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1 Review

Mechanistic Insights into Tau Protein-Mediated Regulation of Oxidative Stress

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Abstract Abnormal hyperphosphorylation and microtubule-associated protein tau aggregation development in the brain are characteristics of neurodegenerative diseases referred to as tauopathies, which include Alzheimer's disease (AD). The current review summarizes the complex relationships that exist between oxidative stress and tau illness, with particular attention to the roles played by the tau protein, reactive oxygen species and their consequences, and tau phosphorylation and oxidative stress. Two key elements of detrimental cycle that are critical in neurodegenerative tauopathies are tau hyperphosphorylation and oxidative stress. When tau and microtubules are not connected properly, microtubule instability, issues with microtubule transport, and ultimately neuronal death result. While the causes of the more prevalent sporadic late-onset variants and the connections between tau hyperphosphorylation and neurodegeneration remain largely unknown, mutations in the microtubule-associated protein tau (MAPT) gene have been identified in familial cases of early-onset tauopathies. Another detrimental feature of tauopathies is oxidative stress, but the exact role it plays in the development of the disease is unclear. The source of reactive oxygen species (ROS), which lead to oxidative stress within neural tissue, remains an unresolved topic. Although mitochondria have historically been thought to be a primary source of oxidative stress, microglial cells have recently been discovered to create reactive oxygen species in tauopathies. In conclusion, enhancing our comprehension of the impact of oxidative stress on various diseases could facilitate the identification of new disease markers and lead to the formulation of treatment strategies aimed at halting, reversing, or mitigating disease progression.

Keywords Alzheimer's disease, Tau hyperphosphorylation, Oxidative stress, Mitochondrial dysfunction, Neurodegenerative tauopathies

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Introduction

A fully soluble, naturally unfolded, and phosphorylated protein, tau is found in the nucleus, neuronal somatodendritic compartments [1-3], adult neuron axons [4,5], and, to a lesser degree, astrocytes and oligodendrocytes [6]. Six distinct tau isoforms are expressed in the adult central nervous system (CNS) as a result of alternative splicing of a single gene [7]. Exons 1, 4, 5, 7, 9, 11, and 13 are translated into these isoforms, which have lengths varying from 352 to 441 amino acids and molecular weights between 45 and 65 kDa [8]. The presence of 31 amino acid sequences with three (3R) and four (4R) carboxy terminal repeats in accordance with microtubule binding domains (MBDs).

The MAPT gene, located on chromosome 17q21.31, codes for the human TAU protein. With over 30 distinct isoforms expected, alternative splicing generates a wide range of isoforms in the human central and peripheral nervous systems. Exons 2, 3, and 10 are the principal targets of alternative splicing, resulting in the formation of six brain-associated TAU isoforms in adult human neurons. These isoforms are distinguished by the number of C-terminal repeat domains (3R or 4R) and N-terminal inserts (0N, 1N, or 2N) (Figure 1) [9, 10]. The number of C-terminal repeat domains is determined by the presence or removal of exon 10, while the number of N-terminal inserts is determined by the splicing of exons 2 and 3. Notably, a weak branch point that favors the exclusion of exon 3 from the final mRNA transcript means that the inclusion of exon 3 depends on the inclusion of exon 2. The shortest isoform, 0N3R, is expressed only during neurogenesis. However, as neurons mature, the isoform composition shifts towards larger TAU isoforms, specifically 2N (including 2N3R and 2N4R) and 4R (including 0N4R, 1N4R, and 2N4R). This results in nearly equal ratios of 3R and 4R-TAU isoform expression in adult brains [11-14].

