
The Cascade of Oxidative Stress and Tau Protein Autophagic Dysfunction in Alzheimer's Disease

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<http://dx.doi.org/10.5772/59980>

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly and a chronic neurodegenerative disease characterized by widespread degeneration of neurons. An estimated 37 million people worldwide currently have AD, which is estimated to increase to 65.7 million by 2030 and 115.4 million by 2050 [1]. It is a growing health concern in society because patients suffer from progressive functional impairments, emotional distress, loss of independence, and behavioral deficits. AD is characterized by the presence of two types of neuropathological hallmarks: senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs). SPs predominantly consist of extracellular amyloid β -peptide ($A\beta$) deposits. NFTs are formed by intraneuronal aggregation of hyperphosphorylated tau. The amyloid cascade hypothesis theory proposes a dysregulation of amyloid precursor protein processing. This event leads to AD pathogenesis, which involves the aggregation of $A\beta$ (particularly $A\beta_{42}$), neuritic plaque formation, and consequently the formation of NFTs followed by the disruption of synaptic connections, neuronal death, and cognitive deficits (dementia) [2]. Increasing evidence suggests that $A\beta$ oligomers may be the primary cause of AD because they have a greater correlation with dementia than insoluble $A\beta_{42}$. $A\beta$ also plays a crucial role in inducing neuronal oxidative stress [3]. $A\beta$ -mediated mitochondrial oxidative stress causes hyperphosphorylation of tau in AD brains [4, 5]. Mounting evidence clearly links tau to neurodegeneration, indicating that tau hyperphosphorylation may be the necessary link in neural dysfunction and death. However, whether autophagic dysfunction is involved in neuronal death during this event still remains unknown. Recent studies have indicated the importance of defective autophagy in the pathogenesis of aging and neurodegenerative diseases, especially in AD. Autophagy may increase the formation of autophagosome in AD, and autophagic

dysfunction may induce the pathogenesis of AD, particularly at the late stage of AD [6]. However, the relationship between oxidative stress, tau protein hyperphosphorylation, autophagic dysfunction and neuronal cells death in AD remains elusive. In this review, we summarize the latest progress in research focused on oxidative stress, tau hyperphosphorylation, and autophagic dysfunction, and their relationship with AD.

2. Oxidative stress in AD

Oxidative stress appears to be one of the earliest events and a major determinant of the pathogenesis and progression in AD. In experimental models and human brain studies of AD, oxidative stress has also been shown to play an important role in neuronal degeneration [7]. Several risk factors for AD may cause or promote oxidative damage, such as advanced age, apolipoprotein E (APOE) $\epsilon 4$ alleles [8], medical risk factors, environmental and lifestyle-related risk factors and so on. Generally, oxidative stress is caused by the imbalance between reactive oxygen species (ROS) ($O^{\cdot -}$, H_2O_2 and OH), which associated with both the chronic formation of ROS derived from the mitochondrial electron transport chain and the acute and high output formation of ROS derived from nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and the breakdown of chemically reactive species, by reducing agents and antioxidant enzymes, such as superoxide dismutase (SOD). This disequilibrium may result from disease, stressors, or environmental factors. High ROS levels lead to the accumulation of oxidized proteins, lipids, and nucleic acids due to mitochondrial dysfunction, increased metal levels, inflammation, and $A\beta$ peptides, thereby directly impairing cellular function if not be removed or neutralized [9]. Oxidative damage to cellular components is likely to result in the alteration of membrane properties, such as fluidity, ion transport, enzyme activities, protein cross-linking, and eventually cell death.

