

Received: 2004.07.06
Accepted: 2004.09.27
Published: 2004.12.15

The influence of aging in one tauopathy: Alzheimer's disease

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Source of support: self financing

Summary

In this short review, the link between aging and the onset of Alzheimer's disease is discussed. It has been widely suggested that aging is the greatest risk factor for Alzheimer's disease, in which a failure in the insulin signal-transduction pathway could occur with age and, thereby, the assembly of senile plaques and neurofibrillary tangles (two aberrant structures present in Alzheimer's disease) could be promoted. The main component of neurofibrillary tangles is the microtubule-associated protein tau, and the assembly of tau protein appears to occur after its modification by phosphorylation. In this phosphorylation, some protein kinases related to the insulin-transduction pathway could play a role.

Key words:

Alzheimer's disease • tau phosphorylation • aging • tauopathies

Abbreviations:

NFT – neurofibrillary tangles, **SP** – senile plaques, **APP** – amyloid precursor protein, **AD** – Alzheimer's disease, **GSK3** – glycogen synthase kinase 3, **FTDP-17** – frontotemporal dementia linked to chromosome 17, **PDPK** – proline-dependent protein kinases, **NPDPK** – non-proline-dependent protein kinases.

Full-text PDF:

http://www.aite-online/pdf/vol_52/no_6/6562.pdf

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ALZHEIMER'S DISEASE, A SENILE DEMENTIA

Alzheimer's disease (AD) is a senile dementia characterized by the presence of two aberrant structures present in the brain of patients suffering from this disease: senile plaques (SPs) and neurofibrillary tangles (NFTs)¹. Neural death also takes place. Senile plaques are composed of a main component, β -amyloid peptide, and other components, such as α -synuclein²⁵. β -Amyloid peptide is a fragment^{9, 18} of a precursor protein (the amyloid precursor protein, or APP) produced upon cleavage by two proteases, β and α secretases. There is also an α secretase that works in non-pathological conditions¹¹. NFTs are composed of a main component, the microtubule-associated protein known as tau, in hyperphosphorylated form, and other components, such as sulfoglycosaminoglycans (for a review see reference⁵). The number of SPs appears to correlate with patient age, whereas the number of NFTs could be related to the level of dementia³.

Apart from AD there are other dementias, known as tauopathies, where tau is in a phosphorylated and aggregated form, but SPs are not present (for a review see reference⁵). Thus, a main difference between AD and the other tauopathies is the presence or absence of SPs. Since the presence of SPs is related to aging, and aging is the main risk factor for AD, we will discuss whether there is any relation between aging and the possible appearance of SPs and NFTs. Therefore we will first discuss aging. Although a main factor to take into account in cell aging could be that related to the consequences of oxidative stress, this point will not be discussed in this short review.

THE GENETIC DISSECTION OF AGING

Aging has been studied in simple model organisms such as yeast, flies, or worms¹³. In yeast it has been found that when it grows in a low glucose medium it increases its life-span¹⁶. The genetic dissection of aging in the worm (*Caenorhabditis elegans*) has indicated that deficient functioning of the Daf pathway results in an extremely long life of the worm¹⁴. The Daf pathway is related to the insulin/IGF1 signal-transduction pathway in mammals²⁸.

In mammals the level of glucose in the blood induces an increase in insulin expression, and insulin is in charge of the glucose uptake by cells. Insulin accomplishes this process after binding to a cell receptor, starting the signal-transduction pathway, where one of the steps is to activate a protein kinase, PKB. This kinase plays a role in the transport of a glucose transporter from an intracellular store to the cell mem-

brane to facilitate the glucose uptake⁶. Thus, a low level of glucose will decrease the function of the insulin signal-transduction pathway or, in other words, a dietary ("caloric") restriction will prolong survival⁷. The insulin/IGF1 signal-transduction pathway is indicated in Fig. 1. It shows that PKB activation results in a decrease in glycogen synthase kinase 3 (GSK3) activity. It can be shown that when it works deficiently, an activation of GSK3 activity will occur. What is, then, the relationship of these factors involved in life-span regulation with the generation of SPs or NFTs?

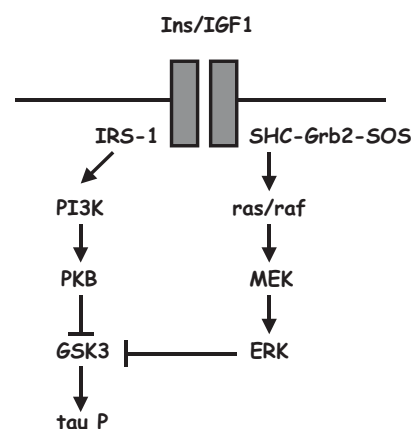


Figure 1. Insulin signaling will result in the inactivation of GSK3, a kinase that phosphorylates tau protein.

The insulin transduction pathway could be affected in starvation conditions, or could be useless in one type of pathology, diabetes type II. When the conditions of diabetes II (insulin resistance) are mimicked in a mouse overexpressing APP, an increase in the generation of β -amyloid peptide was found. This increase could be the consequence of an increase in GSK3 activity, as suggested by Sun et al.²⁷ or Phiel et al.²². This latter group indicated that GSK3 activity could increase the efficiency of the γ -secretase cleavage step (Fig. 2). An increase in GSK3 activity could also result in tau phosphorylation at some of the sites that are modified in the tau protein obtained from the brain of AD patients, and a relation between this tau phosphorylation and failures in the insulin signal-transduction pathway, due to starvation or the mimicking of the diabetes II pathology, has been indicated^{4, 23}. However, not only an increase in GSK3 phosphorylation could be responsible of tau phosphorylation, but also a decrease in the activity of phosphatase PP2A, involved in the dephosphorylation of phosphotau²³ (Fig. 3).

