

Review Article

Amyloid Cascade or Tau Dysfunction: The Cause for Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is an age-related neurodegenerative disorder which has yet to be fully understood. The amyloid cascade hypothesis (ACH) has played the prominent role in explaining the etiology and pathogenesis of AD. It proposes that the deposition of β -amyloid ($A\beta$) is the initial pathological event in AD leading to the formation of senile plaques (SPs) and then to neurofibrillary tangles (NFTs), neuronal cell death, and ultimately dementia. However, ACH has recently come under severe scrutiny as it has been claimed that SPs may be developed independently and might be the effect of the disease rather than the cause of AD. The present review indeed argues that the amyloid cascade is an effect of the disease and not the cause. We argue that excitotoxic processes caused by hyperphosphorylation of tau tangles at dendritic spines are the leading cause of the change in energy metabolism leading to apoptosis. We also propose that there are links among metabolism, the deposition of amyloid plaques, hyperphosphorylation of tau, and the decline of cognitive functions, following the increase of intraspinal cAMP that we claim is associated with decline of lactate.

Keywords: Alzheimer's disease, Amyloid plaques, Neurofibrillary tangles

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Introduction

Alzheimer's disease (AD) has yet to be fully understood diagnostically and therapeutically. The amyloid cascade hypothesis (ACH) has played a prominent role of explaining the etiology and pathogenesis of AD [1]. ACH posits that accumulation of amyloid- β peptide ($A\beta$) initiates the disease process. While there is a substantial body of evidence supporting the ACH, there are also limitations and therefore it has recently come under severe criticism [2]. Here, we argue that the amyloid cascade is the effect of the disease rather than the cause. We propose that prior tau phosphorylation raises the toxicity of amyloid deposits. The result is loss of spines with a decline in glycolysis associated with synaptic activity that explains cognitive decline and dementia (Figure 1). We speculate that excitotoxic processes at dendritic spines are the leading cause of the change in energy metabolism associated with decline of spine numbers. It is the decline of spine numbers that serves as a common substrate for many neuropsychiatric diseases and specifically contributes to the propagation of degenerative changes in AD [3]. As spines are predominantly glycolytic (with absence of mitochondria), the loss leads to a more

oxidative metabolism, but at a lower level. We claim that this series of pathogenetic events manifests itself as increases of the oxygen-glucose index (OGI=oxygen consumption/glucose consumption) [4] and the oxygen extraction fraction (OEF), resulting in decline of brain lactate and cerebral blood flow [5], followed by increase of cAMP with loss of working memory [6]. The low lactate in aged humans is supported also by direct measurements [7]. In contrast, a more recent report claimed otherwise, i.e., increase of brain lactate with aging in mice [8].

Proposed hypotheses and predictions

Brain oxidative metabolism is lower but more oxidative (less glycolytic) in patients with AD compared with healthy elderly and young volunteers. It declines because of damage to dendritic spines caused by neurotoxic $A\beta$ plaques that develop in individuals when phosphorylated tau accumulates in dendrites. This leads to the following predictions:

- 1) Brain energy metabolism is lower in healthy elderly subjects than in healthy young subjects.
- 2) This decline is more pronounced in AD patients than in healthy age-matched subjects, reflecting excitotoxic lesions

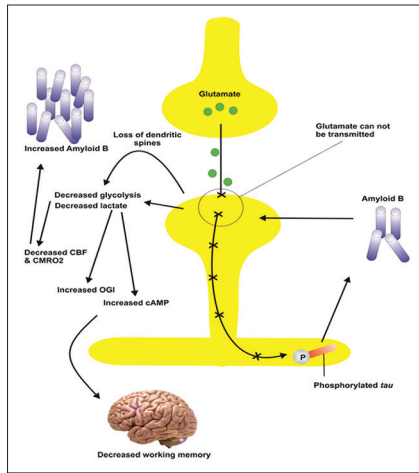


Figure 1. Proposed model of tau induced decline in cognition in AD. As shown below, the phosphorylated tau raises the toxicity of amyloid plaques, which in turn damages the dendritic spines. The loss of spines leads to a more oxidative metabolism. The increase in oxidative metabolism results in increase of only abbreviation (OGI) and therefore, only abbreviation (OEF). The increase of OEF leads to decrease of cerebral blood flow and lactate followed by increase of cAMP and loss of working memory.

generated by defective mitochondrial activity in these patients.

