Phosphorylated tau as a toxic agent in synaptic mitochondria: implications in aging and Alzheimer's disease

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From the Contents

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Abstract

During normal aging, there is a decline in all physiological functions in the organism. One of the most affected organs is the brain, where neurons lose their proper synaptic function leading to cognitive impairment. Aging is one of the main risk factors for the development of neurodegenerative diseases, such as Alzheimer's disease. One of the main responsible factors for synaptic dysfunction in aging and neurodegenerative diseases is the accumulation of abnormal proteins forming aggregates. The most studied brain aggregates are the senile plaques, formed by Aβ peptide; however, the aggregates formed by phosphorylated tau protein have gained relevance in the last years by their toxicity. It is reported that neurons undergo severe mitochondrial dysfunction with age, with a decrease in adenosine 5′-triphosphate production, loss of the mitochondrial membrane potential, redox imbalance, impaired mitophagy, and loss of calcium buffer capacity. Interestingly, abnormal tau protein interacts with several mitochondrial proteins, suggesting that it could induce mitochondrial dysfunction. Nevertheless, whether tau-mediated mitochondrial dysfunction occurs indirectly or directly is still unknown. A recent study of our laboratory shows that phosphorylated tau at Ser396/404 (known as PHF-1), an epitope commonly related to pathology, accumulates inside mitochondria during normal aging. This accumulation occurs preferentially in synaptic mitochondria, which suggests that it may contribute to the synaptic failure and cognitive impairment seen in aged individuals. Here, we review the main tau modifications promoting mitochondrial dysfunction, and the possible mechanism involved. Also, we discuss the evidence that supports the possibility that phosphorylated tau accumulation in synaptic mitochondria promotes synaptic and cognitive impairment in aging. Finally, we show evidence and argue about the presence of phosphorylated tau PHF-1 inside mitochondria in Alzheimer's disease, which could be considered as an early event in the neurodegenerative process. Thus, phosphorylated tau PHF-1 inside the mitochondria could be considered such a potential therapeutic target to prevent or attenuate age-related cognitive impairment.

Key Words: age pathology; aging; Alzheimer's disease; hippocampus; memory; mitochondria; PHF-1; phosphorylated tau; synaptic mitochondria; tau

Introduction

Aging is a natural process characterized by the progressive decrease of functions in tissues and organs, causing an increased risk of mortality (Sen et al., 2016). Among the characteristics of brain aging found aberrant neuronal activity (Reagh et al., 2018), dysregulation of calcium homeostasis, mitochondrial dysfunction (Olesen et al., 2020) and increased reactive oxygen species (ROS), finally all contributing cognitive deterioration (Chakravarti and Chakravarti, 2007). Diverse theories explain aging, one of the most prominent is the "free radical theory". This theory postulates that aging is a consequence of free radical overload, promoting lipid peroxidation of membranes, damage to DNA and proteins, and failure of mitochondrial function (Grimm and Eckert, 2017). However, although some studies show that overexpression of antioxidant enzymes causes an increase in longevity, other authors show a positive correlation between oxidative stress and longevity (Vina et al., 2013), possibly due to free radicals in a moderate concentration act as signalers, modulating different signaling pathways. Over the last decades it has become relevant the idea that damaged mitochondria accumulating over time may be responsible for the aging process; because mitochondria are the principal producer of ROS (Kowald, 2001). Although studies are still lacking to fully elucidate this theory, the current background could help to generate strategies to improve mitochondrial quality and function to reduce aging-related alterations.

During aging, there is an accumulation of diverse abnormal proteins in several brain regions, such as the phosphorylated tau protein (Harrison et al., 2019). Tau is abundant in the central nervous system (Binder et al., 1985) and specifically in neurons, predominantly in axons (Ittner and Gotz, 2011). Tau contains four repeat domains which bind to microtubules (R1–R4) (Tapia-Rojas et al., 2019) and participates in the assembly and stabilization of these structures (Mietelska-Porowska et al., 2014). Tau function is strictly regulated, mainly by post-translational modifications, such as phosphorylation (Barbier et al., 2019; Tapia-Rojas et al., 2019). Tau phosphorylation

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is controlled by a balance between the activity of kinases (such as glycogen synthase kinase-3 beta (GSK-3β) and CDK5, among others) and phosphatases (such as PP2A, and others), which in turn regulate tau binding to microtubules (Tapia-Rojas et al., 2019). However, in several neurogenerative diseases, such as tauopathies and Alzheimer's disease (AD) tau phosphorylation is drastically increased, which leads to tau hyperphosphorylation and disassemble of the microtubules (Barbier et al., 2019). Tau-microtubules interaction is greatly reduced by tau phosphorylation in residues located in the R1-R4 domains (Dickey et al., 2007). In addition, an important site of phosphorylation in tau related to pathologies is known as PHF-1 epitope (phospho-Ser396 and Ser404), since it induces synaptic damage (Mandelkow and Mandelkow, 2012), cognitive decline (Mondragon-Rodriguez et al., 2014) and it may contribute to the formation of intracellular deposits (Hefti et al., 2019). Thus, tau hyperphosphorylation promotes its cytoplasmic aggregation, may contribute to the formation of toxic oligomers and insoluble aggregates, leading to the development of neurodegenerative diseases (Barbier et al., 2019).

