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Review

Alzheimer disease therapeutics: Focus on the disease and not just plaques and tangles

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ABSTRACT

The bulk of AD research during the last 25 years has been Aβ-centric based on a strong faith in the Amyloid Cascade Hypothesis which is not supported by the data on humans. To date, Aβ-based therapeutic clinical trials on sporadic cases of AD have been negative. Although most likely the major reason for the failure is that Aβ is not an effective therapeutic target for sporadic AD, initiation of the treatment at mild to moderate stages of the disease is blamed as too late to be effective. Clinical trials on presymptomatic familial AD cases have been initiated with the logic that Aβ is a trigger of the disease and hence initiation of the Aβ immunotherapies several years before any clinical symptoms would be effective. There is an urgent need to explore targets other than Aβ. There is now increasing interest in inhibiting tau pathology, which does have a far more compelling rationale than Aβ. AD is multifactorial and over 99% of the cases are the sporadic form of the disease. Understanding of the various etiopathogenic mechanisms of sporadic AD and generation of the disease-relevant animal models are required to develop rational therapeutic targets and therapies. Treatment of AD will require both inhibition of neurodegeneration and regeneration of the brain.

Contents

1. Introduction

Alzheimer disease (AD), which is defined by dementia associated with numerous Aβ plaques and phosphotau neurofibrillary tangles in the brain, especially the hippocampus, is a heterogeneous and a multifactorial disorder [1]. Neither Aβ plaques nor phosphotau neurofibrillary tangles are unique to AD. As many as ~30% of normal aged people have as many Aβ plaques in their brains as in typical cases of AD [2,3]. Furthermore, in cases of hereditary cerebral hemorrhage with amyloidosis of Dutch origin (HCHWA-D) and sporadic cerebral amyloid angiopathy (SCAA) there is extensive β-amyloidosis in the absence of neurofibrillary tangles [4,5]. Neurofibrillary tangles of hyperphosphorylated tau is a hallmark of several neurodegenerative

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diseases called tauopathies which include frontotemporal dementia with Parkinsonism linked to chromosome-17 tau (FTDP-17), Pick disease, cortico-basal degeneration, progressive-supranuclear palsy, dementia pugilistica/traumatic brain injury/chronic traumatic encephalopathy and Guam Parkinsonism dementia complex. Thus, several different mechanisms are involved in the etiopathogenesis of both plaques and tangles.

In less than 1% of the cases, AD is caused by specific point mutations in amyloid-β precursor protein, presenilin-1, or presenilin-2 [6]. All of these three are transmembrane proteins. Mutations in these proteins probably lead to Aβ and tau pathologies by altering the signal transduction, especially involving protein phosphatase-2A (PP2A) and glycogen synthase kinase-3β (GSK-3β) [7]. The remaining over 99% of the AD cases represent the sporadic form of the disease. The exact causes of sporadic AD are not yet established. The presence of one or two APOε_4 alleles increases by ~3.5- and ~10-fold the risk for the disease, respectively, and is generally seen in late onset AD cases [see 8]. Despite the evidence for the multifactorial nature of AD and the involvement of several different mechanisms, because of the immense popularity of the Amyloid Cascade Hypothesis according to which Aβ causes AD, to date most of the therapeutic efforts have been focused on inhibition and removal of Aβ plaques. However, none of these treatments have so far shown any improvement or even reduction in the rate of cognitive impairment. In this article we discuss the likely reasons for the failure of the Aβ-based therapies, and why the focus of the future therapeutic attempts has to be the disease and not just the plaques and tangles. The weaknesses of Aβ as a therapeutic target was also discussed previously [e.g., 9–11].

2. Plaques and tangles: loss of functions or gain of toxic functions or both

Plaques are extracellular deposits mainly composed of $A\beta_{1-40}$ and $A\beta_{1-42}$ which are the metabolites of amyloid precursor protein (APP) generated by its β- and γ-secretase cleavage [12–14]. The number of neurofibrillary tangles but not Aβ plaques has been found to correlate with dementia [2,15,16]. APP is a transmembrane protein. Its main function is probably synaptic formation and repair [17]. Consistent with its critical role in the maintenance of membrane, APP level is upregulated during neuronal differentiation [18].