- 3) Brain lactate and blood flow levels are lower in AD compared with healthy elderly and young volunteers (low lactate hypothesis).
- 4) The binding of the marker of A β plaques is elevated in the areas of lesions in AD patients compared to healthy elderly subjects and is inversely correlated with the decline of cerebral blood flow (CBF) (Figure 2) and metabolic rate of glucose (CMR_{glc}).

Energy metabolism and oxidative stress in AD

Brain energy demands in the steady-state are almost entirely fulfilled by oxidative metabolism of glucose, which is extracted from the circulation [9, 10]. Imaging studies of aging have in general shown reductions of CBF and the cerebral metabolic rates of oxygen (CMRO₂) and CMR_{glc} in healthy adults. While some studies have demonstrated decline of CBF, CMRO₂, and CMR_{glc} in neocortical brain regions [11-13], other studies have reported the preservation of CBF in normal aging [14, 15]. Therefore, the stability of CBF and CMRO₂, and CMR_{glc} with normal aging remains uncertain. It has been claimed that mitochondrial dysfunction due to abnormal stoichiometry between CBF and cerebral energy metabolisms is by far the greatest risk factor for neurodegenerative diseases [16-18]. PET-CMR_{glc} studies have revealed regional abnormalities of glucose consumption in several cortical regions [19, 20] and blood flow deficit [21] prior to the development of clinically significant impairment in line with the findings that focally insufficient perfusion may lead to cell death (apoptosis) in neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease (HD), and AD [16, 18, 22, 23].

During the past decade, there has emerged considerable evidence that AD as well as PD and HD may be disorders of flow-metabolism coupling [16, 18, 24, 25]. Lin and Beal [18] proposed

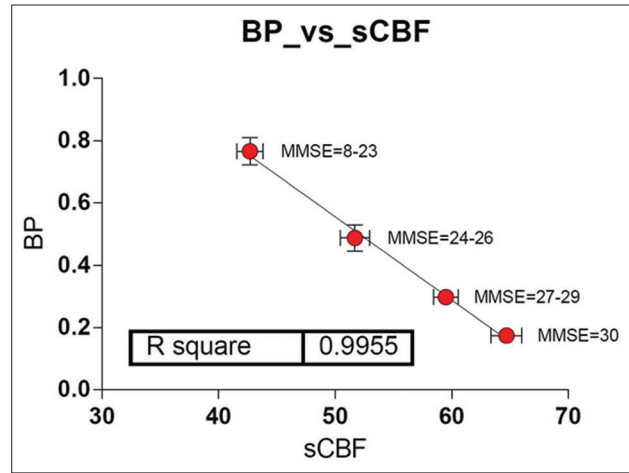


Figure 2. The relationship between the binding potential of A β plaques in AD patients compared to healthy elderly subjects and its correlation with CBF (data provided by A. Gjedde).

that impairment of the relationship between CBF and CMRO₂ and CMR_{glc} as a consequence of defective mitochondrial respiration may induce oxidative stress resulting in excitotoxicity, leading in turn to apoptosis of susceptible neurons. Oxidative stress and damage occur early in the AD brain, before the onset of significant plaque pathology [26] and precedes A β deposition in transgenic mice [27]. Several pathways connecting oxidative stress and AD pathology have recently been uncovered. Frost et al (2012), have shown that misfolded hyperphosphorylated tau causes mitochondrial dysfunction and oxidative stress. Oxidative stress by dysfunctional mitochondria causes DNA and gene damage leading to cell death and apoptosis. Oxidative stress may activate signaling pathways that alter amyloid precursor protein (APP) leading to rise in A β or tau processing. It remains uncertain whether oxidative stress is caused by abnormal metabolism because of a primary mitochondrial defect, or due to impaired oxygen delivery. Irrespective of the underlying mechanism, defective electron transport in mitochondria leads to excitotoxic processes [22].