Since the tau protein in the peripheral nervous system (PNS) has a higher molecular weight than the isoforms found in neurons in the central nervous system (CNS), it is referred to as "big tau" [11]. There are multiple tau isoforms that express differentially in different tissues and at different stages of development because tau plays a crucial role in cytoskeletal plasticity throughout embryogenesis and early development. The human foetal brain expresses only the short tau isoform, while the adult central nervous system (CNS) has all six isoforms [12–14]. Tau undergoes a variety of posttranslational modifications in addition to phosphorylation, which is the essential one. These modifications include cross-linking by transglutaminase, ubiquitination, Sumoylation, nitration, glycation, acetylation, O-glycosylation, isomerization [15], conformational alteration, & proteolytic cleavage in the cerebral cortex & hippocampus of rats, O-GlcNAcylation (a kind of tau O-glycosylation) decreased tau phosphorylation [16-23], and O-GlcNAcylation levels adversely associated with tau phosphorylation in AD. In vitro tau-dependent microtubule assembly was inhibited and tau fibrillization was increased by tau acetylation at lys residue 280 [24, 25]. It has also been discovered

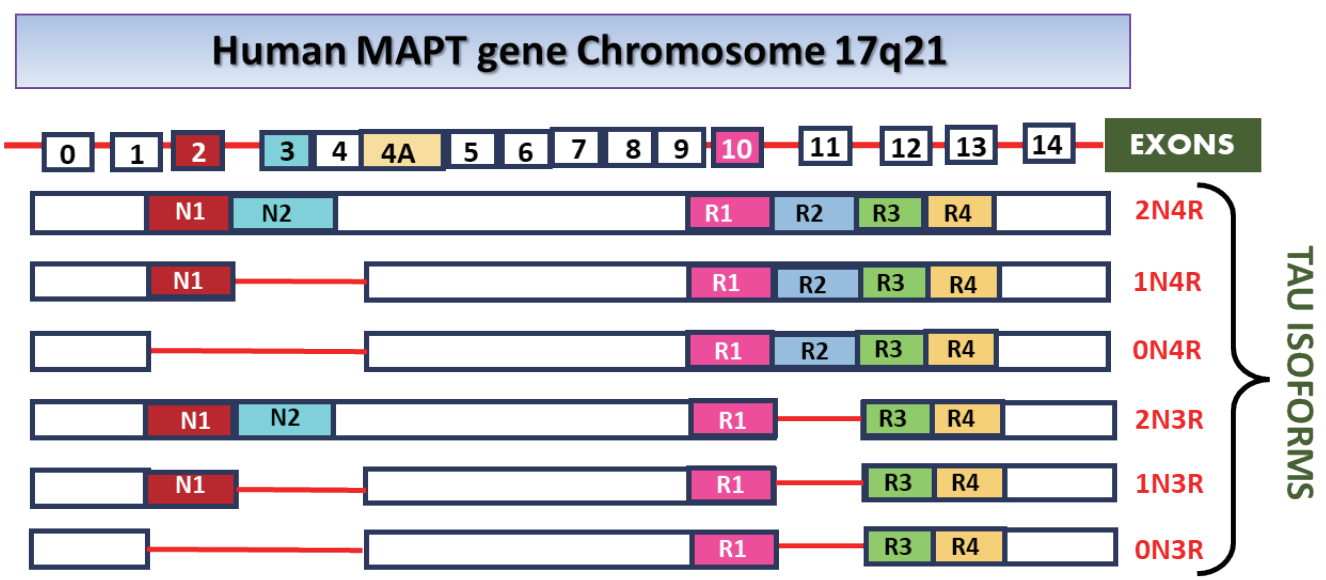

Figure 1: Figure illustrating the primary isoforms of the Tau protein.

that in tau transgenic animal models of tauopathies, AD, and corticobasal degeneration, tau acetylation is tightly linked to tau hyperphosphorylation and tau inclusions. Nevertheless, it is still unknown what precisely these tau changes do [26-29].

There are currently more than 50 MAPT gene mutations known to be linked to neurodegenerative tauopathies. The most significant pathogenic tau mutations are included in Table 1. Numerous of these mutations, which alter the tau sequence, are missense mutation or minor deletions [30]. Particularly, a number of missense mutations, including V337M, P301L, P301S, G272V, G389R, & R406W, reduce tau's in vitro affinity for microtubules, impairing microtubule stability and assembly [31]. Missense mutations S305N & Q336R, on the other hand, modestly enhance tau's capacity to stimulate microtubule assembly. The majority of these missense variants also promote tau aggregation [17,32]. One of the main tau phosphatases in brain neuron, protein phosphatase 2A, is also affected by a number of mutations that prevent tau from attaching to it. In turn, as a result of the higher production of 4R tau, neurodegeneration and neurofibrillary tangles (NFTs) are the end results [33]. Through changes in MAPT gene splicing, further mutations in intronic regions close to stem-loop structures in exon 10 lead to an increase in the accumulation of the soluble 3R tau isoform [34, 35].