Structurally and functionally damaged mitochondria are more proficient at producing ROS [10]. Mitochondrial dysfunction may be an initial trigger for enhanced $A\beta$ production during the aging process [11]. Oxidative stress can promote $A\beta$ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons in the development of AD. Several studies suggest that ROS are involved in $A\beta$ fibrillization and NFT formation in AD and increases with $A\beta$ and NFT pathology in AD. Both soluble and fibrillar $A\beta$ may further accelerate oxidative stress, as well as mitochondrial dysfunction [12-14]. The transgenic (Tg) Thy1-APP751 (SL) mouse model of AD shows increased proteolytic cleavage of APP, increased production of $A\beta$, and impaired Cu/Zn-SOD activity [15]. Furthermore, oxidative stress is considered as a primary factor of NFT formation in AD. However, the relationship between oxidative stress and tau hyperphosphorylation remains unclear. Okadaic acid is used as a research model to induce tau phosphorylation and neuronal death in AD. Oxidative stress combined with Okadaic acid results in tau hyperphosphorylation [16], and mitochondrial SOD_2 deficiency also increases the levels of Ser396 phosphorylated tau in the Tg2576 mouse model of AD [4].

3. Tau protein in AD

3.1. Tau protein physiology and pathology

Tau protein (known as neuronal microtubule associated protein tau) plays a large role in the outgrowth of neuronal processes and the development of neuronal polarity. Tau protein in the central nervous system is predominantly expressed in neurons [17, 18], with its main function to promote microtubule assembly, stabilize microtubules, affect the dynamics of microtubules in neurons [19, 20], and inhibit apoptosis [21], particularly in axons [22, 23]. However, recent reports suggest that excess intracellular tau is released into the extracellular culture medium via membrane vesicles [24]. In the adult human brain, tau consists of six isoforms, and the tau gene contains 15 exons. The isoforms are generated by alternative splicing of exons 2, 3, and 10. Depending on the alternative splicing of exon 10, tau isoforms are termed 4R (with exon 10) or 3R (without exon 10). N-terminal exon (tau 1N), two N-terminal exons (tau 2N), or no N-terminal exons (tau 0N) at the N-terminal inserts mainly depend on the inclusion of exon 2, exon 2 and 3, or the exclusion of both. Biochemical analysis of postmortem AD brains indicate that 4R-tau is more abundant than 3R in isolated NFTs [25].

Tau protein normally stabilizes axonal microtubules in the cytoskeleton and plays a vital role in regulating the morphology of neurons. It has more than 30 phosphorylation sites. When tau is abnormally hyperphosphorylated, it destabilizes microtubules by decreasing the binding affinity of tau and resulting in its aggregation in NFTs. NFTs are composed of paired helical filaments (PHF) of abnormally hyperphosphorylated tau. The severity of dementia in AD was shown to correlate well with NFT load. In the transgenic mouse model, conditionally expressing the human tau P301L mutant, age-related NFTs develop, along with neuronal loss and behavioral impairment. After the suppression of transgenic tau, memory function recovered, and neuron numbers stabilized [26]. The pathogenesis of tau-mediated neurodegeneration is unclear but hyperphosphorylation, oligomerization, fibrillization, and propagation of tau pathology has been proposed as the likely pathological processes that induces the loss of function or gain of tau toxicity, which caused neurodegeneration [27]. Tau phosphorylation has been investigated at AD-related sites by using recombinant human tau phosphorylated by DNA damage-activated checkpoint kinase 1 (Chk1) and checkpoint kinase 2 (Chk2) in vitro [28]. This study identified a total of 27 Ser/Thr residues as Chk1 or Chk2 target sites. Among these sites, 13 sites have been identified to be phosphorylated in AD brains [29]. The generation of a Tg mouse line overexpressing human tau 441 via V337M and R406W tau mutations has been shown to accelerate the phosphorylation of human tau, inducing tau pathology and cognitive deficits [30].

3.2. Tau protein kinases and phosphatase

Tau phosphorylation is mainly determined by a balance between the activation of various tau protein kinases and phosphatases, and its disruption results in the abnormal phosphorylation of tau, which is observed in AD. Each tau site is phosphorylated by one or more protein kinases. Tau kinases are grouped into three classes: (1) proline-directed protein kinases (PDPK) containing glycogen synthase kinase-3 (GSK3), cyclin-dependent protein kinase-5 (CDK5), and