A clear relationship between phosphorylated tau and mitochondrial dysfunction has been described; however, the causality is still a matter of study. Overexpression of mutated forms of tau that favor its phosphorylation are related to abnormal mitochondrial distribution and mitochondrial dysfunction in neurons from mice models of tauopathies and AD (Kopeikina et al., 2011; Perez et al., 2018). However, the mechanism associated currently is unclear. Neurons are polarized cells; therefore, mitochondria are classified into synaptic and non-synaptic mitochondria (Graham et al., 2017). Synaptic mitochondria include those located in both pre and postsynaptic regions (Graham et al., 2017); and synaptic mitochondrial dysfunction has been associated with neuronal failure in diverse diseases including AD (Attwell and Laughlin, 2001). Therefore, phosphorylated tau could be a key factor promoting synaptic mitochondrial dysfunction in aging and age-related pathologies. In fact, we and other laboratories have observed an early decrease in bioenergetic and calcium buffering function in aged hippocampal synaptic mitochondria compared with non-synaptic mitochondria (Lores-Arnaiz et al., 2016; Olesen et al., 2020). This mitochondrial failure could be caused by the interaction between phosphorylated tau with several mitochondrial proteins (Manczak and Reddy, 2012a, b), or by our recent finding that demonstrated for the first time that phosphorylated tau PHF-1 accumulates within the mitochondria during aging, both in the intermembrane space and with a minor proportion in the mitochondrial matrix, preferentially into mitochondria located in the synapses (Torres et al., 2021). With these and other antecedents is possible to suggest that age-related synaptic mitochondrial deterioration in aging and neurodegenerative diseases could be, almost in part, by the accumulation of tau PHF-1 in the mitochondria, which in turn may lead to synaptic failure and cognitive decline (Torres et al., 2021).

In this review, we mention how post-translational modifications, mainly tau phosphorylation promotes mitochondrial dysfunction, as well as the possible mechanism(s) involved. In addition, we mention and discuss evidence from our laboratory showing that tau PHF-1 accumulates within synaptic mitochondria, suggesting that it may contribute to synaptic and ultimately cognitive impairment in aging. More relevant, we show new evidence that tau PHF-1 also accumulates in mitochondria in a mouse model of AD, thus we also discuss that tau PHF-1 accumulation in the mitochondria could be an early event during the neurodegenerative process in AD. This could have a great impact on the search for new therapeutic targets, that help prevent or attenuate cognitive deterioration during aging as well as the development of neurodegenerative diseases, such as AD.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed (from 1975 to 2021), using various keywords related to "phosphorylated tau and mitochondria" and "phosphorylated tau and synaptic failure" in both aging and AD. Only papers published in English were reviewed.

Post-Translationally Modified tau Protein: from Function to Pathology

Tau is a protein of the family of microtubule-associated proteins (MAPs) (Weingarten et al., 1975; Perez et al., 2018). In the human's central nervous system, tau is encoded by a single gene MAPT situated on the long arm of chromosome 17 (17q 21) (Perez et al., 2018; Tapia-Rojas et al., 2019). This gene contains 16 exons that by alternative splicing of exons 2, 3, and 10 renders six different tau isoforms containing either three or four microtubule-binding domains: 0N/3R, 0N/4R, 1N/3R, 1N/4R, 2N/3R, and 2N/4R, in which "R" represents the number of microtubules repeats and "N" indicates the number of N terminal inserts (Guo et al., 2017; Kang et al., 2020). Tau protein was discovered by Weingarten et al. in 1975, which was identified as a crucial protein promoting microtubules stabilization (Weingarten et al., 1975). Tau is mainly an intracellular protein, though recent evidence shows that it is also actively secreted with functions and implications still not well understood (Dong et al., 2021; Lussier et al., 2021). In mature neurons, tau is present to great extent in axons, with minimal presence in soma and dendrites (Zempel et al., 2017; Ittner and Ittner, 2018); and its function regulating microtubules dynamics supports neuronal development (Barbier et al., 2019), neuronal polarity (Zempel et al., 2017), axonal transport (Dixit et al., 2008), and other processes involving the cytoskeleton (Dixit et al., 2008; Tapia-Rojas et al., 2019).