Causes of Oxidative stress: Common pathological conditions and mechanisms

Oxidation of Lipids

Phospholipids, which provide the foundation of neuronal connections, neurotransmission, and cognition, are abundant in the brain [16,17]. Poly-unsaturated fatty acids (PUFAs), especially docosahexaenoic acid & arachidonic acid, make up a significant portion of the brain's phospholipids. Research has shown that when the production of free radicals increases, the amount of polyunsaturated fatty acids (PUFA) in the brain progressively decreases. Furthermore, in the presence of iron, the lipid hydroperoxides spontaneously breakdown into a variety of compounds, such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA) ketones, epoxides & hydrocarbons. Studies have shown that people with AD & mild cognitive impairment (MCI) have higher levels of MDA and 4-HNE in their brains. Another result of lipid peroxidation is the generation of isoprostane. F2-isoprostane (F2-IsoPs) levels are higher in AD. It is noteworthy that there is an inverse relationship between brain weight and the concentration of F2-IsoPs in ventricular fluid. Furthermore, another study indicated that patients with Mild Cognitive Impairment (MCI) exhibit elevated levels of F2-IsoPs [18-21].

It is a frequent biochemical feature of cancer cells to produce ROS and have an altered redox status. Polyunsaturated fatty acids in lipid membranes can react with ROS to cause lipid peroxidation. The end product of lipid peroxidation, 4-HNE, has been regarded as a secondary messenger of oxidative stress.

Oxidation of Proteins

As a significant indicator of protein oxidative damage, carbonyl protein levels have been found to be significantly elevated in the brains of individuals diagnosed with Alzheimer's Disease (AD). Tyrosine combines with different reactive oxygen and nitrogen species to form 3-nitrotyrosine and di-tyrosine. One significant oxidative alteration linked to neurodegenerative diseases is protein nitration. Patients with mild cognitive impairment (MCI) have notably elevated levels of total protein nitration in the hippocampus and inferior parietal lobule in comparison to healthy control participants [22]. Degradation of lipids and carbohydrates into highly reactive intermediate, which ultimately damage proteins at diverse functional locations, is another ability of oxidative stress. As a result, protein

Table 1: Major Pathogenic Tau Mutations

Mutation	Type	Effect	Reference
P301L	Substitution	Neuronal impairment, NFT formation	[84-86]
P301S	Substitution	Tau hyperphosphorylation and aggregation	[87]
ΔK280	Deletion	Tau aggregation and decreased microtubule affinity, neural loss	[88]
R406W, P301L, V337M	Substitution	Tau hyperphosphorylation, aggregation, and decreased microtubule affinity	[89]
N296N	Silent	Greater 4R to 3R ratio (splicing)	[90]

oxidation, glycoxidation, & lipoxidation produce a wide range of distinctive posttranslational protein changes. Because they are formed in huge numbers and have a stable chemical structure, several protein oxidation products show great promise as oxidative damage indicators. Additionally, improvements in quantification and detection techniques have shortened the time and effort required for analyses, increasing their potential for application in clinical settings in the future [19-22].

Oxidation of Nucleic Acids

8-hydroxy-2'-deoxyguanosine (8-OHdG) can be produced as a result of DNA oxidation. When compared to control people, the 8-OHdG levels in mitochondrial Genome isolated from the frontal cortex of Patients with AD is much higher (three times). In the AD brain, there is also an increase in oxidative alteration of RNA. It's interesting to note that 8-OHG appears to develop decades before all of the classic signs of AD, including NFTs and A plaques. 8-OHG also manifests in AD patients' decades before A aggregation. DNA strand breakage can also be used to gauge DNA oxidation [23-26]. According to reports, AD sufferers have twice as much DNA damage in their cerebral cortex as healthy controls. All of these by-products of lipid, protein, and nucleic acid oxidation have been regarded as blood biomarkers for diagnosing early-onset AD. Further research is required to determine their efficacy as AD early biomarkers [27].

