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Amyloid goes global

Ilya Bezprozvanny

Dept of Physiology, UT Southwestern Medical Center at Dallas, Dallas, Texas, USA

Abstract

The brains of Alzheimer's disease (AD) patients contain abundant amyloid plaques composed of A β peptides. It is generally assumed that amyloid plaques and soluble A β oligomers induce neuronal pathology in AD. The mechanism of amyloid-mediated pathological effects is not clearly understood. Recent *in vivo* calcium (Ca²⁺) imaging studies with AD mouse models provide novel insights into changes in brain function resulting from accumulation of amyloid plaques. The unexpected lesson from these studies is that amyloid plaques result in both localized and global changes in brain function. The amyloid-induced effects include "short-range" changes in neuronal Ca²⁺ levels, "medium-range" changes in neuronal activity and "long-range" changes in astrocytic Ca²⁺ signaling and induction of intracellular Ca²⁺ waves spreading via astrocytic network. These results have potential implications for understanding synaptic and neuronal network dysfunction in AD brains.

The dominant idea in the AD field is the "amyloid hypothesis" which states that increased production of amylogenic A β 42 peptide (or an increase in A β 42/40 ratio) is a major cause of neuronal and synaptic loss in AD [1]. The experimental support for the "amyloid hypothesis" comes from (i) accumulation of amyloid plaques in the brains of AD patients; (ii) the familial AD (FAD) cases resulting from missense mutations in A β -precursor APP protein; (iii) the FAD cases resulting from missense mutations in presenilins (PS), which form a catalytic subunit of APP-cleaving enzyme γ -secretase. It is postulated that formation of soluble A β oligomers and insoluble amyloid plaques drive the pathological processes in the AD brains. Based on these assumptions the "amyloid-targeting" therapies have been the main focus of the current AD drug development [2]. The key unanswered question about the "amyloid hypothesis" is how exactly amyloid impairs brain function? Several recent *in vivo* Ca²⁺ imaging studies performed in APP-PS1 mouse models provide first look at changes in brain function resulting from accumulation of amyloid plaques. The unexpected lesson from these studies is that amyloid plaques result in both localized and global changes in brain function.

Usually pathogenic actions of A β oligomers are assumed to be highly localized - at the level of individual synapses or spines. Local effects of A β oligomers on AMPA receptors internalization [3,4] and NMDAR trafficking and function [5–7] have been described. A β oligomers are also able to generate Ca²⁺-permeable pores in plasma membrane directly [8]. The ability of A β oligomers to form Ca²⁺ permeable channels in neuronal plasma membrane

is consistent with the recent *in vivo* Ca^{2+} imaging experiments performed with APP (APPsw) and APP-PS1 (APPsw, PS1- E9) transgenic mice [9]. These authors found that resting Ca^{2+} levels were significantly elevated in approximately 35% of neurites located in an immediate vicinity ($< 25 \mu\text{m}$) from the $\text{A}\beta$ plaques. The most likely explanation to these results is that high local concentration of $\text{A}\beta$ oligomers in the area surrounding amyloid plaques causes formation of Ca^{2+} -permeable ion channels in the neuronal plasma membrane. The neurites with elevated Ca^{2+} levels lacked spines and displayed abnormal morphology [9]. These studies provide strong support to “local” ($< 25 \mu\text{m}$) pathogenic effects of amyloid, which result in destabilization of intracellular neuronal Ca^{2+} signaling and impaired synaptic function (Fig 1).

Another *in vivo* Ca^{2+} imaging study with APP-PS1 (APPsw, PS1-G384A) transgenic mice reported disturbances in neuronal excitability in an area surrounding amyloid plaques [10]. It has been observed that in the area close to the plaques the fraction of “hyperactive” neurons was increased by 16-fold and the fraction of “silent” neurons was increased by 3-fold when compared to the wild type mice [10]. These “medium-range” effects of amyloid ($< 60 \mu\text{m}$) have been linked to impaired local synaptic inhibition, which resulted in hyperactivity of “disinhibited” neurons [10] (Fig 1). Similar hyperactivity has been previously described in electrophysiological studies of APP transgenic mice [11]. It has been speculated that the loss of inhibition is due to local anatomical remodeling of synaptic contacts in the vicinity of amyloid plaque, which in turn occurs as a response to amyloid-induced activation of microglia.