mitogen activated protein kinases (MAPK) (e.g. p38, Erk1/2 and JNK1/2/3); (2) non-PDPK, including tau-tubulin kinase 1/2 (e.g. casein kinase 1 α /1 δ /1 ϵ /2), dual specificity tyrosine-phosphorylation-regulated kinase 1A/2, microtubule affinity regulating kinases, phosphotyrosine kinase, cAMP-dependent protein kinase A (PKA), PKB/Akt, protein kinase C, protein kinase N, and Ca²⁺/calmodulin-dependent protein kinase II (CaM kinase II); and (3) tyrosine protein kinases, including Src family kinase (SFK) members (e.g. Src, Lck, Syk, and Fyn), and c-Abelson kinase or Abl related gene kinase. Phosphatases are also usually classified into three classes according to their amino acids sequences, the structure of their catalytic site, and their sensitivity to inhibitors. These groups include: (1) phosphoprotein phosphatase (PPP), (2) metal-dependent protein phosphatase, and (3) protein tyrosine phosphatase (PTP).

GSK3 (particularly GSK3 β) plays a key role in the pathogenesis of AD, contributing to A β production and A β -mediated neuronal death by phosphorylating tau in most serine and threonine residues and inducing hyperphosphorylation in paired helical filaments [31]. Inhibition of GSK3 prevents A β aggregation and tau hyperphosphorylation [32, 33]. The involvement of CDK5 in tau phosphorylation is shown by the increase in its enzymatic activity and the absence of MT-2 cells neurite retraction in the presence of roscovitine or CDK5 siRNA [34]. Therefore, CDK5 may be a key candidate target for therapeutic gene silencing [35]. p38 MAPK has been identified as one of the kinases involved in the regulation of tau phosphorylation. Thus, under pathological conditions this kinase is likely to play a role in the hyperphosphorylation of tau [36]. CDKs and casein kinase 1 (CK1) are involved in the aggregation of A β peptides (forming extracellular plaques) and hyperphosphorylation of tau (forming intracellular NFTs). The expression pattern of CK1 δ (an isoform of CK1) plays an important role in tau aggregation in AD [37]. Ser214, Ser262, and Ser409 are major phosphorylation sites of tau that are affected by PKA [38]. In P19 cells stably expressing human tau441, CaM kinase II has been shown to be involved in retinoic acid (RA)-induced tau phosphorylation-mediated apoptosis [39].

Tau protein phosphatase PPP group includes protein phosphatase [PP]1, PP2A, PP2B and protein phosphatase-5 [PP5]. In vitro, Overexpression of PP5 resulted in dephosphorylation of tau at multiple phosphorylation sites [40] and protected neurons against apoptosis induced by A β [41]. In vivo, PP5 interacts with the regulatory subunit A of PP2A [42], and the enzymatic activity level of PP5 has been reduced by 20% in AD brains [40]. PP2A contributes to abnormally hyperphosphorylated tau protein, and is the most efficient phosphatase. The inhibition of PP2A significantly plays a role in tau hyperphosphorylation [43-45]. PP2A is regulated by endogenous inhibitor-1 of PP2A (I1PP2A) and inhibitor-2 of PP2A (I2PP2A) in mammalian tissues [46].

Recently inactivation the nuclear translocation signal (179KRK181-AAA) along with 168KR169-AA mutations of I2PP2A (mNLS-I2PP2A), it was translocated from nucleus to the cytoplasm. Cytoplasmic retention of I2PP2A physically interacted with PP2A and inhibited its activity, induced Alzheimer-like abnormal tau protein hyperphosphorylation by the direct interaction of I2 PP2A with PP2A and GSK-3 β [47]. In AD brain, I2PP2A is also translocated from neuronal nucleus to cytoplasm, leading to the inhibition of PP2A and abnormal phosphorylation of tau. I2PP2A directly inhibits the activity of PP2A activity without affecting its expression [48]. Over activation of GSK-3 β inhibits PP2A through up regulation of I2PP2A. GSK-3 activation significantly contributes to tau hyperphosphorylation by inhibiting PP2A via

the up-regulation of I2PP2A [49]. These data indicate that up-regulation or down-regulation of the phosphorylation system or dephosphorylation system, respectively of tau protein may be implicated in tau pathologies.