For its proper function, tau phosphorylation requires an equilibrium between kinases and phosphatases (Tapia-Rojas et al., 2019). Tau is phosphorylated by kinases, such as MAPK, PKA, system CDK5/p35, and GSK3β, among others, and these post-translational modifications regulate their ability to associate with microtubules and other cytoskeletal filaments (Tapia-Rojas et al., 2019). In contrast, one of the causes for tau dysfunction is excessive phosphorylation in specific sites, predominantly in serine or threonine (Ser/Thr) residues followed by a proline (Pro), such as pSer202/pT205, Ser212/Thr214, Ser262, and Ser396/404 (Augustinack et al., 2002; Tapia-Rojas et al., 2019). In neurodegenerative diseases, tau is hyperphosphorylated in crucial sites, which favor the loss of tau binding ability to microtubules, modifies its secondary structure, the charges distribution, and their intramolecular interactions, which contribute to its auto-aggregation that result in aberrant conformational and functional modifications (Augustinack et al., 2002). Progressive hyperphosphorylated tau aggregation leads to the formation of soluble aggregates, such as oligomers, and insoluble deposits, including paired helical filaments (PHFs) and neurofibrillary tangles, one of the main neuropathological hallmarks of AD (Lasagna-Reeves et al., 2012). Tau disassembly of microtubules and its accumulation also cause destabilization of the cytoskeleton network and interruption of axonal transport (Perez et al., 2018), including mitochondrial transport, depleting the synapses of functional mitochondria, and inducing synaptic dysfunction and eventually cell death (Guo et al., 2017; Jara et al., 2020).

Although phosphorylation is considered as one of the most numerous posttranslational modifications of tau, also suffers other posttranslational modifications. Tau is also a substrate of methylation, acetylation, ubiquitination, nitration, sumoylation, and caspases cleavage, among others (Tapia-Rojas et al., 2019; Alquezar et al., 2020). All these modifications may differentially regulate tau function (Wesseling et al., 2020). For example, lysine methylation regulates tau metabolism by competing with ubiquitylation and acetylation directing tau turnover (Balmik and Chinnathambi, 2021). Besides, methylation in specific residues, such as K267 and K290 assists in the stability of tau and has a protector effect, because it prevents tau phosphorylation and aggregation (Funk et al., 2014; Huseby et al., 2019). An oppositive effect is observed if residues like Lys24 and Lys44 (that are normally methylated) are acetylated since they favor tau hyperphosphorylation and aggregation as found in PHFs (Funk et al., 2014; Kontaxi et al., 2017). Therefore, a decrease in acetylation in these residues can have a neuroprotective role and beneficial consequences including microtubule stabilization (Cook et al., 2014b; Cook et al., 2014a). In contrast, decreasing HDAC6 activity and therefore inducing the acetylation in KXGS motifs (conserved motif located in the R-domains that comprises Ser262, Ser293, Ser324, and Ser356 phosphorylation, regulating tau-mediated microtubule assembly) (Kolarova et al., 2012) inhibits tau phosphorylation and reduces potential aggregation (Cook et al., 2012, 2014b).

Proteomic studies with samples of both healthy and AD brains have shown that several posttranslational modifications are present just in AD brains, including majority phosphorylated, ubiquitinated, acetylated, and in fewer degree methylated specific residues (Alquezar et al., 2020; Wesseling et al., 2020). Phosphorylation is predominant in the proline-rich region of tau, as well as its C-terminus. Besides, truncation of the C-terminus of tau, following by the microtubule-binding domain, was also a feature of AD

brains (Wesseling et al., 2020). Curiously, both ubiquitination and acetylation in the microtubule-binding domain (R-domains) are specific changes occurring in AD (Wesseling et al., 2020) that could be promoting aggregation propensity (Sohn et al., 2016; Tapia-Rojas et al., 2019). Studies suggest that ubiquitination is more predominated in the R1–R3 domain and acetylation in the R4 domain (Wesseling et al., 2020). Therefore, altogether these observations suggest that the phosphorylation could start with an early pre-symptomatic period of disease, and enhance up over time, other later modifications could stimulate hyperphosphorylation and aggregation as occurring in symptomatic stages of AD and tauopathies.

Interestingly, tau phosphorylation also has been described in normal aging (Rodriguez-Callejas et al., 2020; Torres et al., 2021). These abnormal forms of tau lead to alterations in mitochondrial structure and function, accompanied by neuronal dysfunction and alterations in synaptic communication in absence of any pathological condition (Jara et al., 2020; Torres et al., 2021), suggesting that accumulation of tau phosphorylation could trigger a cascade of event that culminates in age-related cognitive deficit. Studies in diverse models and at different aging stages have shown that tau phosphorylation increase along with aging in non-demented aged brains (Gil et al., 2017; Rodriguez-Callejas et al., 2020). Studies using Positron Emission Tomography scan detecting tau found an increase in phosphorylated tau in older individuals, related to initial changes in memory impairment (Marks et al., 2017; Ziontz et al., 2019). Thus, for example, phosphorylated tau at Thr212 and Ser214 (recognized by AT100 antibody) has an age-related increase in human hippocampal cells (Gil et al., 2017). In the same way, it is reported that tau PHF-1 accumulates during aging in the hippocampus (Torres et al., 2021), suggesting that tau phosphorylation (and eventually hyperphosphorylation) started during normal aging and could be an early marker of AD predisposition.

