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Review Article

Synaptic vesicle cycle and amyloid β: Biting the hand that feeds

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Abstract The synaptic vesicle cycle (SVC) holds center stage in the biology of presynaptic terminals. Through recurrent exocytosis and endocytosis, it facilitates a sequence of events enabling chemical neurotransmission between functionally related neurons. As a fundamental process that links the interior of nerve cells with their environment, the SVC is also critical for signaling and provides an entry route for a range of pathogens and toxins, enabling detrimental effects. In Alzheimer's disease, the SVC is both the prime site of amyloid β production and toxicity. In this study, we discuss the emerging evidence for physiological and pathological effects of Aβ on various stages of the SVC, from postfusion membrane recovery to trafficking, docking, and priming of vesicles for fusion and transmitter release. Understanding of the mechanisms of Aβ interaction with the SVC within the unifying calcium hypothesis of aging and Alzheimer's disease should further elucidate the fundamental biology of the presynaptic terminal and reveal novel therapeutic targets for Alzheimer's disease and other age-related dementias.
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1. Alzheimer's disease as a synaptic pathology

Alzheimer's disease (AD) is a chronic neurodegenerative brain disorder and the most common cause of dementia in the elderly. Progressive depositions of amyloid plaques and neurofibrillary tangles together with degeneration of neurons and synapses in selected brain areas are the most recognized histopathological features of the disease. From histochemical and functional studies, it emerges that the extent of synaptic loss in AD correlates closely with cognitive decline and memory deficit, with dysregulations of neuronal calcium and subtle impairments in synaptic function detectable from early preclinical stages, before the emergence of plaques and neurofibrillary tangles [4,5,60,133]. In the cerebral cortex, a 25%–35% decrease in synaptic connections has been reported within the first 2–3 years of clinical AD, while in the hippocampus these numbers exceed 50% [5,28]. Elucidating the mechanisms of synaptic impairments, thus, are of special interest for a better understanding of AD pathobiology and early therapeutic intervention, before slowing down the onset of irreparable damage with synaptic loss and cognitive decline [27,46].

According to the amyloid hypothesis of AD [45,47], synaptic impairments are triggered by a pathological increase in the amyloid β (Aβ) level in the brain, with soluble oligomers of Aβ42 known to be especially detrimental. Among the best-characterized negative effects of Aβ, the dysregulation of Ca^{2+} homeostasis and disruption of the fine balance between a wide range of kinases and phosphatases are of special relevance to the synaptic deficit and altered neuronal excitability [8,12,43]. Most reports of

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the synaptic effects of Aβ have been focusing on the postsynaptic side, with impairments of NMDA [126], metabotropic GluR5 [109], and M1 muscarinic cholinergic [37] receptors as well as deregulation of insulin and insulin growth factors [77], ephrin [24] and neurotrophin signaling [26,90]. The stimulation of Fyn kinase downstream of NMDAR and PrP activation appears to hold centre stage in the postsynaptic toxicity of Aβ, causing collapse of dendritic spines and synaptic degeneration [21,137]. Misplacement of microtubule-associated tau protein from axon to dendrites also contributes toward postsynaptic deficits with loss of dendritic spines, leading to degeneration of synaptic connections [50,149]. Reports also suggest a key role for GSK3β, CDK5, and other kinases in postsynaptic pathology of AD [25,86,114].

The presynaptic facets of AD, in the meantime, remain poorly elucidated, despite mounting evidence implying axon terminals as the prime site for Aβ production and the starting point of synaptic pathology [89,120]. Results of human and animal AD model studies demonstrate considerable changes in the expression and functions of presynaptic proteins, attributed in parts to direct effects of Aβ on the synaptic vesicle cycle (SVC) (Box 1). In this study, we present a detailed account of Aβ interference with different stages of SVC and transmitter release. Discussed herein, Aβ-related changes in presynaptic biology suggest a considerable overlap between the physiological and pathological effects of Aβ, unveiling numerous previously unrecognized challenges and therapeutic opportunities.

