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Review

GSK3 and Tau: Two Convergence Points in Alzheimer's Disease

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Abstract. Glycogen synthase kinase 3 (GSK3) is a ubiquitously expressed serine/threonine kinase that plays a key role in the pathogenesis of Alzheimer's disease (AD). GSK3 phosphorylates tau in most serine and threonine residues hyperphosphorylated in paired helical filaments, and GSK3 activity contributes both to amyloid-β production and amyloid-β-mediated neuronal death. Thus, mice generated in our laboratory with conditional overexpression of GSK3 in forebrain neurons (Tet/GSK3β mice) recapitulate aspects of AD neuropathology such as tau hyperphosphorylation, apoptotic neuronal death, and reactive astrocytosis, as well as spatial learning deficit. In this review, we describe recent contributions of our group showing that transgene shutdown in that animal model leads to normal GSK3 activity, normal phospho-tau levels, diminished neuronal death, and suppression of the cognitive deficit, thus further supporting the potential of GSK3 inhibitors for AD therapeutics. In addition, we have combined transgenic mice overexpressing the enzyme GSK3β with transgenic mice expressing tau with a triple FTDP-17 mutation that develop prefibrillar tau-aggregates. Our data suggest that progression of the tauopathy can be prevented by administration of lithium when the first signs of neuropathology appear. Further, it is possible to partially reverse tau pathology in advanced stages of the disease, although the presence of already assembled neurofibrillary tangle-like structures cannot be reversed.

Keywords: Alzheimer's disease, GSK3, tau

In 1906, Alois Alzheimer described two aberrant components found in the brain of a demented patient after death: senile plaques and neurofibrillary tangles [1]. In the 1980 s the main components of plaques (amyloid-β (Aβ) peptides) and tangles (tau protein) were described [2, 3]. By the end of the twentieth century, genetic studies discovered a monogenic origin for the familial form of Alzheimer's disease (FAD) [4]. Mutations at specific sites in one of three genes (AβPP, PS-1, PS-2) result in the onset of neurodegeneration and the appearance of dementia. Since those three genes codify for proteins related to the generation of Aβ peptide, it was suggested that, at least for FAD, the origin of the disease was the accumulation of Aβ peptide [5], with tau pathology being a further step in the development of the disease. In that way, tau pathology should be promoted by the accumulation of Aβ peptides.

Tau pathology in AD is related to tau phosphorylation and aggregation. The involvement of Aβ peptide in tau phosphorylation was first tested mostly by looking for the activation of a possible tau kinase upon Aβ peptide addition. At least one of these tau kinases was found to be GSK3, based on the fact that lithium, a GSK3 inhibitor, protects cultured neurons against Aβ-induced neurodegeneration [6]. Other studies [7–10] resulted in the same conclusions, and later it was shown that the production of Aβ peptide interferes with

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insulin or wnt pathway [11, 12]. Additionally, in the 1990 s, GSK3β (an isoform of GSK3) was identified as a tau protein kinase I [13] and as such was able to phosphorylate tau in several sites hyperphosphorylated in the paired helical filaments present in the tangles of the brain of AD patients [14–16]. At that time it was also found that GSK3 accumulates in the cytoplasm of pretangle neurons, and its distribution in brain for AD neurofibrillary changes was coincident with the sequence of development of those changes [17, 18].

Based on the evidence linking Aβ peptide, GSK3 activation, and tau phosphorylation, it was hypothesized that GSK3 deregulation in neurons may be a key point in the development of AD. Thus, a conditional transgenic mouse overexpressing GSK3β in the forebrain was generated and the characterization of that mouse showed increased tau phosphorylation in AD relevant epitopes and neurodegeneration [19]. Afterward, memory impairment in this transgenic mouse model [20], which correlated with a clear degeneration of the dentate gyrus [21], was observed.

Meanwhile, in FAD due to PS-1 mutations, the increase in Aβ peptide for each mutation did not correlate with the reported age of onset of FAD caused by that mutation and the appearance of dementia was not always dependent on Aβ peptide accumulation [22]. Indeed, it was found that some PS-1 mutations resulting in the appearance of dementia could activate GSK3 and promote tau phosphorylation by an alternative pathway from Aβ peptide, involving cadherin and PI3K/Akt signaling [23]. Also, other groups' results indicated that the presence of tau might be needed for the induction of Aβ toxicity [24–26]. Thus, GSK3 and tau phosphorylation could be points of convergence for the development of dementia initiated in different ways, and our conditional transgenic GSK3 mouse model could be a suitable model to test the effects of GSK3 overexpression and the possible toxicity of tau phosphorylated by GSK3. This last point was tested by analyzing the effect of GSK3 overexpression in a mouse lacking tau, and the results indicated that an increase in phospho-tau could be toxic for neurons, although there are other toxic factors that, in addition to phospho-tau, could act on a neuron after GSK3 overexpression [27]. Also, tau hyperphosphorylation and neurodegeneration resulted in glia activation that was observed in the mouse overexpressing GSK3 [19, 21]. One important point was to determine if some of these features could be reversible if GSK3 overexpression decreased to normal expression level of the kinase. This was the basis of the work that we highlight in this review. In this work [28], by using the conditional

