Review Article

Trans-Synaptic Spread of Amyloid-β in Alzheimer's Disease: Paths to β-Amyloidosis

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Neuronal activity has a strong causal role in the production and release of the neurotoxic β-amyloid peptide (Aβ). Because of this close link, gradual accumulation of Aβ into amyloid plaques has been reported in brain areas with intense neuronal activity, including cortical regions that display elevated activation at resting state. However, the link between Aβ and activity is not always linear and recent studies report exceptions to the view of "more activity, more plaques." Here, we review the literature about the activity-dependent production of Aβ in both human cases and AD models and focus on the evidences that brain regions with elevated convergence of synaptic connections (herein referred to as brain nodes) are particularly vulnerable to Aβ accumulation. Next, we will examine data supporting the hypothesis that, since Aβ is released from synaptic terminals, β-amyloidosis can spread in AD brain by advancing through synaptically connected regions, which makes brain nodes vulnerable to Aβ accumulation. Finally, we consider possible mechanisms that account for β-amyloidosis progression through synaptically linked regions.

1. Introduction

Gradual accumulation of β-amyloid peptide (Aβ), the proteolitic product of amyloid precursor protein (APP), is the principal cause of synaptic dysfunction and cognitive loss in Alzheimer disease [1]. The events leading to amyloidogenic APP processing have been a subject of intense research, with implications for understanding regional vulnerability of specific brain regions to progressive Aβ accumulation (see glossary in Table 1 for a definition of the different aggregation states).

APP is a type-I transmembrane protein highly expressed in neurons, where it regulates synaptic function and neurite outgrowth [2–4]. Two alternative enzymatic pathways process APP: in the nonamyloidogenic pathway, APP is subjected to consecutive cleavage steps through α- and γ-secretases that cut APP within the Aβ fragment. In the amyloidogenic APP processing, β-secretases cut the Aβ fragment at its beginning

and the consecutive γ-secretase cleavage releases Aβ peptides (see [5] for an exhaustive review of APP processing).

Neuronal activity directly regulates APP processing. Upon neuronal activation, APP is trafficked into endocytic compartments, where it is processed [6, 7]. In neurons that overexpress APP, activity favours β-secretase-mediated APP processing [8] and lowers the endocytosis of the α-secretase enzyme ADAM10 [9]. In line with this, in AD brains, amyloid aggregates in regions with intense neuronal activity, like the ones with baseline high levels of activity, making those regions particularly prone to AD degeneration.

However, several studies have reported some exceptions to the activity Aβ relation. On one side, baseline active regions become hypoactive once Aβ has accumulated and start to damage neurons, and stratifications between pre- and postamyloid stages must be taken into account when considering the impact of activity on AD progression [10].

Aβ type/aggregation state	Detection method	References
Aβ oligomers	ELISA	[8, 13–17, 48, 52] [12, 19, 32]* [18, 38, 40, 41, 47]*# [37]#
	Western blot	[16, 17, 48] [44]* [46]*# [47]#
Aβ protofibril	Immunoistochemistry	[19]*
Aβ plaques	Immunoistochemistry	[12, 19, 44, 45]* [16, 17, 33, 48] [16, 37, 38, 40–42, 46, 47]*#
Amyloid deposition in human brain	Pittsburgh compound B (PIB) PET	[11, 25, 29]* [19–22, 31]

Amyloid-β (Aβ) refers to peptides derived from cleavage of the amyloid precursor protein (APP) by β- and γ-secretase. *Soluble Aβ oligomers* indicate Aβ species formed by the aggregation of more than one Aβ peptide (monomers). Oligomers are commonly detectable in sample solutions following centrifugation. *Aβ protofibrils* are aggregates of Aβ oligomers, with lengths of over 40 nm. *Aβ fibrils* are Aβ aggregates composed predominantly of β-sheet structure and resistant to degradation. These aggregates are often found in proximity of amyloid plaques. *Amyloid plaques* consist in deposits of insoluble Aβ; ∗ indicates studies that report progressive of Aβ accumulation; # indicates studies that demonstrate Aβ spread between distinct brain regions.

For instance, longitudinal studies indicate that Aβ accumulation can start 10–15 years before the occurrence of cognitive symptoms and that regions which are more active and accumulate more Aβ are the ones that later degenerate and then become hypoactive in concomitance with cognitive loss [10, 11]. On the other side, not all regions that display high baseline activity are subject to Aβ accumulation, suggesting that neuronal activity is not the only player in regional vulnerability.

In the present review, we propose a critical analysis of possible mechanisms involved in regional accumulation of Aβ and try to extend the understanding of the complex relationship between neuronal activity and AD progression.