Mitochondrial Dysfunction

Since the mitochondria are the primary generator of ROS and the location of the electron transportation chain for the synthesis of ATP, they are significantly more vulnerable to oxidative stress [28]. Hippocampal neurons from AD patients have been reported to have mitochondrial malfunction and associated metabolic abnormalities. The rise in ROS production and the decline in energy reserves in AD are brought on by cytochrome oxidase deficiency, a critical electron transport enzyme. In amyloid precursor protein (APP) mouse models, the antioxidant enzyme manganese superoxide dismutase (Mn-SOD), which protects mitochondria from oxidative stress, is rendered inactive. Manganese superoxide d-imutase (Mn-SOD) inactivation further encourages mitochondrial damage, oxidative stress & death [29].

Alzheimer's Disease (AD) is linked to an elevated production of ROS, largely due to the role of amyloid-beta (Aβ) in mitochondrial dysfunction. Emerging evidence indicates that Aβ alters mitochondrial dynamics and diminishes the activity of crucial enzymes, thereby disrupting the electron transport chain. Figure 2 demonstrates the connections between mitochondrial DNA (mDNA) mutations, oxidative stress, and reduced mitochondrial axonal transport, all of which contribute to these pathological changes. [30, 31]. It also causes oxidative damage to the membrane. For example, skin fibroblasts derived from myoclonic epileptic patients with red ragged fibres exhibit increased internal hydrogen peroxide levels & oxidative damage, as well as an imbalanced expression of antioxidative enzymes genes. Patients with mitochondrial encephalomyopathy, lactic acidosis with stroke-like events (MELAS), and Lebar's hereditary optic neuropathy (LHON) have also shown similar symptoms [31, 32].

Accumulation of Metals

Abnormal amounts of copper, zinc, and iron have been found in the hippocampus, amygdala, and other brain areas in AD individuals with severe histopathological abnormalities. These metals can cause oxidative stress through their interactions with amyloid-beta (Aβ). Metal chelators lower the amounts of Aβ and stop it from aggregating by reducing metal overload, whereas Aβ binds to copper or iron and produces ROS through redox activity. With great affinity, Aβ binds Cu^{2+} to create a complex that resembles a cuproenzyme. An electron moves from Aβ to Cu^{2+} during this reaction, turning Cu^{2+} into Cu^{+} and creating the Aβ radical. Cu^{+} may also give two electrons to oxygen to create H_2O_2, which releases more hydroxyl radicals [32]. Inflammation and oxidative stress caused by aluminium also contribute to AD neurodegeneration. Zinc is regarded as a possible link between AD and amyloid plaques, cerebrovascular amyloidosis, and other conditions [33-38].

Tau hyperphosphorylated

The hyperphosphorylated tau protein, a key component of NFTs and a hallmark of AD, is closely linked to neurodegeneration and cognitive decline. Interestingly, despite significant oxidative damage, neurons with NFTs show significantly lower levels of 8-hydroxy guanosine (8-OHG). This suggests that tau phosphorylation and NFT formation may help protect neurons against oxidative stress. However, most research indicates that tau is involved in the neurodegeneration associated with oxidative stress in AD. In a Drosophila brain model of tauopathy, a reduction in the gene dose of thioredoxin reductase or mitochondrial superoxide dismutase-2 (SOD-2)