Abnormal tau Interaction with Mitochondrial Proteins

Abnormal interactions between tau protein, especially its phosphorylated form, with different proteins have been described (Liu et al., 2016). Within membrane-bound proteins that interact with tau, nearly 40% are mitochondrial proteins, being the largest fraction (Liu et al., 2016). In the same way, one of the most enriched pathways containing tau-interacting proteins is mitochondrial dysfunction, suggesting an important relation between tau and mitochondria (Liu et al., 2016). An interactome study of phosphorylated tau at epitope PHF-1 showed that tau PHF-1 interacts with several mitochondrial proteins (Drummond et al., 2020). One of these proteins is dynamin-related protein (Drp1), which mediates mitochondrial fission through its oligomerization into membrane-associated tubular structures that constrict and sever the mitochondrial membrane (Koirala et al., 2013). Studies using post-mortem brains of AD patients and brain samples of the murine AD model 3xTg (mutations APPswedish, MAPT P301L, and PSEN1 M146V) showed the interaction between phosphorylated tau and Drp1. Co-immunoprecipitation assays showed that this interaction increases the GTPase activity of Drp1 in both the frontal cortex of AD patients and cortical tissues of 3xTg mice, suggesting an increase in mitochondrial fission, which could lead to mitochondrial dysfunction and oxidative stress in mitochondria, resulting in neuronal damage (Manczak and Reddy, 2012a). Nevertheless, how phosphorylated tau induces the increase in the activity of Drp1 is still not well understood and more studies are required to clarify the effect of this abnormal interaction on exacerbated mitochondrial fragmentation, and neuronal dysfunction.

In the outer mitochondrial membrane, the voltage-dependent anion channel 1 (VDAC1) contributes to maintaining cellular Ca^{2+} homeostasis, by mediating the transport of Ca^{2+} in and out of mitochondria (Shoshan-Barmatz et al., 2017) and thus preventing Ca^{2+}-mediated apoptosis (Giacomello et al., 2007). Moreover, VDAC1 allows the entry of metabolites as pyruvate, malate, succinate, nucleotides, NADH, and cholesterol into the mitochondria (Shoshan-Barmatz et al., 2010). Thus, VDAC1 appears to be a convergence point for a variety of cell survival and death signals. VDAC1 is another mitochondrial protein reported interacting with phosphorylated tau in postmortem brains of AD patients and the 3xTg AD mice (Manczak and Reddy, 2012b). In addition, the VDAC levels are increased in the cortical tissues from AD patients compared with control subjects (Manczak and Reddy, 2012b). This abnormal interaction between VDAC and phosphorylated tau could explain the alterations in the pattern of interactions of VDAC with its regulators, in addition to the hyperphosphorylated state of the channel and the impairment in its conductance reported in pathological conditions (Kerner et al., 2012; Lemasters et al., 2012). However, this idea has not been studied.

Recently, new important interactions of phosphorylated tau with mitochondrial proteins had been described (Drummond et al., 2020). Several proteins of the electron transport chain co-immunoprecipitate with tau PHF-1, including subunits of cytochrome-c oxidase, NADH ubiquinone oxidoreductase 75KDa subunit, adenosine triphosphate (ATP) synthase subunit beta (ATP5B), subunit O (ATP5O), subunit delta (ATP5D), subunit gamma (ATP5C1), subunit d (ATP5H), subunit g (ATP5L) and ATP synthase-coupling factor 6 (ATP5J) (Drummond et al., 2020). Subunits of ATP synthase and cytochrome-c oxidase complex interacting with tau PHF-1 could explain the bioenergetics mitochondrial dysfunction observed in neurodegenerative disorders and aging, evidenced by an increase in ROS generation and decrease of ATP production (Grimm and Eckert, 2017; Jara et al., 2019; Olesen et al., 2020). Similarly, in isolated neurofibrillary tangles from AD patients, an association with the ATP synthase alpha-chain (ATP5a1) was described (Sergeant et al., 2003). The accumulation of ATP5a1 with tau aggregates in the cytosol is observed even in the early stages of the neurofibrillary process (Sergeant et al., 2003). As ATP5a1 is a nuclear-encoded mitochondrial protein, its accumulation in the cytosol could lead to an inefficient import to the mitochondria, contributing to failure in the functionality of complex V (Sergeant et al., 2003). However, none of these ATP synthase subunits were confirmed to be interacting with tau by biochemical assays in addition to interactomics assay, making them interesting targets to better elucidate the impact of tau and its pathological species in neuronal energy homeostasis.

