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# Tau kinases and phosphatases

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Alzheimer disease (AD) is characterized by the presence of two aberrant histopathological structures: the senile plaques and the neurofibrillary tangles. In the decade of the 1980s it was described that Aβ peptide is the major component of senile plaques [1]. Also, in the same decade, the pioneer works of Grundke-Iqbal *et al.* described the presence of tau [2], in hyperphosphorylated form [3], in the neurofibrillary tangles. Thus, two main features appear to be related with the tau pathology found in AD: tau phosphorylation and tau aggregation. Whereas the toxicity of tau aggregates is discussed at the present, there are some indications of a toxic behaviour for hyperphosphorylated tau (P-tau). In fact, it has been described that P-tau can sequester different microtubule-associated proteins, affecting the neuronal microtubule network [4], and, very recently, toxicity has been demonstrated in some animal models [5]. Also, the presence of P-tau has been correlated with cognitive impairment [6].

The level of P-tau is a consequence of the action of protein kinases, which favour tau phosphorylation, and of protein phosphatases, which decrease this post-translational modification. Tau kinases has been classified as proline-directed (PDPK) and non-proline-directed protein kinases (NPDPK) [7], one of the PDPK being glycogen synthase kinase 3 (GSK-3), the enzyme that could modify more sites in tau molecule [8]. Some of these sites are modified as well in mouse models overexpressing GSK3 [9].

On the other hand, tau phosphatases have also been described [10], the most significant one being protein phosphatase 2A (PP2A), a protein that accounts for more than 70% of the total phosphatase activity found in human brain [11].

One of the main objectives to understand tau pathology associated to AD is to identify the external signals that could favour the increase of tau phosphorylation. For instance, it was described that starvation may induce tau hyperphosphorylation in mouse brain [12]. Thus, alterations in glucose metabolism that induce hypothermia lead to tau hyperphosphorylation, mainly by inhibition of tau phosphatases [13]. More recently, it has also been reported that insulin dysfunction (a feature that has been related to AD [14] ), may induce *in vivo* tau hyperphosphorylation [15].

Insulin dysfunction results in a decrease of both tau kinases and tau phosphatases (Fig. 1). In the case of tau phosphatase PP2A, composed of a catalytic subunit (PP2Ac) and two regulatory subunits, A and B, it was described that in peripheral tissues PP2Ac could be modified at tyrosine residues in response to insulin [16–18]. Tyrosine phosphorylation of PP2Ac mainly occurs at tyrosine 307, located at the C-terminus of the molecule, close to the carboxy-terminal end (residue 309), where a leucine residue, which could be modified by methylation, is present [19]. Thus, the analysis of tyrosine 307 phosphorylation could be an important task to understand tau phosphorylation in AD.

In a work that is published in this issue of the *Journal of Cellular and Molecular Medicine*, Liu *et al.* [20] describe the presence of PP2Ac tyrosine phosphorylation in AD brains, a finding that could further explain tau hyperphosphorylation found in AD. For a future work it will be of interest to analyse if there is a decrease in this tyrosine phosphorylation process in response to external stimuli that could result in a dysfunction of insulin (or related factors) signalling pathways.

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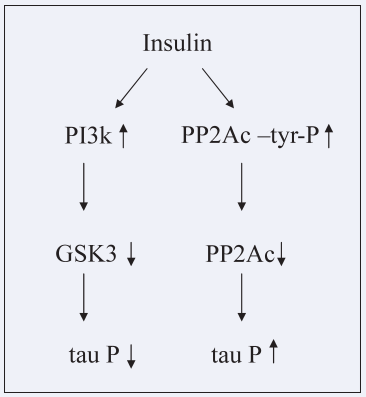


**Fig. 1** Insulin (or related compounds) signalling could affect, in two opposite ways, to tau phosphorylation. In one way (left), it will inhibit the main tau kinase (GSK3), decreasing the modification in tau molecule. On the other hand (right), it will decrease PP2A activity, increasing the level of tau phosphorylation. It seems that the overall effect, from these opposite effects, is an increase in tau phosphorylation.

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