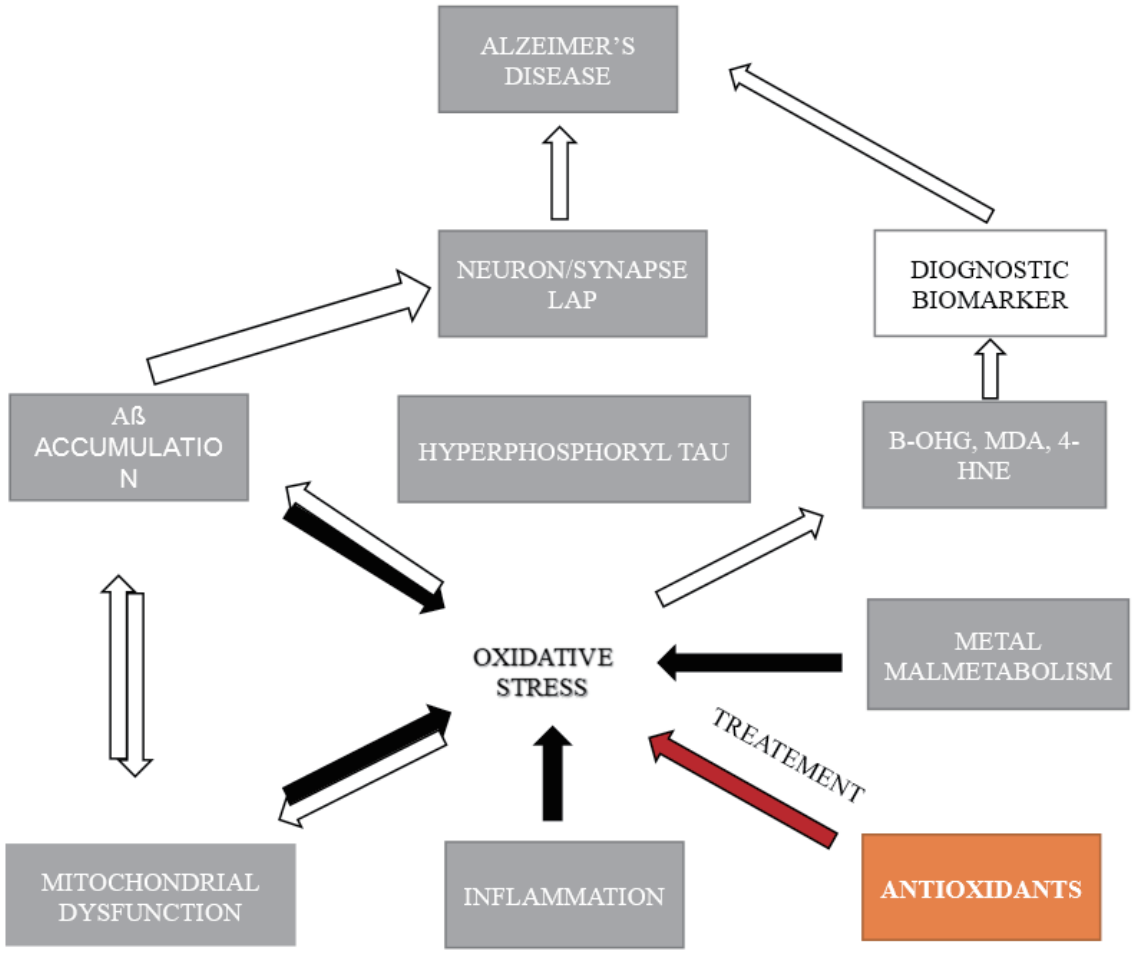

Figure 2: Alzheimer's disease and oxidative stress. The diagram demonstrates how hyperphosphorylated tau, A build-up, inflammation, metal malmetabolism, and mitochondrial dysfunction can all lead to oxidative stress in AD. Additionally, the brain's oxidative stress by-products 8-OHG, MDA, & 4-HNE can be used to diagnose AD. Antioxidants may also be employed as a treatment due to the crucial function that oxidative stress plays in AD.

enhances tau-induced neurodegenerative histological abnormalities and neuronal death. On the other hand, therapy with vitamin E or overexpression of these antioxidative enzymes reduces tau-induced neuronal death. The primary component of NFTs and a defining characteristic of AD, hyperphosphorylated tau protein, is significantly associated with shortened tau, which shows elevated levels of ROS. Antioxidants, such as vitamin C, can reverse this change. Furthermore, studies with P301S and P301L transgenic mice have demonstrated a link between oxidative stress and tau pathology. [39].

