Role of presynaptic calcium stores for neuronal network dysfunction in Alzheimer’s disease

Alzheimer’s disease (AD) is the most common form of dementia representing a major problem for public health. In 2017 there were an estimated 35 million patients worldwide and this number is expected to almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050 (https://www.alz.co.uk/research/statistics). Clinically there are two forms of the disease: the sporadic form (also called late onset AD, LOAD) and the familial form (FAD).

LOAD is the most common form. Its prevalence increases with advancing age from 1% in the 65–70 years old cohort to more that 30% after the age of 85. It is characterized by moderate to extreme severity with the advancing age being the main risk factor for LOAD. Familial AD represents some 5–10% of all AD cases. FAD is linked to mutations in a specific set of genes, most often in the genes encoding amyloid precursor protein (APP) and the presenilins (PS1 and 2). Interestingly, the vast majority of AD related mutations are located on PS1 (Steiner et al., 2008; Mattsson, 2010) thus identifying this protein as one of the main targets for FAD-modifying therapies. Here we address the role of AD-related presenilin mutations for Ca2+ homeostasis and in vivo neural network dysfunction in AD.

The role of presenilins: Presenilins are transmembrane proteins that harbor the catalytic site of the γ-secretase complex, which mediates the intramembranous cleavage of many type 1 membrane proteins, including APP (Steiner et al., 2008). Numerous FAD-associated presenilin mutations were shown to affect the cleavage specificity of γ-secretase, thus increasing the production of the so called “amyloidogenic” APP cleavage products (Steiner et al., 2008). Gradual accumulation of Aβ plays the central role in the so called “amyloid hypothesis” of AD (Selkoe, 2002; Selkoe and Hardy, 2016). Consistently, over the last decades therapeutic strategies mainly focused on decreasing Aβ levels inside the brain by either downregulating its production/accumulation or upregulating its clearance. So far, however, the results obtained were rather disappointing. In several trials using antibodies against Aβ, however, post hoc analyses hinted towards a reduction of cognitive decline in patients with mild, but not moderate, form of AD (Selkoe and Hardy, 2016).

Besides playing an important role in the γ-secretase complex, presenilins also have other functions, mostly related to the intracellular Ca2+ homeostasis (Hermes et al., 2010; Mattsson, 2010; Briggs et al., 2017; Popugaeva et al., 2017). Accordingly, PS mutations were reported to modify intracellular Ca2+ signaling in various experimental AD models. As illustrated in Figure 1, multiple AD-related human mutations (IP, receptors (reviewed in Hermes et al., 2010; Briggs et al., 2017; Popugaeva et al., 2017). Similarly, mutant presenilins were reported to upregulate the expression levels of RyRs, and to increase RyR-mediated Ca2+ release from the intracellular Ca2+ stores, likely through an enhancement of the open probability of the IP, receptors (reviewed in Hermes et al., 2010; Briggs et al., 2017; Popugaeva et al., 2017). Importantly, the ageing-related neuronal hyperactivity is prominent already in 10–14 months old mice. Such animals are not yet considered old and their age roughly corresponds to humans in their fourth or fifth decade of life. Furthermore, neurons are not the only cell type in the brain getting hyperactive with ageing. Similar trend was previously observed in vitro for cortical in leak channels (Brauske et al., 2014). Thus, during normal ageing the brain of middle-aged mice (and possibly also humans) reaches a different set point with more active neurons and microglia. Such conditions render the...
Figure 1 Main components regulating store-operated Ca\(^{2+}\) signaling in pre- and postsynaptic neuronal compartments.

Schematic representation of the key player regulating store-operated Ca\(^{2+}\) signaling as well as their interactions with presenilins. Arrows indicate the direction of ion flux. ER: Endoplasmic reticulum; RyR: ryanodine receptor; IP\(_{3}\)R: inositol triphosphate receptor; P2X: inositol 1,4,5-triphosphate; PIP\(_2\): phosphatidylinositol 4,5-bisphosphate; SERCA: sarcoplasmic/ endoplasmic reticulum Ca\(^{2+}\)-ATPase; NMDA: N-methyl-D-aspartate; AMPA: q-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; VGCC: voltage-gated Ca\(^{2+}\) channels; PLC: phospholipase C; SOCC: store-operated Ca\(^{2+}\) entry channel.

brain vulnerable to both neuroinflammation and seizure development, thus alleviating the development of AD.