Amyloid plaques and amyloid cascade hypothesis

The clinical features of AD are accompanied by characteristic histological changes in brain, especially cerebral cortex, which include the presence of extracellular senile plaques, intraneuronal neurofibrillary tangles mainly hyperphosphorylated tau, and loss of synapses and neurons and neurotransmitter deficits [28, 29]. The A β peptide is a major component of the extracellular senile plaques, which naturally arises from the metabolic processing of the amyloid precursor protein (APP) in the endoplasmic reticulum (ER), the Golgi apparatus, or the endosomal-lysosomal pathway [30]. The importance of A β in the pathogenesis of AD is suggested by several findings. It has been shown that the accumulation of A β is specifically toxic to cultured neurons in vitro, initiating a series of downstream events, including the hyperphosphorylation of tau, which results in neuronal dysfunction and death [31]. Apoptosis is a reaction to neurotoxicity, and is linked to activation of apoptotic pathways via perturbation of calcium homeostasis in mitochondria [30].

Increases in the concentration of A β may contribute to neuronal shrinkage, resulting in progressive decline in cognitive function in AD. The ACH has been proposed to explain the pathogenesis of the AD. It proposes that the deposition of A β peptide is initial pathological event in AD leading to the formation of SPs and then to NFTs, neuronal cell death and ultimately dementia. In spite of its popularity, there are also limitations that first, SPs and NFTs may develop independently, and SPs and NFTs may be the products rather than causes of neurodegeneration [32].

The imaging of the amyloid load in patients with AD seems to be a promising tool for early diagnosis of AD and for the assessment of new treatment strategies. The so-called Pittsburgh Compound-B ([¹¹C]PIB) is particularly suited for PET assays of amyloid load. Increased [¹¹C]PIB binding is most prominent in the brain regions where amyloid plaques are observed in *post mortem* brain [29, 33, 34]. However, the suitability of the amyloid imaging agents such as [¹¹C]PIB has been challenged due to extent of amyloid deposition in cognitively normal individuals and high degree of activity detected in the frontal lobe and white matter [35]. It also remains unclear if there is a unique initiator for AD.

Neurofibrillary tangles and neurodegeneration

More recently, it has been argued that AD is being initiated by neurofibrillary tangles which are aggregates of hyperphosphorylated tau proteins and tauopathies are ultimate cause of neurodegenerative diseases such as AD. Tauopathies are histopathologically defined by insoluble filamentous deposits of abnormally phosphorylated tau protein within neurons and glia [36]. Identifying the causes of abnormal tau phosphorylation and subsequent aggregation has been the focus of major research, and is currently a major target for the development of therapeutic interventions for tauopathies including AD. Given the close association between tau pathology and severity of disease, and together with evidence that tau acts downstream of A β plaques to induce neuronal death [37, 38], it has become increasingly recognized that tau-based therapies may be effective in treating AD. A decrease in number and density of synapses, disproportionate to the loss of neurons, implies that synapse loss proceeds neuronal loss [36]. Synapse loss appears to be an early event in neurodegeneration. Extracellular NFTs are only confirmed in regions with intraneuronal NFTs, suggesting that the inclusions of NFTs formed inside of neurons proceeds apoptosis. In AD, an inverse correlation between surviving neurons and amounts of extracellular NFTs suggests that hyperphosphorylated tau do proceeds neurodegeneration. Aberrant tau deposition can mediate A β toxicity as seen in AD [39]. The pathological cascade of A β plaque formation in dendritic spines results in synapse loss, and eventually neuronal loss [40]. The A β plaque formation correlates with level of accumulating tau protein targets tyrosine protein kinase Fyn to the spine, where Fyn mediates the downstream toxicity of A β plaque by over activation of the NMDA-glutamate receptor [38].

We assume that disproportionate flow/metabolism is the leading cause of excitotoxic processes at dendritic spines resulting in decline in their numbers. It is the decline in spine numbers which serves as a common substrate for many

neuropsychiatric diseases and specifically contributes to the propagation of degenerative changes in AD. We predict that a series of pathogenetic events manifest itself as increases of the OGI and OEF, with decline of lactate and hence of blood flow [5] and increase of cAMP with loss of working memory [6].