3.3. Tau protein and oxidative stress

3.3.1. *Tau protein hyperphosphorylation and oxidative stress*

Oxidative stress is believed to be a prominent early event in the pathogenesis of AD, contributing to tau phosphorylation and the formation of neurofibrillary tangles. However, the relationship and underlying mechanisms between oxidative stress and tau hyperphosphorylation remains elusive. Fatty acid oxidative products provide a direct link between the mechanism of how oxidative stress induces the formation of NFTs in AD [50]. Chronic oxidative stress increases the levels of tau phosphorylation at paired helical filaments (PHF-1) epitope (serine 399/404) via the inhibition of glutathione synthesis with buthionine sulfoximine (BSO) in an *in vitro* model of chronic oxidative stress [5]. In primary rat cortical neuronal cultures stimulated by the combination of the copper chelator, cuprizone, and oxidative stress ($\text{Fe}^{2+}/\text{H}_2\text{O}_2$), tau phosphorylation is significantly increased by the elevated activity of GSK-3 [51]. Furthermore, treatment of rat hippocampal cells and SHSY5Y human neuroblastoma cells with H_2O_2 at the early stages of oxidative stress exposure results in tau dephosphorylation at the Tau1 epitope by CDK5 via PP1 activation [52]. Several studies have suggested that oxidative stress is a causal factor in tau-induced neurodegeneration in *Drosophila* [53], and ROS generation is a key intracellular event that contributes to an induction of p38-MAPK activation and tau phosphorylation.

3.3.2. *GSK3 β , PP2A, and oxidative stress*

Oxidative stress is likely to play a critical role in tau hyperphosphorylation, which is regulated by tau protein kinase activation and the suppression of phosphatase. Tau hyperphosphorylation may be induced by oxidative stress through the direct interaction with tau protein kinase and phosphatase, particularly GSK-3 β and PP2A, respectively because they are predominant and play an important role.

The main site of ROS formation is mitochondrial complex I, inhibition of complex I induces a decrease in ATP levels and excessive production of ROS [54]. GSK-3 β has been situated in the mitochondria and highly activated. Mitochondrial GSK3 β activity controlled the mitochondrial complex I activity, promoted ROS production, and perturbed the mitochondrial morphology [55]. In contrast, GSK-3 β activity is up-regulated under oxidative stress [56]. For example, in human embryonic kidney 293/Tau cells, H_2O_2 increases GSK-3 β activity and tau is hyperphosphorylated at Ser396, Ser404, and Thr231. Mitochondrial superoxide activates the mitochondrial fraction of GSK-3 α/β , resulting in the phosphorylation of the mitochondrial chaperone cyclophilin D [57]. This effect also provides a link between GSK-3 β and oxidative stress.

Studies have also focused on the link between PP2A and oxidative stress. A recent report shows that rat cortical neurons treated with okadaic acid inhibits PP2A activity, resulting in an abnormal increase in mitochondrial ROS and mitochondrial fission [58]. Other findings reveal

that ROS inhibits PP2A and PP5, leading to the activation of JNK and Erk1/2 pathways and subsequently caspase-dependent and -independent apoptosis of neuronal cells [59]. In vivo, after hypoxia exposure, the levels of activated form of GSK-3 β was significantly increased in the hippocampus, while activated form of PP2A were significantly decreased [60]. Despite these studies, however, the relationship of GSK3 and PP2A with oxidative stress remains to be further investigated.