The role of presynaptic calcium stores for neuronal network hyperactivity: Intracellular Ca\(^{2+}\) stores are part of the endoplasmic reticulum, which in neurons is present both pre- and postsynaptically (Figure 1, see also Mattson, 2010; Briggs et al., 2017). The majority of in vivo data emphasized the involvement of the postsynaptic Ca\(^{2+}\) stores in the pathophysiology of AD. Thus, the postsynaptic Ca\(^{2+}\) stores in somata and dendrites of cortical and hippocampal neurons of AD mice were shown to release more Ca\(^{2+}\) in response to the application of IP\(_3\), RyR or RyR agonists and to strongly potentiate synaptic and NMDA-receptor mediated Ca\(^{2+}\) transients (reviewed in Mattson, 2010; Chakroborty and Stutzmann, 2014). Excessive RyR-mediated Ca\(^{2+}\) release was also observed in dendritic spines of AD mice and was suggested to deregulate the maintenance of mossy fiber-associated mushroom spines via inhibition of the Ca\(^{2+}\) store-operated Ca\(^{2+}\) entry channels (SOCCs).

Figure 1: Briggs et al., 2017; Popugaeva et al., 2017. Our recent in vivo data, however, revealed a rather minor contribution of store-mediated Ca\(^{2+}\) release both to somatic and synaptic Ca\(^{2+}\) signals in layer 2/3 cortical neurons (Lerdkrai et al., 2018). Although somatic RyR-mediated Ca\(^{2+}\) release signals were somewhat longer in AD compared to age-matched WT mice, we did not observe any increase in their amplitudes, much in contrast to more than 200–300% increase in amplitudes of RyR-mediated Ca\(^{2+}\) release signals in vitro (see above). Among cells with different activity patterns (i.e., silent, normal and hyperactive; for details of cell classification see Busche et al., 2008), hyperactive cells showed the longest RyR-mediated Ca\(^{2+}\) release signals (Lerdkrai et al., 2018). Consistently, only in hyperactive cells spontaneous synaptically-driven dendritic Ca\(^{2+}\) transients showed a store-mediated component, which was blocked by emptying the intracellular stores. We concluded, therefore, that hyperactive cells are the only cells exhibiting AD-related overfilling of postsynaptic Ca\(^{2+}\) stores in vivo. Although for somatic and dendritic Ca\(^{2+}\) stores the degree of such overfilling is rather low, it cannot be excluded that somewhat larger dysfunction might be observed for Ca\(^{2+}\) stores in dendritic spines (Figure 1). Assuming that such dysfunction causes spine destabilization (see above), our recent data suggest that in vivo spine destabilization occurs in hyperactive cells only. In contrast to what is known about the postsynaptic side, the role of presynaptic Ca\(^{2+}\) stores for synaptic and neural network dysfunction in AD is much less clear. Under physiological conditions presenilins seem to modulate the evoked glutamate release in a Ca\(^{2+}\) store-dependent manner, and RyRs of AD mice were shown to mediate an increase in frequency of spontaneous vesicle release from presynaptic terminals (Chakroborty and Stutzmann, 2014). This increase, however, was believed to deplete the pool of readily releasable vesicles and to cause a Ca\(^{2+}\)-dependent activation of SK2 K\(^{+}\) channels (see above), both leading to weakening of synaptic transmission (Chakroborty and Stutzmann, 2014; Briggs et al., 2017). In contrast, our in vivo data suggest that an AD-related mutation in PSEN1 gene causes heighten- ed presynaptic release of glutamate already in 6–7 months old mice, thus strongly contributing to AD-related neuronal hyperactivity. Consistently, emptying the Ca\(^{2+}\) stores in AD and presenilin mutant mice normalizes cortical neural network activity in these animals (Lerdkrai et al., 2018). Interestingly, ageing- or APP mutation-induced neuronal hyperactivity are not sensitive to store depletion. Together, these data suggest that a single allele of mutated PS1 is sufficient to induce an early and a profound neuronal hyperactivity, mainly caused by the dysfunction of presynaptic intracellular Ca\(^{2+}\) stores. This early hyperactivity is likely to enhance activity-dependent generation and release of amyloid \(\beta\) and tau as well as formation of amyloid plaques (Palop and Mucke, 2016). By this mechanism a single mutation in the PSEN1 gene can lead to early onset full-blown disease in humans. The validity of this hypothesis is also supported by the fact that drugs which either selectively dampen presynaptic release of neurotransmitters (e.g., levetiracetam) or block RyRs releasing Ca\(^{2+}\) from the intracellular stores (e.g., dantrolene), were recently shown to improve memory and cognition in mice and humans (reviewed in Palop and Mucke, 2016; Popugaeva et al., 2017; Lerdkrai et al., 2018).

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Chommanad Lerdkrai, Olga Garaschuk* Institute of Physiology, Department Neurophysiology, Eberhard Karls University of Tübingen, Tübingen, Germany (Lerdkrai C, Garaschuk O)
Department of Physiology, Faculty of Veterinary Medicine, Kasetsart University, Bangkok, Thailand (Lerdkrai C).

*Correspondence to: Olga Garaschuk, Ph.D., olga.garaschuk@uni-tuebingen.de.
orcid: 0000-0001-7400-5654 (Olga Garaschuk)
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References