The latest *in vivo* Ca^{2+} imaging study [12] indicates that pathological effects of amyloid can spread even farther in the brain. These authors studied Ca^{2+} dynamics in astrocytes from APP-PS1 transgenic mice (APPsw, PS1- E9). They found that resting Ca^{2+} levels were globally elevated in the astrocytic network in the APP-PS1 mice. They also found significant (4-fold) increase in a fraction of spontaneously active astrocytes in the brains of APP-PS1 mice. The spontaneous Ca^{2+} signals in APP-PS1 astrocytes were also 50% higher in amplitude than the Ca^{2+} signals in wild type mice. The effects on resting Ca^{2+} levels and spontaneous activity of astrocytes were observed globally and did not depend on proximity to the plaques. The increase in astrocyte Ca^{2+} activity was not blocked by TTX and appear to result from direct interactions of $\text{A}\beta$ oligomers with the astrocyte network and not mediated by neuronal activity. In addition to these effects, the authors also observed increased correlation between astrocytic Ca^{2+} signals and frequent occurrence of intracellular Ca^{2+} waves (ICW) spreading via astrocytic network [12]. The correlation in astrocyte activity and propagation of ICW was observed at distances reaching as far as $200 \mu\text{m}$ from the plaques. Although some of the effects observed by the authors were reported to be global, the study was performed in 6–8 months old mice with dense plaques (mean astrocyte-to-plaque distance was $50 \mu\text{m}$ [12]). Thus, it is clear that presence of the plaques affects astrocytic Ca^{2+} signals at least as far as $200 \mu\text{m}$ (Fig 1). Additional imaging studies with “sparse” plaques brains (at earlier age of the mice) will be needed to determine upper limit for long-ranging effects of amyloid plaques on astrocytic Ca^{2+} signals. The mechanism involved in plaque effects on the astrocytic Ca^{2+} signals appear to involve “local” stimulation of initiator astrocytes (within $25 \mu\text{m}$ from the plaque) followed by long-range ICW propagation via astrocytic network [12].

The results of *in vivo* Ca²⁺ imaging studies in APP-PS1 mice [9,10,12] indicate that amyloid plaques have “short-range” (< 25 μm), “medium-range” (< 60 μm) and “long-range” (< 200 μm) effects on Ca²⁺ signaling and excitability (Fig 1). What is an importance of these findings for understanding AD pathogenesis? AD has been proposed to result from “synaptic failure” due to local attack by Aβ oligomers on synapses and dendritic spines [13]. On another hand, the manifestation of AD symptoms have been proposed to result from a neuronal network dysfunction [14,15]. It has been reasoned that the localized synaptic loss and activation of microglia and astrocytes may affect properties of the neuronal network as a whole [14,15]. The results from the *in vivo* Ca²⁺ imaging studies discussed here indicate that presence of amyloid plaques may affect properties of neuronal networks by acting both locally and at the distance. For example, long-range changes in astrocytic Ca²⁺ signals may affect glutamate clearance mechanisms, which in turn may affect neuronal network behavior. It will be very interesting to determine if inhibition of ICW in astrocytes of APP-PS1 mice can result in improvement in behavioral performance of these mice in memory tasks. If it is, it would suggest that block of astrocytic Ca²⁺ waves may have a therapeutic potential for treating AD or at least for alleviating some of the symptoms in human AD patients.

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Fig. 1. “Short-range” (< 25 μm), “medium-range” (< 60 μm) and “long-range” (< 200 μm) effects of an amyloid plaque are shown. The presence of an amyloid plaque in brains of APP-PS1 mice causes increase in neuronal resting Ca $^{2+}$ levels at the short range [9], increases local neuronal spontaneous activity in the medium range [10] and causes spread of intracellular Ca $^{2+}$ waves via astrocytic network in the long-range [12]. The resulting changes in neuronal and astrocytic properties are likely to lead to dysfunction of neuronal network in the proximity of the amyloid plaques in AD brains.