Among other ways to disrupt the mitochondrial ATP production, tau may act interfering with the function of the adenine nucleotide translocator (ANT), possibly through interaction between ANT and the N-terminal region of tau (Atlante et al., 2008). Electron transport chain function was dramatically impaired by NH(2)-26-44 tau fragment, through completely preventing ADP/ATP exchange by ANT (Atlante et al., 2008). Therefore, tau could be affecting mitochondrial ATP production through a direct effect on ADP/ATP translocase ANT in neuropathological diseases and aging. Proteins of the tricarboxylic acid cycle also are present in cytosolic neurofibrillary tangles microdissected from the brain of AD patients (Drummond et al., 2020), such as aconitate hydratase 2. Aconitate hydratase 2 is an enzyme that catalyzes the stereo-specific isomerization of citrate to isocitrate and whose activity and expression is diminished in blood samples of AD and mild cognitive impairment patients compared to older adults with normal cognition (Mangialasche et al., 2015), therefore, modified tau could also interfere with previous stages to oxidative phosphorylation, limiting the availability of oxidative substrates.

The increasing evidence of phosphorylated and/or other modified tau forms interacting with mitochondrial proteins suggests that abnormal tau has an important role in the mitochondrial dysfunction seen during aging and in AD. Although further investigations are needed to elucidate the mechanism underlying these interactions, they are important data for searching new therapeutic targets that contribute to the improvement of mitochondrial function and thus the aging and AD phenotype.

Phosphorylated tau and Its Effects on Mitochondrial Function: Possible Mechanisms

It is clear that phosphorylated tau triggers a deleterious effect on mitochondrial function; however, the mechanism involved is not completely known. Thus, phosphorylated tau could act controlling and presumably damaging the mitochondrial transport, dynamics, mitophagy, and function.

Primary neurons from the APP transgenic mice model of AD present Aβ-mediated deficits in anterograde axonal transport of mitochondria (Kopeikina et al., 2011; Schulz et al., 2012; Rodriguez-Martin et al., 2016); however, these defects are prevented by tau ablation. Mechanistically Aβ would activate GSK-3β, which in turn phosphorylates tau blocking axonal transport, more severely inhibiting anterograde than retrograde transport (Vossel et al., 2015). This idea is supported by assays of tau overexpression, which reduces the anterograde mitochondrial movement in neurons (Stamer et al., 2002). In fact, tau phosphorylation at Ser199, Ser202 and Thr205 residues (epitope AT8) have a more significant effect blocking

mitochondrial transport compared with non-phosphorylated tau (Stamer et al., 2002); similar to observed in cells SH-SY5Y stably overexpressing either human WT tau, or the P301L tau mutation that favor tau hyperphosphorylation and aggregation (Schulz et al., 2012), and in rTg4510 mice overexpressing P301L mutation (Kopeikina et al., 2011). Therefore, tau phosphorylation impedes mitochondrial transport (Rodriguez-Martin et al., 2016) and mainly anterograde transport, by increasing the distance among the microtubules (Shahpasand et al., 2012) and by direct tau interaction with kinesin-1 (Dubey et al., 2008; Kanaan et al., 2011), an interaction that is regulated by GSK-3β-mediated tau phosphorylation (Cuchillo-Ibanez et al., 2008; Kanaan et al., 2011). Thus, this could explain, almost in part, the perinuclear localization of the mitochondria (Dubey et al., 2008; Shahpasand et al., 2012; Rodriguez-Martin et al., 2016), the reduced number of axonal mitochondria (Rodriguez-Martin et al., 2016), and because the synapses are depleted of mitochondria in the hippocampus and cortex of AD patients (Pickett et al., 2018). In contrast, diverse reports propose that phosphorylation of tau by GSK-3β increases mitochondrial movement toward the synapses in hippocampal neurons of a chronic stress mouse model or *in vitro* using primary hippocampal neurons (Zhang et al., 2012). In concordance with the anterior, overexpression of GSK-3β in primary cultures enhances the movement of mitochondria in the axons, an effect that is not observed when tau is depleted (Llorens-Martin et al., 2011); whereas inhibition of GSK-3β by lithium reduces mitochondrial movement (Zhang et al., 2012). Then, is highly probable that tau regulates mitochondrial transport to and from the synapse in response to fine control of its phosphorylation state and GSK-3β activity, with a dual effect depending on its grade of phosphorylation.

