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Review - Part of the Special Issue: Alzheimer's Disease - Amyloid, Tau and Beyond

Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease

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ABSTRACT

Considerable progress has been made in the past few years in the fight against Alzheimer's disease (AD) and Parkinson's disease (PD). Neuropathological studies in human brains and experimental *in vivo* and *in vitro* models support the notion that synapses are affected even at the earliest stages of the neurodegenerative process. The objective of this manuscript is to review some of the mechanisms of synaptic damage in AD and PD. Some lines of evidence support the notion that oligomeric neurotoxic species of amyloid β, α-synuclein, and Tau might contribute to the pathogenesis of synaptic failure at early stages of the diseases. The mechanisms leading to synaptic damage by oligomers might involve dysregulation of glutamate receptors and scaffold molecules that results in alterations in the axonal transport of synaptic vesicles and mitochondria that later on lead to dendritic and spine alterations, axonal dystrophy, and eventually neuronal loss. However, while some studies support a role of oligomers, there is an ongoing debate as to the exact nature of the toxic species. Given the efforts toward earlier clinical and preclinical diagnosis of these disorders, understanding the molecular and cellular mechanisms of synaptic degeneration is crucial toward developing specific biomarkers and new therapies targeting the synaptic apparatus of vulnerable neurons.

Contents

1. Introduction

The past few years have witnessed considerable progress in the fight against Alzheimer's disease (AD), with the introduction of the revised clinical [1] and neuropathological [2] criteria for the diagnosis of AD, identification of new biomarkers [3–5], better characterization of the poly-genetic aspects of AD [6,7], and a more clear understanding of the contribution of neurotoxic aggregates of amyloid β (Aβ) [8–10] and microtubule associated protein τ (Tau) [11,12], to the pathogenesis of neurodegeneration in AD. Likewise, in disorders with parkinsonism and dementia such as Parkinson's disease (PD), PD with dementia (PDD) and dementia with Lewy bodies (DLB) (jointly denominated Lewy body disease [LBD]) [13] dramatic progress has been made in identifying new genes involved in familial [14] and sporadic [15] forms, several of them possibly converging on the α-synuclein (α-syn) pathway [16,17].

In 2013 an estimated 5.2 million Americans of all ages have AD and 1 million have PD [18]. This year an estimated 450,000 people in the US will die with AD, making AD the sixth-leading cause of death in the US [18]. Without a cure, the number of cases of AD, as defined by the 1984 and DSM-IV criteria, will double by the year 2050, with western states experiencing the highest rates [18]. The new criteria published in 2011 proposed three stages of the disease, namely preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD [1]. The 2011 criteria proposes that AD begins before the development of symptoms and that new

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positron emission tomography (PET) and cerebral spinal cord fluid (CSF) biomarkers are able to identify brain alterations before the onset neurological alterations [1]. However, the predictive value of such biomarkers is not yet proven in sporadic preclinical cases [19]. If AD can be detected earlier, as defined by the 2011 criteria, the number of people reported to have AD will be much larger than 5 million.

In 2011, a workgroup of experts was organized to revise the 1997 neuropathological criteria for the diagnosis of AD and related disorders [2]. The 1997 criteria required a history of dementia [20], while the new criteria disentangle the clinico-pathologic term "Alzheimer's disease" from *AD neuropathologic change* [2]. Using the new criteria, AD neuropathologic change would be ranked along three parameters (Amyloid, Braak, CERAD) to obtain an "ABC score". For this purpose a modified version of Thal phases of Aβ plaque accumulation was proposed [21], adapted to a four-point scale, continued use of the staging scheme for neurofibrillary tangles as described by Braak [22], reduced to four stages that improves inter-rater reliability, and continued use of CERAD protocol for neuritic plaque scoring [23]. The new criteria provided guidance on clinico-pathologic correlations for pathologists reporting autopsy findings based on the literature and analysis of the National Alzheimer's Coordinating Center (NACC) database. The new criteria also emphasized the importance of assessing non-AD brain lesions in recognition of commonly co-morbid conditions in cognitively impaired elderly. Among the co-morbid conditions, synucleinopathies such as PD, PDD and DLB, are important given that over 75% of patients with AD display LB's in the amygdala [24,25] and about 25% of patients with AD develop parkinsonism [26].

The main purpose of this manuscript is to review evidence supporting the synapse failure hypothesis of AD and LDB and the role of Aβ, α-syn, and Tau accumulation in the pathogenesis of this process. We conclude that synaptic dysfunction occurs early, followed by pre-synaptic and spine loss, axonal dystrophy and eventually neuronal loss. We focus on synapses because Aβ is released at the synaptic terminal [27] and α-syn localizes to the synaptic vesicles [28] where they can effect synaptic transmission. However, a number of other cellular substrates play an equal important role (e.g., neuro-inflammation, vascular, glial) and deserve close consideration. For example, a recent GWAS study highlighted the association of AD with innate immune response [29–33].