Inflammation

The formation of ROS is also aided by inflammation. Both microglia & astrocytes emit cytokines, chemokines, ROS, & complement proteins, which are proinflammatory mediators [40-42]. Microglia gather around Aß deposit in the brain as a consequence of Aß attracting and activating them. Additionally, microglia produce scavenger receptors that interact with A to release ROS and immobilise cells. Astrocytes are also stimulated by Aß, and as a result, they release chemokines, cytokines, & ROS that can harm neurons [17,43].

Impact of tau protein on oxidative stress

Oxidative stress and tau protein interact in a complex relationship that is pivotal to understanding the mechanisms underlying neurodegenerative diseases, especially AD. Oxidative stress, characterized by an overproduction of ROS and a compromised antioxidant defence system, leads to cellular damage and dysfunction. In the context of tau proteins, which are primarily known for stabilizing microtubules in neurons, oxidative stress induces a cascade of

pathological changes [46]. ROS can directly modify tau proteins through oxidative modifications such as carbonylation and nitration, altering their structure and function. Furthermore, oxidative stress activates several kinases, including glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), which phosphorylate tau at multiple sites. Hyperphosphorylated tau loses its affinity for microtubules, resulting in the destabilization of the cytoskeleton and the formation of neurofibrillary tangles (NFTs), a hallmark of AD. These tangles disrupt neuronal function and contribute to cell death [44-47].

Oxidative Stress Induces Tau Hyperphosphorylation

Oxidative stress plays a crucial role in inducing tau hyperphosphorylation, a key pathological event in neurodegenerative diseases such as Alzheimer' s disease. Under conditions of oxidative stress, the cellular production of ROS exceeds the capacity of the antioxidant defence system, leading to damage of cellular components and disruption of normal cellular functions. In neurons, this oxidative imbalance has a profound impact on tau proteins, which are essential for stabilizing microtubules and maintaining neuronal structure and transport. ROS directly affect tau by inducing oxidative modifications such as carbonylation and nitration, which alter tau's conformation and predispose it to pathological changes. More importantly, oxidative stress activates several kinases, including glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and mitogen-activated protein kinases (MAPKs). These kinases phosphorylate tau at numerous sites, resulting in hyperphosphorylation [48]. Hyperphosphorylated tau detaches from microtubules, leading to microtubule destabilization and impaired axonal transport. Detached tau tends to aggregate, forming neurofibrillary tangles (NFTs) that disrupt neuronal function and connectivity. Additionally, hyperphosphorylated tau can sequester normal tau and other microtubule-associated proteins, exacerbating the cytoskeletal disruption. The relationship between oxidative stress and tau hyperphosphorylation creates a vicious cycle: oxidative stress promotes tau hyperphosphorylation and aggregation, which in turn impairs mitochondrial function and increases ROS production. This cycle contributes to progressive neuronal damage and loss, underscoring the importance of targeting oxidative stress and tau phosphorylation in therapeutic strategies. By mitigating oxidative stress and preventing tau hyperphosphorylation, it may be possible to slow or halt the progression of tauopathies and related neurodegenerative diseases [49].

Tau Aggregates Promote Oxidative Stress

Tau aggregates significantly contribute to the promotion of oxidative stress, creating a deleterious feedback loop that exacerbates neurodegeneration. In neurodegenerative diseases such as Alzheimer' s, tau proteins undergo pathological modifications, including hyperphosphorylation, which leads to their detachment from microtubules and subsequent aggregation into NFTs. These aggregates disrupt normal cellular processes and contribute to oxidative stress in several ways. Firstly, tau aggregates impair mitochondrial function, a primary source of cellular ROS. Mitochondrial dysfunction results in increased ROS production, overwhelming the cell's antioxidant defences and leading to oxidative damage of cellular components, including lipids, proteins, and DNA [50]. Additionally, tau aggregates can physically block the transport of essential cellular components along microtubules, leading to impaired axonal transport and energy deficits that further strain mitochondrial function. Moreover, tau aggregates can sequester antioxidant proteins and enzymes, reducing the cell's ability to neutralize ROS and exacerbating oxidative stress. This oxidative stress can, in turn, enhance tau pathology by promoting further tau hyperphosphorylation and aggregation, thereby establishing a vicious cycle. The interplay between tau aggregates and oxidative stress results in progressive neuronal dysfunction and cell death, contributing to the clinical manifestations of neurodegenerative diseases [51].