First, we report studies that found Aβ accumulation in specific brain areas and we focus on the evidence that regions with elevated neuronal activity due to the convergence of several synaptic pathways (brain nodes) are more vulnerable to Aβ accumulation. Next, we will examine data in support to the idea that, since Aβ spreads through synaptically connected regions, the elevated concentration of synapses makes brain nodes vulnerable to Aβ accumulation. Lastly, we consider some possible mechanism to explain propagation and gradual accumulation of Aβ, which received little attention so far.

2. Nonlinear Link between Neuronal Activity and Aβ Accumulation

One hypothesis that has emerged over the past decade suggests that intense neuronal activity makes brain regions more vulnerable to Aβ accumulation. This hypothesis originates from evidences reporting that regions with elevated basal activity are more prone to accumulate Aβ aggregates [12] and is supported by studies demonstrating a causal role of neuronal activity in Aβ generation and secretion [8, 13]. In this context, two pivotal studies have reported that the amount of small monomeric Aβ species rises in the interstitial brain fluid (ISF) while awake or in conditions of active neurological status but decreases during sleep [14, 15], thereby providing strong physiological proof to the idea that neuronal activity can dynamically regulate extracellular Aβ in vivo.

2.1. Experimental Modulation of Neuronal Activity. The idea of inactivity-vulnerability link received further support with studies that have modulated neuronal activity in specific brain regions of living AD mice.

A few studies investigated the effects of whisker manipulation on Aβ levels in the barrel cortex, a neuronal circuit that receives physiological inputs from the vibrissae of mice [12, 16, 17]. In AD Tg2576 mice, 30 minutes of mechanical vibrissae stimulation, which associates with rises of neuronal activity in the barrel cortex, was sufficient to increase the amount of ISF Aβ in this region [12]. On the contrary, acute vibrissae trimming that inhibited neuronal activity of the barrel cortex reduced extracellular Aβ (and thereby amyloid plaques) in the same cortical region [12, 16], an effect that was likely due to a significant rise of intracellular Aβ [16, 17].

More recently, one study on A7 AD mice [18] used optogenetics to stimulate the presynaptic fibers of the perforant pathway (PP) that links the entorhinal cortex (EC) and the hippocampal dentate gyrus (DG), a region particularly prone to Aβ accumulation. ISF Aβ levels were increased more than 20% in the hippocampus after short pulses of PP light stimulation. Furthermore, postmortem immunohistochemistry revealed that repeated optogenetic stimulations over a 5-month period significantly increased the Aβ burden in the hippocampal DG.

On the same experimental train of thought, another study [19] used a chemogenetic approach [20] to modulate neuronal activity in the posterior parietal association and posterior somatosensory cortex of aged 5xFAD and PS/APP

mice. In this study, chronic chemogenetic activation led to a significant increase in thioflavin-positive plaques and chronic chemogenetic inhibition reduced plaques and the surrounding oligomeric $A\beta$ species in activated and silenced regions, respectively.

2.2. Default Mode Network and Brain Hubs. In humans, one important branch of studies on the impact of neuronal activity on $A\beta$ levels has focused on the default mode network (DMN), a set of interconnected brain regions that are most active at resting state. Buckner and collaborators used functional magnetic resonance imaging (fMRI) to identify patterns of network activity and positron emission tomography (PET) with PIB compound to visualize amyloid deposits in elderly patients. Their studies reported spatial overlap between the topography of amyloid deposition and the regions of DMN (including posterior cingulate and parietal cortex, medial temporal lobe, and medial frontal subsystem) [21, 22]. Using aerobic glycolysis, a parameter that is based on the excess of glucose utilization as a measure of basal metabolic activity, other researchers [23, 24] found a strong correlation between baseline metabolic activity in DMN regions and $A\beta$ deposition. Also, Sperling et al. [11, 25] found that in at-risk subjects that are still clinically intact, aberrant DMN activity is predictive of amyloid deposition, thereby providing support to the corollary idea that hyperactivity is a "prime" event in $A\beta$ accumulation. We will come back to hyperactivity later in this paper.

However, hypoactivity has been also reported in some of DMN regions in healthy subjects carriers for APOEε, an important risk factor for the development of late-onset AD [26] (see also [27]). APOE is a lipoprotein involved in cholesterol removal, but in the brain, it is involved in development and plasticity mechanisms. Of note, APOE interacts with $A\beta$ and accelerates the processing of amyloid deposition [28]. As mentioned above, hypoactivation can be found in DMN regions upon amyloid deposition, and it is possible that hypoactivation reported in APOEε carriers depends on advanced amyloid deposition.