Additionally, mitochondria are highly dynamic organelles, which respond to environmental stimulus, through events of mitochondrial fusion and fission (Tilokani et al., 2018). It is known that *in vitro* overexpression of human tau promotes mitochondrial fusion (DuBoff et al., 2012; Li et al., 2016), accompanied by increased levels of the fusion proteins Mitofusins 1 and 2 (Mfn1 and Mfn2) and Opa1, generating longer and dysfunctional mitochondria that accumulate in the perinuclear region (DuBoff et al., 2012; Li et al., 2016); effects that are prevented using shRNA to Mfns (Li et al., 2016). A more increased mitochondrial fusion was observed when the mutant tau R406W highly prone to hyperphosphorylation, or the pseudo-hyperphosphorylated tau were expressed, almost in part due to mislocation of Drp1 (DuBoff et al., 2012). In addition, tau mutated in P301L block mitochondrial fission and fusion, possibly as a consequence of reduced levels of fusion and fission proteins: Mfn1 and Opa1, as well as Fis1 and Drp1 respectively (Schulz et al., 2012). Therefore, phosphorylated tau alters mitochondrial dynamics, producing an imbalance between fission and fusion events that favor the appearance of elonged mitochondria, incapable to be transported to synaptic sites; this last due to mitochondria present in synaptic sites need to be smaller (Seager et al., 2020).

On another hand abnormal tau also impairs mitophagy, overexpression of WT human tau reduces the transport of autophagosomes and the levels of Parkin in the mitochondria (Amadoro et al., 2014; Hu et al., 2016). Also, tau mutations that mimic phosphorylation at Thr231 and acetylation at Lys274 and Lys281 inhibit mitophagy (Guha et al., 2020). In AD brains, mitophagy defects also are observed, indicated by increased levels of COX IV, TOMM20, and the ratio of mtDNA to genomic DNA, but these mitophagy alterations only are detected when tau levels are increased in AD brains (Hu et al., 2016). Mechanistically, tau increased autophagy flux by enhancing the degradation phase; however, both human wild-type (hTau) and more severely the mutant tau P301L inhibit mitophagy, by tau sequestration of Parkin in the cytosol and ultimately impairing Parkin translocation to the mitochondria (Cummins et al., 2019), which contribute to the accumulation of damaged mitochondria.

Considering that mitochondrial transport, dynamics, and mitochondrial turnover are key events for the proper mitochondrial function (Seager et al., 2020), is logical to think that tau affects mitochondrial functionality. In fact, overexpression of a pseudo-phosphorylated tau PHF-1 in primary cultures reduces the mitochondrial membrane potential (Quintanilla et al., 2014), similar to observed by overexpression of human WT tau (Li et al., 2016), or in a mouse model of Down's Syndrome with hyperphosphorylated tau (Esteras et al., 2017), with reduced ATP production and ATP/ADP ratio, inhibition of the complex I activity and ROS production (Li et al., 2016). In addition, *in vitro* overexpression of tau P301L, a tau highly prone to hyperphosphorylation, reduces ATP, mitochondrial membrane potential and the activity of the complex I (Schulz et al., 2012); whereas in P301L transgenic mice from 12-month-old, the observations previously described are accompanied by a loss of activity in the complex V, and a major severity of the mitochondrial function according to the mice aged, reducing basal respiration and more increased ROS production (David et al., 2005). This could be explained, almost in part, by the interaction of tau with diverse mitochondrial proteins, such as different subunits of the ATP synthase in the complex V (Liu et al., 2016; Drummond et al., 2020). However, considering that the proteomic and interactomics assays are performed in tissue lysates, still is unclear if the negative effects of tau on the mitochondrial function are indirect or by direct interaction with the mitochondria, for example, due to tau is imported to mitochondria, explaining our recent finding showing phosphorylated tau PHF-1 inside mitochondria during aging (Torres et al., 2021). More detailed studies are necessary to understand how phosphorylated tau affects these and other mitochondrial functions.

Despite the questions, it is known that the absence of tau is protective or beneficial for mitochondrial function. Tau deletion in wild-type mice improves mitochondrial functionality, reducing ROS generation and increasing ATP production in young mice, enhancing your attention and exploratory capacity (Jara et al., 2018), as well as preventing memory loss in stressed animals (Lopes et al., 2017), or preserving the mitochondrial function in the hippocampus of aged animals (Jara et al., 2020). Thus, the absence of tau and thus its hyperphosphorylation could attenuate the mitochondrial damage observed at advanced age and reduce the risk of developing neurodegenerative diseases, such as AD. Thus, the great challenge is to describe the precise mechanism(s) involved in phosphorylated tau-mediated mitochondrial dysfunction.

