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Ryanodine receptors: Dual contribution to Alzheimer disease?

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The hypothesis that calcium (Ca^{2+}) homeostasis perturbation could play a pivotal role in Alzheimer disease (AD) was introduced more than 20 years ago. Data obtained from experiments on dissociated cells, brains slices, and more recently on live AD animal models highlighted the key role of the endoplasmic reticulum (ER)-associated Ca2+ dysregulation in the setting and the development of AD.[1]

Ryanodine Receptors (RYRs) are ER-resident Ca^{2+} channels implicated in Ca^{2+} release from the lumen of the ER to the cytosol and in Ca^{2+} propagation along the axon from the synaptic button to the nucleus, thus controlling membrane excitability, neuronal function, and learning and memory paradigms. A large number of studies suggested that alterations of the expression and the function of RyR may occur in AD. Thus, increased RyR expression was reported in in vitro and in vivo AD study models, particularly in familial AD mutations transgenic mice models and in mild cognitive impairment and in human AD-derived brains.[2,3] These findings paved the way to study the role of RyR dysregulation in AD development. Pharmacological approaches targeting the blockade of RyR channels gave rise to puzzling results pointing out a possible dual role of RyR in the development of AD.[2,4,5] The consequence of RyR dysregulation in AD was elegantly demonstrated by Bezprozvanny's group in a recent paper,[6] by using a genetic approach to modulate RyR expression in a transgenic AD mice model.

A first set of studies using dantrolene-targeting blockade of RyR built a network of evidences suggesting that RyR may contribute to the setting of histopathological lesions and synaptic deficits associated to AD. Thus, acute and short-term dantrolene treatment was shown to stabilize Ca^{2+} signals and synaptic transmission, to reduce amyloid β (Aβ) production, and to prevent learning and memory deficits in 3 distinct AD mice models.[2,4,5] Conversely, another study revealed that long-term feeding with dantrolene triggered an opposite effect in 8 month old APPPS1 mice (double transgenic mice expressing mutated βAPP (precursor of Aβ) and PS1 (presenilin 1/γ-secretase catalytic core), i.e., exacerbated Aβ plaques formation, loss of hippocampal synaptic markers and neuronal deterioration.[7] Discrepancies in the above-described data may rely on the kinetics of AD-like set-up and progression as well as the duration of RyR blockade specifically linked to various models examined. The specificity of dantrolene toward RyR is also a matter of debate. Thus, studies using complementary approaches were warranted to clarify the real impact of RyR in AD.

The recent paper by Bezprozvanny's group sheds new lights on the complex dual role of RyR in the development of AD pathology.[6] The originality of this study relies on the use of a genetic approach to modulate RyR expression along AD development in APPPS1 mice model. As already reported in other AD mice models, authors first demonstrate a time-dependent upregulation of both RyR2 and RyR3 protein in the hippocampus of APPPS1 mice model. To manipulate RyR levels, authors used RyR3 Knockout mice presenting a mild neuronal phenotype as compared with RyR2 knockout mice. By using the APPPS1xRyR3−/− mice as a study model, they demonstrate that the deletion of RyR3 in young APPPS1 mice increases hippocampal neuronal network excitability and accelerates AD pathology characterized by a loss of mushroom spines and increased Aβ accumulation. In contrast, the deletion of RyR3 in older APPPS1 mice rescues the network excitability and the loss of mushroom spines, and reduces Aβ plaques and spontaneous seizure occurrence.

All together, these studies suggest a complex dual role of RyR in AD pathology. In this paradigm, RyR may function as a compensatory/protective actor at early disease stages, and acts as a pathogenic molecular determinant contributing to the setting of histopathological lesions and synaptic deficits observed at the late disease stages. These data appear to corroborate previous observations of RyR expression that is elevated in hippocampal regions of AD-affected cases with early neurofibrillary pathology while being apparently reduced in the subiculum, and CA1-CA4 regions at late stages.[8]

Targeting of ER Ca^{2+} homeostasis as a therapeutic approach for AD has not been fully investigated. As far as data obtained in animal models can be extrapolated to human beings, these findings allow envisioning novel drug-design strategies targeting RyR at the late stages of AD pathology.

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