Together, the above studies highlight strong correlations between neuronal activity of DMN and $A\beta$ deposition, but the relationship between the two is not always linear. One longitudinal study [29] that combined fluoreodeoxiglucose (FDG) for metabolic measure and Pittsburgh compound B to detect $A\beta$ deposits found that regions of high metabolic consumption in young adults overlap with regions of fibrils later in life, but this linear relation was not detectable in some of the brain regions that were included in the study. For instance, increased amyloid burden in the anterior cingulate cortex, medial frontal cortex, and lateral temporal cortex was not associated with a high metabolic rate during the lifespan. Conversely, visual cortex was spared by $A\beta$ accumulation despite its high metabolic activity.

One important clue to understanding this apparent paradox comes from studies on brain hubs, represented by nodes with an elevated number of connections, largely overlapping with heteromodal association cortices included in the DMN. Buckner and coworkers [30] run a complex computational analysis with the goal to extend their previous DMN studies

to research on hubs [21, 22]. The authors found that cortical regions with elevated interconnectivity (including posterior cingulate, lateral temporal, lateral parietal, and medial/lateral prefrontal cortices) display elevated $A\beta$ deposition. Interestingly, the study also showed that primary sensory areas have relatively little connectivity, which could explain the reason for low $A\beta$ depositions in the visual cortex despite intense activity in this region [29].

Hence, strong network connectivity rather than elevated baseline activation can be at the origin of vulnerability to $A\beta$ accumulation in active brain regions. In a study that directly explored this possibility through stepwise connectivity method in PIB-PET images, Sepulcre et al. [31] found connectivity links between regions that display elevated amyloid-β accumulation. In particular, strong links were evident between the hippocampal region and orbitofrontal, lateral temporal, and posterior cingulate cortex.

Bero et al. replicated these results in an AD mouse model [32]. By mapping functional connectivity through optic intrinsic signal (fcOIS) in the brain of young APP/PS1 transgenic mice, the authors found that some regions display elevated interconnectivity, and the magnitude of this interconnectivity is predictive of plaque deposition at successive age points [32].

3. β-Amyloidosis Spreads through Synaptically Connected Regions

Since synapses are the principal sites of $A\beta$ release [8, 13], one possible explanation of why $A\beta$ accumulates in brain nodes is that $A\beta$ peptides released from synaptic terminals gradually accumulate in the extracellular space of downstream regions.

This prediction has been confirmed at the synaptic circuits between EC and the DG. Sheng et al. [33] found that APP processed in the EC neurons is the major $A\beta$ source on the hippocampus. In this study, APP Swedish/preselinin1 mice subjected to unilateral ablation of EC had 45% reduction in thioflavin-positive $A\beta$ deposits in hippocampal DG of the lesioned hemisphere with respect to the control (nonlesioned) one. Since APP is axonally transported from EC neurons to nerve terminals in the DG through PP projections [34–36], Sisodia and collaborators [37] asked if blocking this access pathway can prevent $A\beta$ deposits in the DG. Using transgenic mice that overexpress FAD-linked mutant APP and PS1, the authors demonstrated that transection of PP is sufficient to decrease amyloid burden 2-3-fold in the hippocampus (and up to 5.5–10-fold in the DG) with respect to nonlesioned controls.

A more direct evidence of spreading from EC to DG came from Mucke's group [38]. These authors crossed Tet-APP mice with NOP-tTA mice, in order to generate chimeric EC-APP mice with expression of APP with humanized $A\beta$ domain restricted to the II and III layers of the EC. $A\beta$ deposits, which were initially present only in the EC of these mice, became progressively evident in the DG, thereby leading the authors to argue that $A\beta$ spread from the EC to the hippocampus. Even though the following paper discussed the validity of the APP-EC mouse model [39], Harris' study [38] was confirmed by other researches, which also expanded

their results to different brain regions. Among these, a set of experimental framework generated a transgenic mouse model of AD expressing single Arctic APP mutation selectively in the subiculum (TgAPParc) [40, 41]. In these mice, Aβ deposition was found to start from the subiculum and then spread in a time-dependent manner to synaptically connected brain regions (including the thalamus retrosplenial cortex, mammillary bodies, fimbria, fornix, motor cortex, and sensory cortex), and this spreading pattern was abolished by ablation of the subiculum [42].

Collectively, the above data indicate that Aβ is preferentially released at brain nodes and those connections between nodes represent preferential routes for the spreading of β-amyloidosis.