3.3.3. Antioxidants and the tau protein

In recent years, antioxidant therapy has received considerable attention as a promising approach for slowing the progression of AD. Research has focused on endogenous antioxidants (e.g. vitamins, coenzyme Q10, and melatonin) and the intake of dietary antioxidants, such as phenolic compounds that are flavonoids or non-flavonoids. This increased interest has thus strengthened the hypothesis that oxidative damage may be responsible for the cognitive and functional decline in AD patients. Melatonin is a free radical scavenger, clinical trial revealed that add-on prolonged-release melatonin had positive effects on cognitive functioning and sleep maintenance in AD patients compared with placebo [61]. The mechanism may be that melatonin can block tau hyperphosphorylation and microtubule disorganization under in vivo and in vitro conditions [62-64] and also decreases the activity of GSK-3 β [65]. Moreover, melatonin may be a potentially useful agent in the prevention and treatment of AD [66]. Demethoxycurcumin has been shown to inhibit the phosphorylation of both tau pS262 and pS396 in murine neuroblastoma N2A cells [67]. Curcumin reduced soluble tau and elevated heat shock proteins involved in tau clearance [68]. In addition, curcumin downregulated levels of phosphorylated tau, which may be concerned with the upregulation in BAG2 levels in the neurons [69]. In addition, an association also exists between beta carotene and tau in AD patients [70]. Other experiments have shown that the active component of Ginkgo biloba, ginkgolide A, inhibits GSK3 β and suppressed the phosphorylation level of tau [71]. Other antioxidants, such as Vitamins E and C [72, 73] and gossypin [74] are also reported to have a protective effect against neurotoxicity. These results have therefore led to further investigations of this compound as an antioxidant therapy strategy for AD.

4. Autophagy in AD

4.1. The Autophagic pathway

Autophagy is an essential lysosomal degradation pathway that turns over cytoplasmic constituents, including misfolded or aggregated proteins and damaged organelles, to facilitate the maintenance of cellular homeostasis. Autophagy is usually activated during nutrient deprivation and stress to enhance cellular survival, and its constitutive activity is recognized to control neuronal survival. Autophagic dysfunction has been reported to contribute to AD [75].

Autophagy includes macroautophagy, chaperone-mediated autophagy, and microautophagy. The most familiar of these types is macroautophagy, which is a process of cellular self-cannibalism in which portions of the cytoplasm are sequestered within double- or multi-

membraned vesicles (autophagosomes) and then delivered to lysosomes for bulk degradation. Autophagy is induced by two pathways in macroautophagy - mammalian target of rapamycin (mTOR)-dependent and -independent signaling pathways. mTOR is an important convergence point in the cell signaling pathway. mTOR kinase activity is modulated in response to various stimuli, such as trophic factors, mitogens, hormones, amino acids, cell energy status, and cellular stress. Rapamycin, as mTOR inhibitor, is a very important tool for autophagy [76, 77]. mTOR complex (mTORC) 1 is involved in autophagy and is the master regulator of cell growth enhancing the cellular biomass by up-regulating protein translation [78]. For cells to control cellular homeostasis during growth, a close signaling interplay occurs between mTORC1 and two other protein kinases, AMP-activated protein kinase (AMPK) [79] and Unc51-like kinase (ULK1) [80]. Autophagy is inhibited by cytosolic p53 via the direct inhibition of AMPK [81]. mTORC1 controls autophagy by directly interacting with the ULK1, focal adhesion kinase family-interacting protein of 200 kDa (FIP200) and Atg13 complex [82]. Several mTOR-independent signals affect the autophagy pathway. When the level of free inositol and myoinositol-1,4,5- trisphosphate (IP3) decreases, autophagy is reduced [83]. Furthermore, lower levels of Bcl-2 lead to the release of more Beclin 1, thus forming the Beclin 1-PI3KCIII (class III phosphoinositide 3-kinase) complex to activate autophagy via the PI3K-AKT-mTOR pathway [84].