Tau Accumulation in Synaptic Mitochondria: Contribution to Synaptic Failure and Cognitive Impairment

Despite that phosphorylated forms of tau are described to interact with mitochondrial proteins with possible negative effects on mitochondrial function, the form by which tau influence mitochondrial function is still unclear. All the studies focused on the effect of tau on the mitochondria describe a correlation between the presence of abnormal tau and mitochondrial dysfunction, corroborating an impact of tau in mitochondrial functions (Grimm et al., 2016; Szabo et al., 2020). However, if tau-mediated mitochondrial damage is triggered by a direct or indirect mechanism is still a mystery. In neurons, mitochondrial function is particularly relevant, because in these cells, there are two mitochondrial populations: synaptic mitochondria and non-synaptic mitochondria. The first are the ones located in the synapses, both in pre-synaptic and post-synaptic regions, and the latter are the mitochondria located in soma and axon (Stauch et al., 2014). It is reported that mitochondria moved along the axon through cellular trafficking, which allows them to reach the synaptic region (Schwarz, 2013). In this region, mitochondria provide ATP for the neurotransmitter release and act buffering the calcium that enters the neuron during the synapsis process (Cai and Tammineni, 2017). Interestingly, synaptic mitochondria are described to be more susceptible to damage and in aging are reported to fail earlier than non-synaptic mitochondria in both hippocampus and cortex (Stauch et al., 2014; Olesen et al., 2020). During aging, there is an increase in dysfunctional synaptic mitochondria in the presynaptic and postsynaptic zone of the hippocampus, shown as an increase in swollen mitochondria and a decrease in intact mitochondria (Rybka et al., 2019; Torres et al., 2021). Also, we previously reported that synaptic mitochondria of the hippocampus of aged mice had a severe reduction in ATP production, accompanied by an overproduction of ROS and a major susceptibility to calcium overload which correlates with memory loss in these animals (Olesen et al., 2020). This strongly suggests that the functionality of synaptic mitochondria is very important for memory and cognitive processes; however, the factor(s) responsible for this sensitivity and early dysfunction is unknown.

Relevantly, a deficit in synaptic mitochondrial oxidative capacity both in the hippocampus and cortex from the 3xTg AD mice model was reported (Espino de la Fuente-Munoz et al., 2020). The bioenergetic function of synaptic mitochondria of these mice was age-related decreased, at the same time that phosphorylated tau

in mitochondria from synaptosomes was increased observed by transmission electron microscopy (Espino de la Fuente-Munoz et al., 2020), suggesting a possible direct effect of tau on mitochondrial function. More importantly, in a recent study of our laboratory, we showed data that strongly suggest that phosphorylated tau have a direct impact on mitochondria, specifically on synaptic mitochondria. We demonstrate by biochemical and immunogold assays that the phosphorylated form of tau PHF-1 is located inside hippocampal synaptic mitochondria in young and old mice, with a higher accumulation of tau PHF-1 in mitochondria of aged mice (Torres et al., 2021). We showed clear evidence that tau PHF-1 accumulates mainly in the intermembrane space with a minor proportion in the mitochondrial matrix (Torres et al., 2021). These results suggest that during aging occur an imbalance between tau phosphorylation and degradation that leads to tau disassembly of microtubules and the accumulation of tau PHF-1 in the cytosol and cytoplasmic structures, including the mitochondria in absence of pathology, which could contribute to the early failure of these pools of mitochondria during aging. Therefore, we hypothesize that the accumulation of tau PHF-1 in the synaptic mitochondria could be contributing to the synaptic impairment and cognitive decline in a non-pathological aged organism (**Figure 1**); however, this hypothesis needs to be probed in further studies.

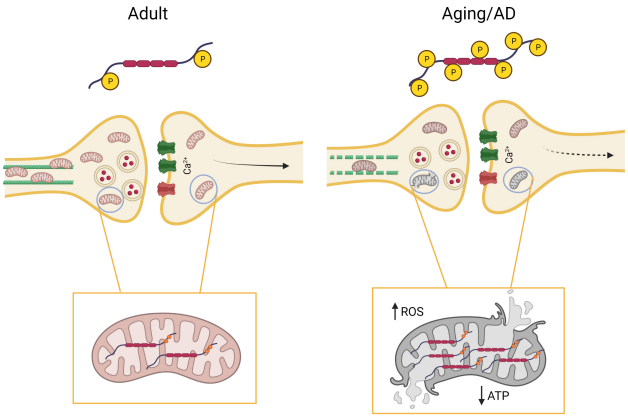

Figure 1 | Accumulation of tau PHF-1 in synaptic mitochondria impairs synaptic transmission.
Schematic representation of the proposed hypothesis that the accumulation of tau PHF-1 in synaptic mitochondria in a context of hyperphosphorylated tau, like aging and AD, leads to mitochondrial dysfunction in synapses and therefore to impairment in synaptic transmission, thus explaining the memory deficit. AD: Alzheimer's disease; ATP: adenine triphosphate; Ca^{2+}: calcium ion; ROS: reactive oxygen species.