OTHER TAUOPATHIES APART FROM AD

Thus, a possible relationship between aging and the appearance of those aberrant structures present in

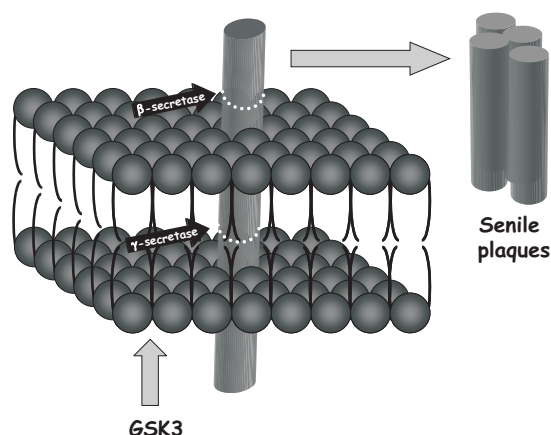


Figure 2. An increase in GSK3 activity facilitates the formation of β -amyloid peptide (■) that aggregates into senile plaques.

AD can be suggested. However, there are other tauopathies where aging is not the main risk factor for disease. An example is the dementia, of familiar origin, known as frontotemporal dementia, linked to chromosome 17 (FTDP-17)²⁶. In this case an aberrant hyperphosphorylation and aggregation of tau protein takes place without the presence of SPs. A feature of this dementia of familiar origin is the identification of mutations in the tau gene that are sufficient to cause dementia^{12, 26}. An interesting observation was that these mutations prevent the binding of phosphotau to PP2A phosphatase and, therefore, tau can be hyperphosphorylated¹⁰. That hyperphosphorylation is the consequence of the modification by kinases, but it is mainly the consequence of the absence of dephosphorylation of phosphorylated tau by phosphatase PP2A. Two different types of kinases could modify tau protein, i.e. the proline-directed protein kinases (PDPK) and the non-PDPK (NPPDK)¹⁹. Among the former is GSK3, and among the latter is PAR-1 (for a review see reference⁵). Of interest is that the modification at PDPK

sites in the tau protein has been identified in tau from FTDP-17 patients²⁶.

As a model to study the tau pathology found in FTDP-17, some transgenic mice models overexpressing the human tau cDNA bearing some of the FTDP-17 mutations have been characterized. One of these mice, containing the mutations G202V, P301L, and R404W (tau^{VLW}), expresses human tau in hyperphosphorylated form, but also at PDPK sites¹⁵, and this phosphorylated tau can be assembled into thin filaments¹⁵. Curiously, thin filaments could be isolated from the brains of not only FTDP-17 patients, but also patients with another tauopathy, progressive supranuclear palsy², where PDPK phosphorylation on the tau protein also occurs.

In the FTDP-17 model previously indicated it was found that GSK3 (a PDPK) plays an important role in the formation of tau aberrant aggregates, since upon inhibition of this kinase, no tau filaments were assembled²¹. This result also suggests a relation between tau phosphorylation and assembly.

Thus, since GSK3 could be important for tau pathology, a conditional transgenic mouse overexpressing GSK3 was isolated¹⁷ and some characteristics related with tau pathology, observed in some tauopathies, were found, but tau filaments were not observed. It suggests that in this model, tau phosphorylation by GSK3 could be necessary but not sufficient for tau assembly into filaments.

TAUOPATHIES WITH SPs

On the other hand, it was previously indicated that AD is different from other tauopathies in that in AD, in addition to the presence of aberrant aggregates of phosphorylated tau, senile plaques are also present. Different models of transgenic mice overexpressing human APP cDNA bearing some mutations present in AD patients have been isolated. Among them is one bearing the Swedish mutations that form amyloid aggregates similar to senile plaques²⁰. When this mouse was crossed with one overexpressing human tau, with three FTDP-17 mutations (tau^{VLW}), the resulting mouse was phosphorylated in tau protein not only at PDPK sites, but also at NPPDK sites, and a huge increase in thick tau filaments was observed (Pérez et al., unpublished results). These results support the previous data suggesting that β -amyloid peptide aggregates could facilitate the phosphorylation and aggregation of tau^{8, 24, 29}.

Hence it should be indicated that β amyloid peptide could play a role as an antagonist of insulin receptor,

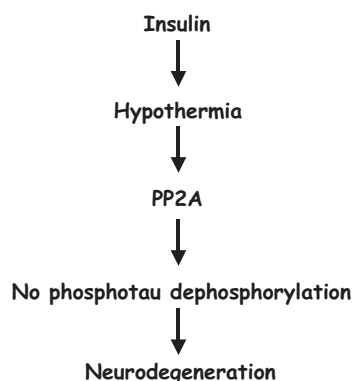


Figure 3. A reduced glucose metabolism could result in hypothermia, one condition that decreases PP2A phosphatase activity that is unable to dephosphorylate phosphotau.

facilitating the phosphorylation of tau by GSK3, although β -amyloid peptide in aggregated form could additionally facilitate the phosphorylation of tau by other kinases⁸.

Thus, in this short review I have tried to focus on one of the main differences between AD and other

tauopathies. This difference is that aging is the greatest risk factor for AD, that a failure in the insulin signal-transduction pathway could occur in aging, and that, based on this failure, the assembly of SPs and NFTs could be promoted. Finally, although the presence of SPs is not needed for tau aberrant aggregation, it could facilitate it.

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