4.2. Autophagic dysfunction in AD pathology

A growing body of evidence suggests a link between AD and autophagy. Therefore, the pathological functions of autophagy may be a critical mediator of neurotoxicity [85]. Autophagy develops in AD brains because of the ineffective degradation of autophagosomes, which is controlled by many kinds of autophagy-related genes (Atg), including Atg1-Atg35. Atg8 (mammalian homolog is LC3) is an autophagosomal membrane protein and a marker of autophagosome formation [86]. Beclin-1 (the mammalian ortholog of yeast Atg6) plays a pivotal role in autophagy [87]. In an *in vitro* study of the pathogenesis of AD, Atg8/LC3 colocalizes with APP and LC3-positive autophagosomes are present [88]. Beclin-1 knockdown increases APP, APP-like proteins, APP-C-terminal fragments, and A β [89]. Atg5, Atg12, and LC3 are also associated with plaque, tangle pathologies, and neuronal death in AD [90]. Generally, autophagic vacuoles (AVs) are rare in the normal brain, but are increased in brains of AD patients. In the early stages of AD, the expression of lysosome-related component is significantly increased prior to the formation of plaques and NFTs, and autophagy is also induced at this stage, thus its activity is independent of extracellular A β deposition and NFT formation [91]. In the late stage of AD, AVs continue to accumulate in large numbers in dystrophic neurites. There are several causes for the dysfunction of autophagy in late-stage AD, including the enhanced processing of APP and A β degradation [92], and the toxic effect of high levels of intracellular A β on lysosomal function [93]. Inhibition of the AV-lysosome fusion is caused by impaired microtubule-associated retrograde transport, which in turn leads to increased accumulation of AV in dystrophic neurites. Lysosomal enzyme dysfunction may be associated with the accumulation of AVs [94, 95]. Autophagy plays an important role in the degradation of impaired mitochondria in AD. Dysfunction of the autophagy - lysosome system causes insufficient degradation of mitochondria [96]. Conversely, mitochondrial dysfunction may also impair this pathway [97].

4.3. Autophagy and the tau protein

4.3.1. *Tau protein degradation via autophagy*

A variety of forms of tau proteins have been shown to be degraded by the ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathway (ALP). UPS may play an important role in the primary clearance of pathological tau. However, the importance of autophagy-mediated tau degradation, particularly at the late stage of NFT formation, is becoming more recognized. The autophagy-lysosomal pathway has the capacity to engulf protein aggregates and keep tau levels at a low level [98]. Autophagy is believed to be an evolutionarily conserved mechanism for intracellular degradation of proteins, such as A β and tau. mTOR in negatively regulating autophagy is an important convergence point in cell signaling. Increasing mTOR signaling facilitates tau pathology, and reducing this signaling ameliorates tau pathology [99]. Rapamycin has been reported to decrease tau phosphorylation at Ser214 in vitro, and reduce tau tangles and insoluble tau in vivo [100, 101]. In a tetracycline-inducible model [tau DeltaC (tau Δ C)], tau is abnormally truncated at Asp⁴²¹, and is cleared predominantly by macroautophagy and degraded significantly faster than full-length tau [102]. Autophagy activation suppresses tau aggregation and eliminates cytotoxicity [99]. Moreover, trehalose (an enhancer of autophagy) directly inhibits tau aggregation in primary neurons [103]. Under in vitro conditions, the accumulation of tau species is increased with the autophagic inhibitor, 3-methyladenine, and decreased with trehalose [104]. Overall, these results suggest that tau degradation involves autophagy, and this activity is beneficial for neurons to prevent the accumulation of protein aggregates.

4.3.2. *Tau protein hyperphosphorylation leads to autophagic dysfunction*

The physiological function of tau protein is well known to be associated with microtubule binding and assembly. Autophagosome transport mainly depends on the movement along microtubules in the autophagic pathway. However, the link between tau hyperphosphorylation and autophagic dysfunction is still under debate. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) - mediated tau mutations can disrupt lysosomal function in transgenic mice expressing human Tau with four tubulin-binding repeats (increased by FTDP-17 splice donor mutations) and three FTDP-17 missense mutations: G272V, P301L, and R406W [105]. In Tg mice expressing mutant human (P301L) tau, axonal spheroids have been shown to contain tau-immunoreactive filaments and AVs [106]. A recent study has revealed that PP2A upregulation stimulates neuronal autophagy, thus providing link between PP2A downregulation, autophagy disruption, and protein aggregation [107]. Furthermore, autophagosomes have been shown to be increased in rat neurons treated with okadaic acid [108]. Altogether, tau is known to regulate the stability of microtubules, and tau hyperphosphorylation may result in the destabilization of neuronal microtubules, thus affecting the placement and function of mitochondria and lysosomes. Therefore, tau hyperphosphorylation is likely to play a critical role in the process of autophagic dysfunction.

