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Review

GSK3: A possible link between beta amyloid peptide and tau protein

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ABSTRACT

Tau is a neuronal microtubule-associated phosphoprotein that is highly phosphorylated by glycogen synthase kinase 3 (GSK3). Tau phosphorylation by GSK3 regulates tau binding to microtubules, tau degradation and tau aggregation. Tau phosphorylation is important in Alzheimer disease pathology and in other tauopathies. In Alzheimer disease, it has been proposed that the peptide beta amyloid promotes GSK3 activation, resulting in tau phosphorylation. In this work, we review the links between beta amyloid peptide, tau protein and GSK3 that occur in familial Alzheimer disease. We also discuss the possible links between GSK3 and sporadic Alzheimer disease. Finally, we include a brief review of the pathology of animal models overexpressing GSK3.

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Contents

Introduction

Alzheimer disease (AD) is characterized by the presence of two aberrant structures in patients' brains: senile plaques and neurofibrillary tangles (Alzheimer, 1911). Senile plaques are composed of beta amyloid peptide, a fragment of the amyloid peptide precursor protein (APP) (Glenner and Wong, 1984; Masters et al., 1985), whereas the main component of neurofibrillary tangles is the cytoskeleton protein known as the tau protein, in hyperphosphorylated form (Grundke-Iqbal et al., 1986a,b). Onset of familial Alzheimer disease (FAD) may be attributed to accumulation of amyloid peptide due to one of two factors: (1) mutations in APP that facilitate its cleavage to generate amyloid peptide or (2) mutations in presenilin-1 (PS-1) or presenilin (PS-2) that promote amyloid peptide formation (Price and Sisodia, 1998). Beta amyloid peptide aggregates to form oligomers and other high-order polymerized structures that may be toxic to neurons. The presence of tau protein (probably, in phosphorylated form) also appears to be involved in this toxic process (Rapoport et al., 2002; Roberson et al., 2007). Thus, it has been suggested that amyloid peptide may favor tau phosphorylation by activation of GSK3 (Alvarez et al., 1999; Busciglio et al., 1995).

Amyloid peptide targets the insulin (Townsend et al., 2007) or wnt (Magdesian et al., 2008) signaling pathways resulting in the increased activation state of GSK3β (also known as tau kinase I) (Ishiguro et al., 1993) and subsequent phosphorylation of tau protein (Alvarez et al., 1999). Thus, it can be hypothesized that the link between beta amyloid peptide and tau protein may be protein kinase GSK3. In light

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of this hypothesis, several GSK3 inhibitors are currently being studied as a treatment strategy for AD. These inhibitors range from cations like lithium to small compounds developed by different pharmaceutical companies (see Hernandez et al., 2009; Martinez and Perez, 2008). In this minireview, we will discuss phosphorylation of tau protein by GSK3 and the consequences of that phosphorylation with regard to Alzheimer disease.

Tau phosphorylation and GSK3

Tau is a neuronal microtubule-associated protein that facilitates tau assembly in vitro and is involved in microtubule stabilization (Weingarten et al., 1975), playing an important role in microtubule dynamics (Drubin and Kirschner, 1986) and also in axonal transport (Ebneth et al., 1998). Tau functions can be regulated by its phosphorylation by different kinases. There are 85 phosphorylatable amino acid residues in tau, including 45 serines, 35 threonines and 5 tyrosines (Hanger et al., 2009; Morishima-Kawashima et al., 1995). Some of these residues are modified during early (fetal) stages of development (Morishima-Kawashima et al., 1995), but the overall tau phosphorylation decreases in the mature brain (Hanger et al., 2009). However, tau is abnormally hyperphosphorylated in the brain of patients with AD (Avila et al., 2004).

Tau obtained from the brain of Alzheimer patients has 40 phosphorylation sites, 28 serines, 10 threonines and 2 tyrosines, the majority of which can be modified by GSK3. This kinase can phosphorylate 17 of the serine and 6 of the threonine residues (Hanger et al., 2009).

GSK3 is a constitutively active protein kinase that is present in two highly homologous forms in mammals, GSK3α and GSK3β (Jope and Johnson, 2004; Woodgett, 1990). Because GSK3 is constitutively active, its regulation is primarily based on inhibition of its activity (Jope and Johnson, 2004) through different signaling mechanisms such as the insulin or wnt pathways. GSK3 is inactivated by phosphorylation of Ser21 in GSK3α or Ser9 in GSK3β (Jope and Johnson, 2004). GSK3 typically phosphorylates "primed" substrates (substrates pre-phosphorylated by a priming kinase), including tau; however, phosphorylation of GSK at Ser21 or Ser9 inhibits its primed substrate phosphorylation activity. GSK3 can occasionally act as its own priming kinase, modifying closed sites in the molecule in a hierarchical manner (the recognition motif of the kinase is S-X-X-X-S (P)) (Jope and Johnson, 2004).

