Nelson at al (2007) *J Clin Invest*; Nelson at al (2010) *J Alz Dis*

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



Nelson at al (2010), *J Alz Dis*.

Two causes of FAD pathology

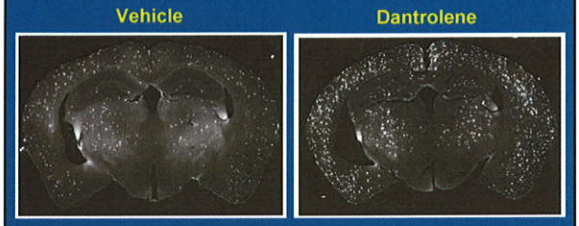
Massive increase in Aβ42/Aβ ratio (PS1ΔE9, APP mutations)

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

Sporadic AD?

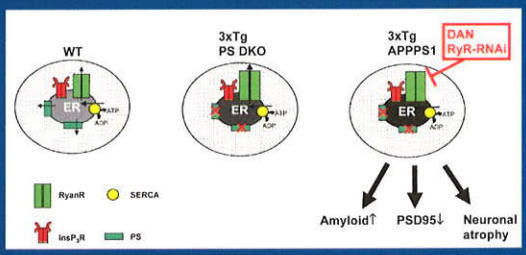
Dantrolene trial in APPPS1 mice: amyloid load

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



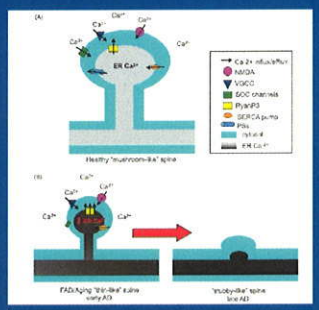
Zhang at al. (2010), *J. Neurosci*

Presenilins and RyanRs in neuronal ER Ca^{2+} homeostasis



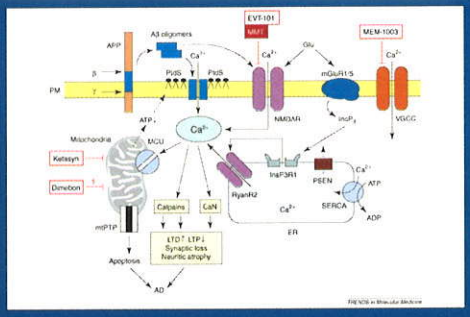
Zhang at al. (2010), *J. Neurosci*

Presenilins, ER Ca^{2+} and synaptic loss in AD



Popugayeva at al. *Messenger* (2012) v 1, pp 53-62

Calcium and amyloid pathways in AD



I. Bezprozvanny, *Trends in Molecular Medicine*, 2009

Acknowledgements

AD project - former
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Ilya's lab (October 2012)