2. Synaptic damage and Aβ in early Alzheimer's disease

For several years the classical definition of neurodegeneration in disorders such as AD and PD was limited to the finding of selective neuronal loss and astrogliosis. This concept has now been expanded to include synaptic loss and neuro-inflammation. Synaptic damage can be detected at the earliest stages of AD. Patients with MCI demonstrate loss of pre-synaptic proteins such as synaptophysin, VAMP2, and SNAP25 and post-synaptic markers such as PSD95 and Shank1 [34]. Likewise ultrastructural [35] and confocal microscopy studies [36] have shown progressive alterations of synapses in early stages of AD and in APP tg models [37]. This has been confirmed in experimental APP transgenic models [38], as well as after acute injection of Aβ oligomers [39]. These studies have shown more severe loss of glutaminergic terminals but not GABAergic terminals in the hippocampus [40,41]. Consistent with the neuropathological and structural studies, recent gene array investigations have shown that in early AD there is altered expression of genes involved in synaptic vesicle trafficking and release, neurotransmitter receptors and receptor trafficking, postsynaptic density scaffolding, cell adhesion regulating synaptic stability, and neuromodulatory systems [42–45]. The memory impairment in patients with AD is related to synaptic loss in the neocortex and limbic system [46–48]. In contrast, cognitive impairment does not correlated with Aβ plaques in the brain. The loss of synapses in AD is greater than the extent of the neuronal loss in the cortex. This suggests that synaptic damage precedes the loss of neuronal cell bodies. This is why synapses are a good correlate to cognitive deficits [43,46,47,49–52]. The remaining synapses appear to be enlarged representing a possible compensatory mechanism [47,53,54].

The mechanisms of synaptic loss in AD might involve axonal transport defects, oxidative stress, mitochondrial damage, and neuroinflammation among others [55]. Increasing levels of $A\beta_{1-42}$, the proteolytic product of APP metabolism are also suspected to be centrally involved in the pathogenesis of synaptic damage in AD [56–60] (Fig. 1A). Accumulation of Aβ in AD is the result of an imbalance in the mechanisms of synthesis, aggregation, and clearance (Fig. 1B). Increased synthesis and aggregation has a prominent role in familial AD, and altered clearance including degradation and autophagy has a role in sporadic AD [61,62]. The mechanisms through which accumulation of Aβ and other APP metabolites might lead to synaptic damage and neurodegeneration are under investigation. More specifically, the potential role of neurotoxic Aβ oligomers has emerged as a topic of considerable interest in recent years [63–66] (Fig. 1).

Monomeric Aβ can aggregate to form amyloid fibrils, protofibrils, annular structures [67], Aβ-derived diffusible ligands (ADDLs) [68] and smaller order oligomeric species (for reviews, see [69–74]). Oligomers of Aβ can organize into dimers, trimers, tetramers, and higher order arrays that can form annular structures [75]. Smaller oligomers are divided into those generated from synthetic peptides and those purified from cells, transgenic (tg) mice, or AD human brains [8,69,76]. However, it is worth noting that there is great heterogeneity in the Aβ arrays accumulating in the brain of AD patients, and more recent studies have highlighted that there is uncertainty around the pathological significance of some of these oligomeric species [76].

An example of a naturally occurring oligomer species is Aβ*56, which was derived from the brains of APP tg mice and has been shown to promote age-dependent memory deficits [77]. Aβ*56 and Aβ trimers secreted by cultured cells could turn out to share common synaptotoxic properties [69]. The Aβ dimers, trimers, and higher order oligomers secreted by cultured neurons inhibit LTP, damage spines, and interfere with activity-regulated cytoskeleton associated protein (Arc) location [64,65,69,78,79]. Additional studies have shown that Aβ dimers extracted from human CSF disrupt synaptic plasticity and inhibit hippocampal LTP *in vivo* [80] (Fig. 1). Together, these studies indicate that Aβ oligomers, ranging in size from 2 to 12 subunits, might be responsible for the synaptic damage and memory deficits [81]. A number of recent studies have begun to investigate the possibility that Aβ oligomers might interfere with synaptic function by altering synaptic proteins such as post-synaptic density-95 (PSD95) [82–85], Shank1 [34], and glutamate receptors [86].

Although the neurotoxic effects of the Aβ have been widely studied in experimental models, less is known about the characteristics of the oligomers across the spectrum of AD and how this correlates with cognition and synaptic proteins. We have previously utilized immunoblot analysis to investigate the relationship between levels of Aβ oligomers and synaptic proteins in fractions from the brains of AD patients and APP tg mice. Our studies show that Aβ oligomers, in particular dimers and pentamers, progressively accumulate in the brains of AD patients, as well as in APP tg mice. This was accompanied by reductions in the levels of synaptic scaffold proteins such as PSD95, Shank1 and Shank3 [34].

While accumulation of Aβ oligomers at the synaptic site has been proposed to be an important trigger in the pathogenesis of