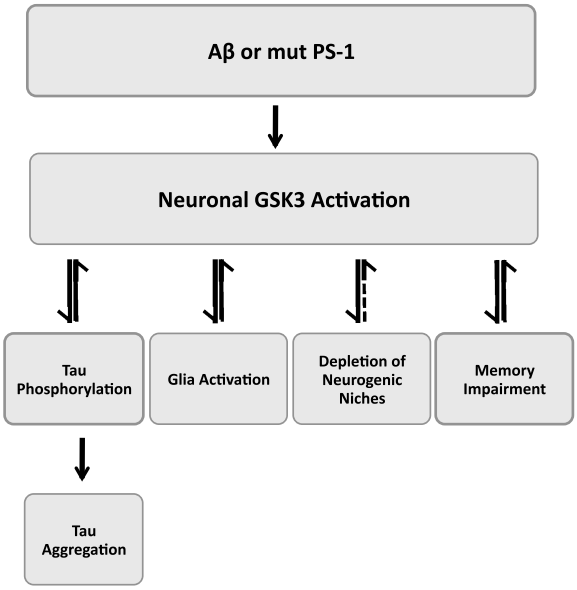

Fig. 1. This figure summarizes our studies on the effect of GSK3 activation in hippocampal neurons of a mouse. GSK3 activation could be activated by overexpression of the protein or by the effect of other components like the presence of Aβ oligomers or that of mutated PS-1 at some specific sites. The consequences of activated GSK3 in a conditional transgenic mouse overexpressing GSK3 in the hippocampus are indicated. Some of the consequences are reverted by decreasing GSK3 overexpression in the conditional model. Memory impairment may be only reverted if remains a population of neuronal precursors (⇋).

GSK3 mouse model, we found that transgene shutdown in symptomatic but young mice leads to normal GSK3 activity, normal phospho-tau levels, diminished neuronal death, and suppression of the cognitive deficit (Fig. 1). These points are of interest since they support the potential use of GSK3 inhibitors for AD therapeutics. However, our analyses were done in young mice, while AD patients are largely elderly humans. Indeed, AD symptoms in humans appear after devastating neurodegeneration has already taken place, thus the use of some therapeutic compounds could be too late for effective treatment.

To address that question, a double transgenic model overexpressing GSK3β in a conditional manner [19] and tau protein carrying three FTDP-17 mutations [21] was treated with lithium, a widely used drug for affective disorders which inhibits GSK3β at therapeutically relevant concentrations [29]. This transgenic line shows tau hyperphosphorylation in hippocampal neurons accompanied by neurofibrillary tangles (aggregated tau can only be found at the age of 18 months). Chronic lithium treatment, and shutdown of GSK3β overexpression with doxicycline prevented

the development of tau pathology when administered early in disease progression. On the other hand, when lithium was administered at late stages of disease, it still reduced tau hyperphosphorylation but could not reverse tau aggregation [30]. The same result has been reported in transgenic mice overexpressing FTDP-17 tau in a conditional model and after turning out the system with doxicycline [25]. Thus, neurofibrillary tangles seem to be very stable structures, and though different treatments revert soluble hyperphosphorylated tau, NFTs cannot be changed back.

To further analyze this point, we tested the possible causes of cognitive impairment at different ages in the GSK3β overexpressing mice [28]. We found degeneration in the dentate gyrus of the transgenic mice [21]. This degeneration was due in part to an aberrant neurogenesis known to take place in the dentate gyrus [31]. Aging of the transgenic mouse correlates with a decrease in the number of precursor cells that can become new neurons because there is a depletion of those precursors in old mice [32]. Our preliminary data [28, 33] indicate that transgene shutdown in symptomatic old mice leads to normal GSK3 activity and normal phospho-tau levels, but cognitive deficit remains without change. Our current hypothesis is that in elderly AD patients a similar process takes place. Likely there is not only degeneration but also absence of new functional neurons at the time of first diagnosis of the disease. More work should be done to determine if this is the case.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1352).

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