APP expression is rapidly upregulated during neural injury, probably to repair the damaged tissue [19]. The APP expression is probably also increased in response to certain genetic, biological, chemical and other environmental insults, all resulting in increased metabolism and production of Aβ. Aβ, though amyloidogenic, is a normal metabolite of APP. Aβ is catabolized by neprilysin and insulin degrading enzyme [20]. An imbalance between the rate of production and clearance of Aβ leads to its deposition as amyloid plaques. APOE and certain other interacting molecules such as heparin sulfates may promote Aβ polymerization in the form of plaques. According to the Amyloid Cascade Hypothesis amyloid-β causes neurofibrillary pathology and the disease [21]. The bulk of the studies, however, suggest soluble, especially the oligomeric, Aβ as the main neurotoxic state of the peptide [22]. Thus, it appears that aggregation of Aβ into fibrils could be a neuroprotective response by which the soluble/oligomeric Aβ is packaged by the affected brain into a relatively inert mass. Furthermore, the neurotoxic concentrations of soluble and oligomeric $A\beta_{1-42}$ in cultured cells are in micromolar whereas its in vivo concentrations seen in the AD brain are in picomolar range.

Despite the evidence for neurotoxicity of Aβ peptide in cultured cells and in vivo in mice and rats reported by several studies [see 23], as many as ~30% of the normal aged humans have as much Aβ plaque load but without corresponding tau pathology in their brains as in typical cases of AD. The brains of cases with hereditary cerebral hemorrhage of the Dutch type show severe Aβ plaque load as congophilic angiopathy but without any tau pathology and dementia [4]. Furthermore, several familial AD presenilin 1 mutations do not result in any increase in Aβ [24]. Thus, the AD-causing APP mutations most likely involve primarily loss of APP function in AD. The mutated APP is unable to maintain synaptogenesis and repair the degenerating synapses; loss of synaptic plasticity precedes any overt Aβ pathology in AD and in transgenic mouse models of AD [25–27].

Tau is the major neuronal microtubule associated protein (MAP). In normal brain tau contains 2–3 moles phosphate per mole of the protein whereas in AD brain it is 3- to 4-fold hyperphosphorylated [28]. Tau is the major protein subunit of paired helical filaments which make the neurofibrillary tangles [29,30]. Tau in neurofibrillary tangles is abnormally hyperphosphorylated [31]. As much as ~40% of the abnormally hyperphosphorylated tau in AD brain is cytosolic [28,32].

Normal tau interacts with tubulin and promotes its assembly into microtubules and stabilizes their structure. This biological activity of tau is regulated by its degree of phosphorylation; hyperphosphorylation suppresses its microtubule assembly promoting activity [33]. In AD brain the cytosolic abnormally hyperphosphorylated tau (AD P-tau) instead of interacting with tubulin, binds to normal tau and thereby inhibits the microtubule assembly [28,34]. Abnormally hyperphosphorylated tau isolated from AD brains sequesters not only normal tau but also the other two neuronal MAPs, MAP1 and MAP2, and disrupts microtubules in vitro [35–37]. While normal tau labels the microtubule network, the AD abnormally hyperphosphorylated tau disrupts it in permeabilized cells in vitro [38]. In vitro dephosphorylation of AD P-tau with protein phosphatase rescues its ability to inhibit microtubule assembly and disrupt the microtubule network [37,39,40].

The AD P-tau readily self-assembles into paired helical filaments and its dephosphorylation with protein phosphatase inhibits this aggregation in vitro [40,41]. While normal tau promotes GTP binding to tubulin and AD P-tau inhibits it, the paired helical filaments have no activity [42]. Unlike AD P-tau, paired helical filaments/neurofibrillary tangles have no effect on microtubule assembly but dephosphorylation of neurofibrillary tangles with protein phosphatases, especially protein phosphatase-2A (PP2A) dissociate the fibrils and the released dephosphorylated protein behaves like normal tau in promoting microtubule assembly [43]. Similarly the in vitro dephosphorylated AD P-tau neither self-assembles nor inhibits but now, instead promotes microtubule assembly [39,40]. Thus, collectively these findings suggest that in AD the abnormal hyperphosphorylation of tau results in both the loss of normal function and the gain of toxic function.

2.1. Oligomerization and spread of tau pathology

Unlike normal tau, the AD P-tau forms oligomers and as a result sediments at 100,000 to 200,000 × *g* [28,34]. The sequestration of normal tau by the AD P-tau is non-saturable and the oligomers so formed lead to their aggregation into filaments [36]. The fine structure and the cytotoxic function of tau oligomers, also called granular tau, has been characterized by Takashima's lab [see 44]. An in vivo confirmation of this seeding of tau pathology was provided by its transmission by intracranial injection of brain extract containing tau filaments from P301S transgenic mice to wild type human tau overexpressing transgenic mice [45,46]. The nature of tau oligomers, which is probably determined by tau isoform, mutation, hyperphosphorylation and other posttranslational modifications including truncation, characterizes the

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