Consequences of tau phosphorylation by GSK3

Phosphorylation of tau by GSK3 takes place in the regions surrounding the microtubule binding domain, and the kinase can also modify four residues inside this domain (Hanger et al., 2009). Phosphorylation of tau at these sites, primarily in the microtubule binding domain, can be crucial for preventing the interaction of tau protein with microtubules and therefore it may affect microtubule stabilization and dynamics. Thus, a possible consequence of tau phosphorylation by GSK3 may be a decrease in the interaction between tau and microtubules. Because tau–tau interaction occurs through the tubulin binding domain (Perez et al., 1996), tau detachment from microtubules may favor self-aggregation. Studies using GSK3-overexpressing transgenic mice suggest that inhibition of the kinase may prevent the formation of tau aggregates (Noble et al., 2005; Perez et al., 2003a, b). Overexpression of GSK3 in a transgenic *Drosophila* model revealed that tau phosphorylation correlates with tau aggregation (Jackson et al., 2002). The use of cell culture models or in vitro assays has yielded similar results (Perez et al., 2002). In addition, tau microtubule binding domain is involved in tau-tau interaction (Perez et al., 2007; Santa-Maria et al., 2004; von Bergen et al., 2000) and partial deletion of this region results in a conformational change that facilitates tau phosphorylation by GSK3 (Perez et al., 2007). This conformational change is also present in aggregated forms of tau (Jicha et al., 1999).

Phosphorylated tau and degradation

Degradation of tau occurs via pathways that involve the proteasome complex (Petrucelli et al., 2004) or through proteases such as caspase (Ding et al., 2006; Petrucelli et al., 2004) and the lysosomal enzyme calpain (Johnson et al., 1989). Phosphorylated tau is more resistant to proteolysis by calpain degradation than unmodified tau (Wang et al., 1995). Tau can be ubiquitinated for proteasome degradation (Morishima-Kawashima et al., 1993) but ubiquitin-independent degradation has also been reported (Baki et al., 2004; Cardozo and Michaud, 2002). In ubiquitin-independent degradation, tau is modified at a site phosphorylated by GSK3, resulting in binding of the co-chaperone BAG2/Hsp70 complex and subsequent delivery to the proteasome for ubiquitin-independent degradation (Carrettiero et al., 2009). This mechanism is probably the most efficient pathway for tau degradation.

How beta amyloid peptide activates GSK3

Beta amyloid peptide can form oligomers that bind to certain cell receptors. The peptide behaves like an antagonist of insulin, preventing the activation of PI3 kinase, and subsequently that of Akt (which phosphorylates GSK3α (Ser21) or GSK3β (Ser9)). Thus, GSK3 increases its activity in the absence of activated Akt (Townsend et al., 2007). Also, amyloid peptide appears to interfere with the canonical wnt pathway, a pathway that results in the inactivation of GSK3. When the wnt pathway is impaired due to the presence of amyloid peptide, GSK3 is no longer inactivated (Magdesian et al., 2008).

More recently, it has been shown that prion protein acts as a beta amyloid oligomer receptor (Lauren et al., 2009). Although a prion protein peptide can activate GSK3 (Perez et al., 2003a,b), researchers have not established, at the present, whether an interaction between beta amyloid and prion protein results in activation of GSK3.

In addition, beta amyloid peptide activates GSK3 resulting in phosphorylation of tau protein. Thus, GSK3 may be the link between amyloid peptide and tau protein. Recently, it was reported that the insulin/Akt signaling pathway is also targeted by intracellular beta amyloid peptide (Lee et al., 2009). On the other hand, presenilin 1 may also regulate GSK3 in a beta amyloid-independent manner (Baki et al., 2004; Takashima et al., 1998).

Activation of GSK3 in sporadic Alzheimer disease

The elderly population is at a greater risk for developing AD and insulin-dependent glucose metabolism has an important role in the regulation of longevity (Gems and Partridge, 2001; Guarente and Kenyon, 2000). Partial impairment of this pathway may result in a longer life for an organism. However, defects in the insulin-dependent pathway may increase the activation of GSK3, although the result of that activation could be counteracted by changes in phosphatase activity that may also result from these defects in the insulin-dependent pathway (Planel et al., 2004).

The apolipoprotein E (ApoE) genotype has been implicated in sporadic Alzheimer disease (SAD), individuals with the ApoE4 genotype have an increased risk for developing SAD (Strittmatter et al., 1993). A link between ApoE and GSK3 has been indicated (Cselenyi et al., 2008; Small and Duff, 2008; Tamai et al., 2000; Townsend et al., 2007). Also, it has been reported that ApoE4 has a higher effect in activating GSK3 than other ApoE isoforms (Cedazo-Minguez et al., 2003). Also, the wnt signaling pathway regulates GSK3 activity; and it is suggested that ApoE inhibits this pathway through its interaction with LRP6, a co-receptor of frizzled (wnt receptor) (Caruso et al., 2006). Finally, a GSK3 polymorphism has been linked to SAD. Indeed,

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