Thus, the relationship between tau and synaptic mitochondria is gaining relevance lately. A recent study in tau transgenic mice overexpressing human tau (hTau) showed increased accumulation of tau only in synaptic mitochondria of 5- and 8-month-old mice, while in non-synaptic mitochondria there are no changes in tau levels (Trease et al., 2021). Surprisingly, tau PHF-1 was the most prominent phosphorylated form of tau accumulating in the synaptic mitochondrial fraction of these transgenic mice (Trease et al., 2021), supporting the idea that tau PHF-1 has a direct impact on synaptic mitochondrial functioning. Moreover, tau phosphorylated in Ser202 also is associated, but to a lesser extent, with synaptic mitochondria (Trease et al., 2021), suggesting that tau phosphorylated in PHF-1, accompanied or not of other phosphorylated residues, enter mitochondria; but this need to be probed.

Finally, it is known that aging is the main risk factor for developing Alzheimer's disease (AD). Also, the mitochondrial dysfunction present during aging is similar to the observed in the early stages of AD (Abate et al., 2020), which suggests that this impairment in aged mitochondria could be a marker of AD predisposition. It is reported that in AD patients, there are several changes in synaptic mitochondria morphology and a 4-fold decrease of pre-synaptic terminals with multiple mitochondria (Pickett et al., 2018). Also, it is reported that synaptic mitochondria are an early target of Aβ peptides, which could contribute to its failure (Mungarro-Menchaca et al., 2002; Du et al., 2010). Surprisingly, we observed that the accumulation of tau PHF-1 in aged mice is also observed in 15-month-old SAMP8 mice (**Figure 2**), a mouse model of AD at this age (Liu et al., 2020). SAMP8 developed an AD-like phenotype from 10 months of age, indicated by the apparition of Aβ plaques, hyperphosphorylated tau, and cognitive impairment, among others (Liu et al., 2020). Therefore, this result strongly suggests that the entrance of tau PHF-1 to mitochondria occurring during aging, also may be occurring in AD, but this needs major confirmation. All these results support the idea that synaptic mitochondrial dysfunction could be an early marker of AD predisposition and also proposed the accumulation of modified forms of tau (specially PHF-1 tau) as a new marker of early stages of AD. It is reported that abnormal forms of tau spread between neurons transynaptically (DeVos et al., 2018), which may increase the probability of synaptic mitochondria to become in contact with abnormal tau, making them more vulnerable to mitochondrial damage.

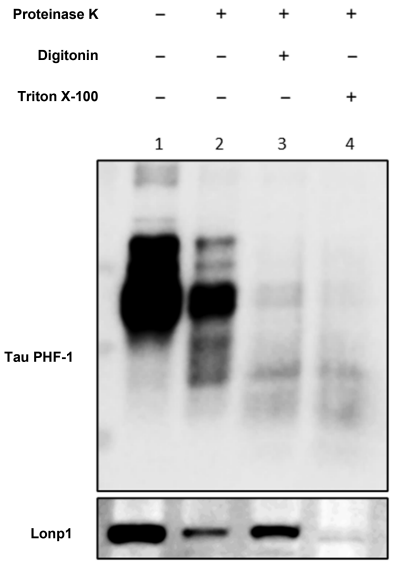

Figure 2 | Tau PHF-1 enters hippocampal mitochondria in SAMP8 mice.
Western blot assay of the proteinase K protection assay in a mitochondrial fraction of the AD mice model Senescence Accelerated Mouse Prone 8 (SAMP8, 15-month-old). The mitochondrial fraction was treated with Proteinase K with or without 0.1% Digitonin (Lane 3) or 1% Triton X-100 (Lane 4). The mitochondrial fraction without Proteinase K was used as a control (Lane 1). Western blot of 1/3 of the volume of sample. Lonp1: LON peptidase 1; Tau PHF-1: Tau phosphorylated in PHF-1 epitope (Serine 396 and Serine 404). Unpublished data.

Future Directions and Conclusion

Nowadays, the relation between phosphorylated tau and mitochondria is gaining relevance, since recent studies suggest that this protein may have a direct effect on mitochondrial function. Several investigators have shown a correlation effect between abnormal tau and dysfunctional mitochondrial in different models of tauopathies, including AD. However, thanks to our study now it is demonstrated that phosphorylated tau enters mitochondria, specifically to synaptic mitochondria, where it may directly impair its functionality, leading to synaptic failure and finally to deficits in cognitive abilities. More importantly, this direct effect is demonstrated in physiological aging and strongly suggested in a mouse model of AD. Nevertheless, the mechanism of how this phosphorylated form of tau could enter synaptic mitochondria and whether this entrance is a cause or a consequence of mitochondrial dysfunction is still a matter of investigation. Anyway, this sets a precedent about phosphorylated tau mislocalization and eventually could be used as a potential therapeutic target to prevent mitochondrial dysfunction in aging and related diseases.

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