4.3.3. Autophagic dysfunction induces tau protein aggregation

The autophagy-lysosomal pathway is well recognized to play an important role in the clearance of abnormally modified proteins in cells. The hyperphosphorylation of tau and NFT formation results in the disruption of the neuronal skeleton, thereby contributing to neuronal dysfunction, cell death, and eventually the symptoms of AD. Abnormal lysosomal proteases are found in brains of AD patients. Several studies have shown that dysfunction of the autophagy-lysosomal pathway contributes to the formation of tau oligomers and insoluble aggregates [109, 110]. Both phosphorylated tau and GSK3 β significantly accumulate in Atg7 conditional knockout brains, although NFTs are absent [111]. Therefore, the ALP system plays a crucial role in the clearance of tau, and its accumulation may be due to autophagic dysfunction in cells.

5. Conclusion

Oxidative stress, as the one of the earliest events in AD, induces tau phosphorylation with protein phosphatase and kinase imbalance. Tau protein hyperphosphorylation destabilizes

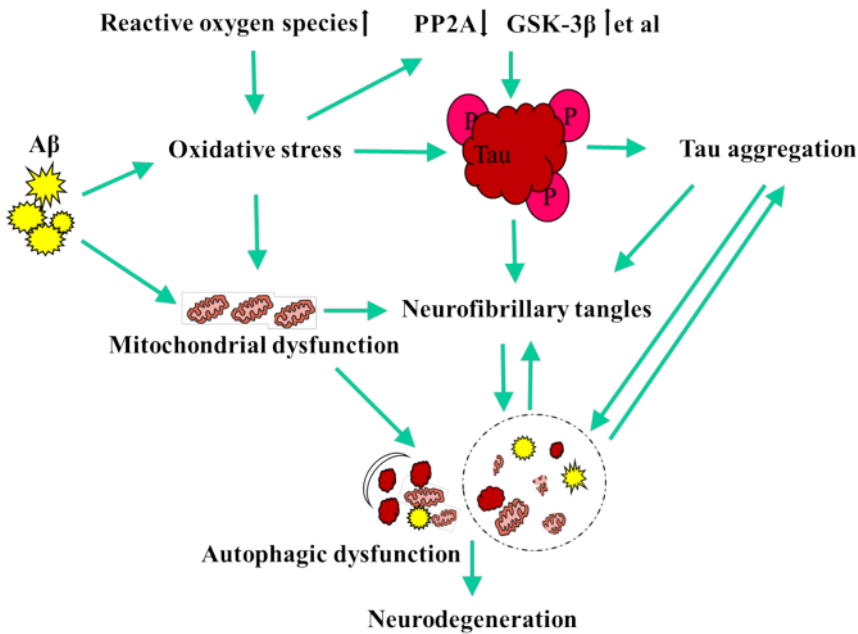


Figure 1. Tau protein NFTs formation and autophagic dysfunction in Alzheimer's disease. A β oligomers and ROS production intrigue oxidative stress and mitochondria dysfunction, which induce tau protein hyperphosphorylation and neurofibrillary tangles formation. These events converge to tau protein aggregation and autophagic dysfunction, then lead to neurodegeneration and cell death in AD.

microtubules by decreasing the binding affinity of tau, thereby resulting in the formation of NFTs in AD. Tau hyperphosphorylation may affect the autophagy- lysosomal pathway, and dysfunction of the ALP also promotes the accumulation of tau protein. These events initiate a series of cascades to induce neurodegeneration and cell death in AD (Figure 1). However, the relationships among oxidative stress, tau hyperphosphorylation and autophagic dysfunction and their accurate mechanisms on neurodegeneration in AD still require further research.

Acknowledgements

The work has been generously supported by grant from the National Natural Science Foundation of China (81271410 to JW). The authors thank all other authors making contributions to the studies cited in this manuscript and apologize to those who made similar contributions in work not being cited due to space limitation. The authors have no competing financial interests.

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