Concluding remarks and future directions

Much progress has been made in identifying the underlying causes of cell death that occur downstream of tau dysfunction (Figure 3). There is strong evidence implicating the role of mitochondrial dysfunction in the pathogenesis of neurodegenerative disorders such as AD [41], PD [42] and Multiple Sclerosis (MS) [43]. In AD, mitochondrial dysfunction may be a consequence of the accumulation of A β plaque within mitochondria which itself might be the result of tau hyperphosphorylation. Mitochondrial dysfunction as a result of oxidative stress contributes to ageing, the greatest risk factor for neurodegenerative diseases. Mitochondrial dysfunction occurs early in all major neurodegenerative disorders, and there is strong evidence that this dysfunction has a role in disease pathogenesis. It has been argued that the abnormal stoichiometry between CBF and CMRO₂ plays a vital role mitochondrial dysfunction [44]. We have argued that abnormal flow-metabolism relation is caused by excitotoxic process at the dendritic spines which have been reduced by hyperphosphorylated tau. It is the decline of dendritic spines numbers that serves as a common substrate for many neurodegenerative disease and specifically AD by raising the toxicity of amyloid deposits and specifically AD. Therefore, there is a cascade of events which starts from hyperphosphorylated tau leading to rise in amyloid plaques. It has been shown that soluble, extracellular species of A β are capable of triggering both acute neuronal death and synaptic

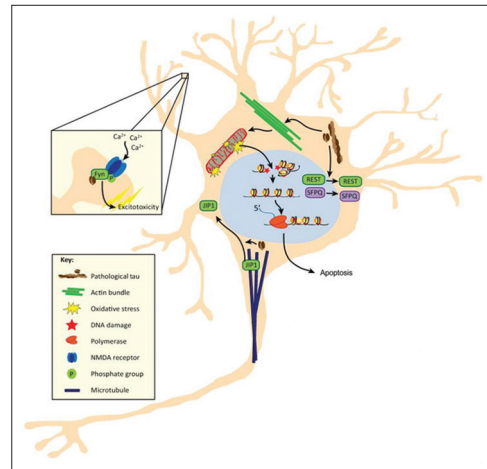


Figure 3. Model of tau induced neurodegeneration (The figure and its legend have been copied from Frost et al, 2012 but modified by the author). Soluble tau becomes abnormally phosphorylated and forms oligomers and larger filamentous aggregates. Misfolded, hyperphosphorylated tau causes the bundling and stabilization of filamentous actin, which gives rise to elongated, dysfunctional mitochondria, and oxidative stress. Oxidative stress induced by dysfunctional mitochondria or lack of nuclear (repressor element 1-silencing transcription factor (REST)) causes DNA damage, which stimulates loss of heterochromatin. Genes that are normally silenced by heterochromatin are aberrantly transcribed, leading to cell cycle activation in postmitotic neurons and subsequent apoptosis.

dysfunction [45]. How do A β plaque and tau interact in the spine is an important issue which needs to be further explored. Ohyagi et al. [46] have shown that in mediating A β toxicity via tau, the Src kinase Fyn has a crucial role. Tau is necessary to target Fyn to the spine where Fyn mediates the downstream toxicity of A β by directly or indirectly overacting cellular receptors such as the NMDA-type glutamate receptor. A β further causes a mis-sorting of tau into dendrites as well as a loss of spines [47].

In general, it seems that the importance of tau dysfunction in causing neurodegeneration is getting more pronounced and progress has been made in identifying the underlying causes of cell death by hyperphosphorylated tau. Drugs that reduce oxidative stress are efficacious in tau transgenic mice, and are currently in clinical trials. These efforts are encouraging but the positive effects of drugs on animal have yet to be tested in humans. There is a long way to go until scientists find a decisive cure for AD and other neurodegenerative disorders. But the amount of research and promising results make us believe that it is the beginning of long overdue wait.

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