4. Possible Mechanisms of Spread

The passage of disease-associated misfolded proteins from neuron to neuron is a key mechanism of progress in neurodegenerative diseases. Although the mechanisms of spreading have been clarified for some neurodegenerative diseases (including α-synuclein in Parkinson and Tau in AD, see [43] for an exhaustive review of spread hypothesis), not much is known about the spread of the β-amyloid protein. In this last section, we provide a short review of possible mechanisms involved in Aβ spread, which have been investigated over the last few years.

4.1. Prion-Like Propagation. Administration of Aβ-containing extracts can accelerate Aβ aggregation in the brain of living animals [44–46]. This piece of evidence led researchers to question if small peptidic Aβ "seeds" which are released from synaptic terminals in one brain region can trigger Aβ accumulation in other regions.

One set of studies directly investigated this possibility [47–49] by performing biominulescence imaging on APP23 gfap-luc mice unilaterally inoculated with purified Aβ aggregates. In these mice, widespread bilateral Aβ signal was found through the whole brain, supporting the possibility that Aβ seeds contribute to the spreading of amyloidosis [47].

In another study, Aβ-containing brain extracts from aged APP23 mice were injected into distinct brain regions (including olfactory bulb, parietal cortex, striatum, and hippocampus) of young and still plaque-free mice of the same transgenic strain [46]. Three months later, Aβ deposition was found in proximity of some of the injected brain regions (including the entorhinal cortex and hippocampus) and six months later Aβ deposits resembling amyloid plaques were also found in adjacent (and otherwise plaque-free) brain regions, indicating that Ab spreads from the injection site and gradually accumulates in other sites.

This evidence raises the question of whether seeds trigger an infectious process that propagates within interconnected regions or rather if the seeds accelerate a process that would spontaneously occur in brain tissues that are prone to β-amyloidosis. A set of experimental evidences excludes the possibility of an infectious process: (i) when other routes of Aβ extract administration are used (including intranasal, intraocular, or oral) Aβ deposits are not evident

in downstream regions [46] as would be expected in case of an infectious transmission; (ii) Aβ depositions have not been found in mice expressing human APP wild-type, which is not prone to β-amyloidosis [44] (see also [49]). Similarly, (iii) Aβ does not accumulate in brain regions that typically do not form plaques, for instance, cortical regions that receive projections from the striatum [46].

Collectively, the above evidence indicates that although Aβ seeds can spread from one brain region to one other, likely passing through synaptic connections, this step is not sufficient to form deposits. Rather, Aβ only accumulates when seeds reach "receiving" regions that are prone to amyloidosis.

4.2. Aβ Generation from Postsynaptic Neurons. The above studies suggest that, even if the convergence of several synaptic inputs makes brain regions particularly vulnerable, factors associated with intrinsic properties of receiving regions are likely participating in the spreading of amyloidosis. No studies so far directly investigated this possibility, which is rather supported by indirect evidences showing that Aβ released into the extracellular space alters the physiological activity of downstream neurons. For instance, Aβ causes reduction of synaptic glutamate reuptake [50] and/or enhanced glutamate release at presynaptic terminals [51] that act together to increase extracellular glutamate level and promote hyperactivity. Aberrant neuronal activity has been viewed as a beneficial compensatory effect aimed at recruiting neuronal resources, but because of its strong positive correlation with APP processing, it could rather participate to a positive feedback loop that triggers further APP cleavage from hyperactive neurons and cause Aβ release from their dendrites [52, 53].

Hence, one possible scenario, which is worthy of future investigation, is that hyperactivity spreads from one brain region to synaptically connected one(s), thereby favouring activity-dependent Aβ release from downstream neurons.

5. Conclusions and Future Prospectives

We here provide one hypothetic model to explain the vulnerability of selected brain regions to Aβ accumulation. We suggest that most of the vulnerable regions in AD brain are nodes that receive high convergence of synaptic connections. One simple explanation for this vulnerability is that synaptic circuits are preferential routes for the release of Aβ, which then progressively accumulates at postsynaptic sites. But other factors intrinsic to neurons within the brain nodes can also contribute to β-amyloidogenesis through the spread of hyperactivity.

This model raises questions which should be addressed in future studies. For instance, if the convergence of synaptic inputs makes brain nodes vulnerable, can we reduce the amount of synaptic inputs without interfering with general cognition? As a first step, this question could be addressed in AD mouse models using the abovementioned optogenetic strategies that allow to silence specific synaptic inputs in selected brain regions of behaving mice.

Systemic administration of antiepileptic drugs can improve memory performance in patients at early AD stages

[54], but with relevant side effects. Hence, it could be therapeutically relevant to investigate if the delivery of these drugs can be restricted to brain nodes in order to potentiate their silencing power and to limit undesired effects.

Conflicts of Interest

The authors declare that there are no conflicts of interests regarding the publication of this paper.

Acknowledgments

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