Is tau a suitable therapeutical target in tauopathies?

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Abstract

Tau is an intracellular protein, found mainly in neurons, but it can also be found in the extracellular space in pathological situations. Here we discuss whether intracellular tau, in aggregated form or modified by phosphorylation, could be toxic inside a neuron. On the other hand, it has been proposed that extracellular tau could be toxic. In this review, we address the question if the elimination of tau would be a possible therapeutic method to avoid tauopathy disorder and we suggest ways to eliminate intracellular and extracellular tau as treatment.

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Key words: Tau; Tauopathy; Alzheimer disease; Therapy; Phosphorylation

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TAU TOXICITY AND TAUOPATHIES

In the tauopathies, tau can be found in an aggregated form. A clear example is the most predominant tauopathy, Alzheimer disease (AD), in which tau protein polymerizes into filaments (paired helical filaments) that are the components of neurofibrillary tangles, one of the hallmarks of AD. In paired helical filaments, tau is present in an abnormally hyperphosphorylated form.

Tau phosphorylation

Tau phosphorylation can be performed by different protein kinases, with glycogen synthase kinase-3 (GSK3) phosphorylating more phosphorylatable sites in the tau molecule. It is not clear if GSK3 dependent phosphorylation of tau could be toxic for a neuron. A GSK3β transgenic mouse model showed tau hyperphosphorylation and increased neuronal death in the hippocampus. Moreover, in double transgenic mice which overexpressed GSK3β and mutated tau (human tau with three mutations associated with frontotemporal dementia FTDP-17), neurodegeneration appeared to be accelerated. Recently, a new transgenic mouse model has been described that overexpresses GSK3β in a tau knockout background. These mice show a slower progression of the degenerative process induced
by GSK3β overexpression and attenuated learning deficits. This evidence supports the suggested toxicity of phosphorylated tau. Due to GSK3 induced neurodegeneration, this enzyme has been proposed as a therapeutic target to avoid neurodegeneration in tauopathies.[15,16]

Also, it has been suggested that tau aggregation could induce neuron death in tauopathies, like AD, although this point is under discussion.[17] In addition, it has been shown that tau overexpression could be toxic for neurons.[18] Thus, an increase in tau, or in phosphotau or aggregated tau, might have pathological consequences.

On the other hand, two different tau-deficient mice models, isolated by gene-targeting, were viable and only some slight differences (muscle weakness and behavioral deficits) were observed in the preliminary analysis.[19,20]. Taking into account all the previous observations, it can be suggested that tau depletion might be a way to prevent the development of tauopathies.

Intracellular and extracellular tau

Previously, it was indicated that tau protein is associated with microtubules mainly in the cytoplasm. This association could be decreased when tau protein was phosphorylated.[6]. Intracellular phosphotau could be toxic for a neuron and it could result in neuronal death. After neuronal death, cytoplasmic proteins are in the extracellular space. Some of these proteins could be toxic agents. Recently, it was shown that tau could be one of these toxic extracellular proteins[21-25] (Figure 1). Extracellular tau can bind to neuron receptors[26], promoting neuron degeneration and the formation of new extracellular (and toxic) tau. If this process is repeated, it could explain how tau pathology could spread through the brain, promoting the development of tauopathies such as AD.

Clinical implications

It has been proposed that tau RNA and tau protein are mainly present in the temporal and frontal lobes[26,27], which are the lobes that are close to the nose in a mammal. A possible way to deplete intracellular tau in vivo could be the delivery of interference RNA (against tau) intranasally. Previous reports have described intranasal delivery of molecules to the central nervous system in rodents, primates and humans[28-31]. As an AD treatment, it has been proposed that the intranasal administration of insulin might improve memory in AD patients[32,33]. Preliminary data with intranasal siRNA (small interfering RNA) tau treatment in mice suggests that it can reach the brain, mainly the temporal and frontal lobes (Gomez de Barreda et al, unpublished data). In the case of extracellular tau, a possible way to deplete it would be the use of a tau vaccine.[16].

CONSEQUENCES OF TAU DEPLETION

All previous observations support the notion that tau depletion could be beneficial to avoid the development of tauopathies. However, it would be important to know the consequences of the lack of tau. Depletion of tau protein would obviously affect the different functions of tau. Some of those functions could be complemented by other proteins, but it is not clear if it would occur with all tau functions.

In fact, tau protein is a sticky protein that not only binds to tubulin but also to actin[34,35], presenilin-1[36], α-synuclein[37,38], calmodulin[39], phospholipase C-γ[40,41], ferritin[42-44], hGas7b[45] or even itself[46]. Moreover, in its phosphorylated state, it can also bind other proteins such as the chaperone protein Pin-1[47,48], 14-3-3 protein[49,50], e-Jun N-terminal kinase-interacting protein 1 (JIP1)[51], and many protein phosphatases (i.e. PP1, PP2A, PP2B and PP5)[52,53].

Figure 1 A possible mechanism for tau toxicity in neuronal cells. Upon modification by extracellular signals, tau is no longer bound to microtubules (MT). Free modified tau could be toxic for a neuron and degeneration could take place. It may result in the presence of extracellular tau that could be toxic for neighboring cells promoting their death.

Figure 2 Tau could have two opposite effects on axonal transport. A: It could facilitate the presence of acetylated microtubules and, therefore, the binding of kinesin to them. It would facilitate axonal transport. B: However, tau and kinesin may compete for the same binding site in microtubules. It could decrease axonal transport. Probably, an optimal amount of tau is needed for an optimal axonal transport. HDAC: Histone deacetylase 6.

Strategy for tau depletion

If the origin of tauopathies is related to an excess of intracellular tau, phosphotau or aggregated tau, it would be of interest to know the main localizations of tau protein in the brain. It has been proposed that tau RNA and tau protein are mainly present in the temporal and frontal lobes[26,27], which are the lobes that are close to the nose in a mammal. A possible way to deplete intracellular tau in vivo could be the delivery of interference RNA (against tau) intranasally. Previous reports have described intranasal delivery of molecules to the central nervous system in rodents, primates and humans[28-31]. As an AD treatment, it has been proposed that the intranasal administration of insulin might improve memory in AD patients[32,33]. Preliminary data with intranasal siRNA (small interfering RNA) tau treatment in mice suggests that it can reach the brain, mainly the temporal and frontal lobes (Gomez de Barreda et al, unpublished data). In the case of extracellular tau, a possible way to deplete it would be the use of a tau vaccine[16].
Recently, it has been found that tau protein binds to histone deacetylase 6 (HDAC6), and the consequence of that binding is an inhibition of HDAC6\(^{[61]}\). This protein deacetylases tubulin assembled in microtubules, which favors axonal vesicle transport\(^{[62]}\). Thus, the presence of tau protein would induce microtubule acetylation and, consequently, axonal transport. On the other hand, since tau competes with microtubule motors (involved in axonal transport) for the same tubulin binding site, an excess of tau protein may impair axonal transport. Thus, it would be an optimal amount of tau, neither too much nor too little, that would favor axonal transport (Figure 2). This optimal amount of tau could be right for other tau functions.

**CONCLUSION**

Modification of tau protein by phosphorylation or aggregation could result in a gain of toxic function in different tauopathies. It suggests that tau depletion could be beneficial in avoiding the development of those tauopathies. However, the absence of tau could promote other dysfunctions in a neuron.

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