2. Modulation of presynaptic functions by Aβ

Discovery of the positive correlation between the cognitive decline and synaptic loss associated with AD [30,133] prompted penetrating research into the effects of Aβ on synaptic mechanisms [97,101]. Until recently, the general consensus was that at high dose, both, natural and synthetic Aβ oligomers suppress synaptic transmission and plasticity [39,71,121,122]. These effects mostly induced under experimental settings by application of exogenous Aβ have been ascribed in part to disruption of SVC and related changes in presynaptic release [57,59]. In extreme cases, over 50% reduction in the frequency of miniature excitatory postsynaptic currents has been observed in brain slices upon acute exposure to Aβ oligomers, implying a potent presynaptic site of action [121]. More recently, the focus has shifted on the effects of endogenous Aβ, with several reports demonstrating that both, the production and secretion of Aβ into the extracellular space is tightly controlled by neuronal activity (Box 1). Within the intact brain, strong association between Aβ secretion and synaptic functions has been observed during pathological events, such as epileptiform activity induced by electrical stimulation [23] and under certain type of physiological activity of brain circuits [53]. Such effects of Aβ were considered as part of a feedback loop that controls local and global neuronal excitability and circuit dynamics.

Detailed analysis of the dose dependence of Aβ effects revealed that at low amounts, Aβ can also act as a positive regulator of presynaptic activity, enhancing the neurotransmitter release probability and increasing the neuronal excitability [2]. The facilitator effects of low Aβ dose on excitatory transmission does not involve postsynaptic NMDAR and AMPAR currents, but has shown dependence on activation of α7–nicotinic acetylcholine receptor, in agreement with the presynaptic action site [81,103,104]. From these studies, it emerges that the directionality of Aβ effects in addition to the dose also depends on the site of action. While in the first instance, the presynaptic modulator effects of exogenous Aβ42 on transmitter release were thought to be mediated only via stimulation of presynaptic α7–nicotinic acetylcholine receptor and downstream changes in the presynaptic calcium [32,139], other mechanisms underlying the presynaptic effects have been subsequently also considered. In terms of the action mode, it is important to note that both local autocrine and long-range paracrine action of Aβ on synaptic transmission have been documented, with potent effects on the strength of synaptic transmission and on the density of synaptic connections described [52,135,139] (Fig. 1A and B).

Soluble Aβ is present in the healthy brain, with its physiological levels in rodents estimated to be within the picomolar range [104,117]. In healthy humans, the concentrations of Aβ40 and Aβ42 in the cerebrospinal fluid are ∼1.5 and ∼2.0 nM, respectively [38]. It is noteworthy that while the level of Aβ in the cerebrospinal fluid of preclinical AD exceeds that of physiological, with the emergence of amyloid plaques and a cognitive deficit of clinical AD, the concentration of Aβ in the CFS declines [14,38,140]. The impact of such slow changes in endogenous Aβ levels on synaptic transmission in the human brain remains to be shown. Evidence from amyloid precursor protein (APP)-KO [118], PS1-KO [116], or BACE1-KO mice [68] lacking endogenous Aβ shows that both synaptic transmission and plasticity are notably reduced. Likewise, pharmacological inhibition of BACE1 caused a reduction in dendritic spine formation and synaptic plasticity in the cerebral cortex and hippocampus [36]. These findings agree with the positive effects of thiorphan (inhibitor of Aβ degradation) on the frequency of miniature excitatory postsynaptic current in mouse brain slices [2] (Fig. 1C and D). While in all these reports, the presynaptic effects of Aβ are viewed as a result of activation of surface receptors, the direct influence of intracellular Aβ42 oligomers injected into axon terminals, causing a blockade of synaptic transmission, has also been also documented [79] (Fig. 1E and F). Unchanged presynaptic Ca^{2+} currents and reduction in the size of the docked synaptic vesicle pool imply direct negative effects of intracellular Aβ with the SVC. As discussed in the following sections, behind these effects underlie Aβ action upon all major steps of the SVC, from postfusion membrane recovery to synaptic

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