Redox Regulation of Tau

Redox regulation of tau protein plays a crucial role in the pathogenesis of neurodegenerative diseases, emphasizing the delicate balance between oxidative and reductive processes within cells. Tau, a microtubule-associated protein, is vital for maintaining neuronal stability and facilitating intracellular transport. However, its function and structure are profoundly influenced by the redox state of the cell. ROS, which are byproducts of normal cellular metabolism, can induce oxidative modifications in tau, particularly at its cysteine residues. These oxidative modifications, including S-nitrosylation, S-glutathionylation, and disulfide bond formation, can alter tau's conformation, reduce its affinity for microtubules, and increase its propensity to aggregate. Oxidative stress, characterized by an

excess of ROS, exacerbates these modifications, promoting tau hyperphosphorylation through the activation of kinases like glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) [14, 52]. Hyperphosphorylated tau detaches from microtubules, destabilizing the cytoskeleton and contributing to the formation of neurofibrillary tangles (NFTs). Conversely, a reductive environment can influence tau's structure and function by promoting the reduction of oxidized cysteine residues, thereby impacting its aggregation propensity and interaction with microtubules. The redox regulation of tau is further complicated by the involvement of antioxidant systems, such as glutathione and thioredoxin, which modulate the cellular redox state and protect against oxidative damage. Dysregulation of these antioxidant systems, as seen in neurodegenerative diseases, leads to an imbalance that favors tau pathology [33, 53].

Antioxidant Defence Mechanisms and Tau

Antioxidant defence mechanisms play a pivotal role in modulating tau pathology, offering protection against oxidative stress and its detrimental effects on neuronal function. In neurodegenerative diseases like Alzheimer's, oxidative stress and tau pathology are intricately linked, with oxidative damage exacerbating tau hyperphosphorylation and aggregation. The body's antioxidant defence system comprises both enzymatic and non-enzymatic components that work synergistically to neutralize ROS and maintain cellular redox balance. Key enzymatic antioxidants include SOD, which converts superoxide radicals into hydrogen peroxide; catalase, which breaks down hydrogen peroxide into water and oxygen; and glutathione peroxidase, which reduces hydrogen peroxide and lipid peroxides [54]. Non-enzymatic antioxidants, such as glutathione, vitamins C and E, and polyphenols, scavenge free radicals and provide additional layers of protection. In the context of tau pathology, these antioxidant defences are crucial. For instance, overexpression of SOD in transgenic mouse models of tauopathy has been shown to reduce oxidative damage and tau pathology, highlighting the protective role of enzymatic antioxidants. Non-enzymatic antioxidants like vitamin E and polyphenols have demonstrated efficacy in decreasing tau hyperphosphorylation and aggregation by mitigating oxidative stress [55, 56]. Numerous antioxidant chemicals have been investigated in several tauopathy models to investigate the hypotheses of oxidative stress in the ageing process and neurodegeneration. These substances appear to have therapeutic promise in at least a few models. Dietary supplementation with vitamin E decreased mortality, lowered the amount of tau-containing inclusions in the spine, & improved behavioural phenotypes in mice overexpressing the shortest human tau isoform, which develops age dependent filamentous tau accompanied by neuronal loss & behavioural changes. Another antioxidant with an intriguing medicinal potential is curcumin, which is a naturally occurring compound found in the spice turmeric (Curcuma longa). Figure 3 shows that curcumin treatment reduced okadaic acid-induced ROS generation and tau hyperphosphorylation in mice as well as A-induced tau hyper-phosphorylation in pheochromocytoma (PC12) cell [55]. Additionally, antioxidant therapy with the catalytic antioxidant EUK189 reduces the build-up of oxidative stress indicators and tau hyperphosphorylation in mice missing superoxide dismutase. Similar to this, lipid peroxidation was decreased and survival and behavioural deficits were significantly alleviated with chronic injection of the antioxidant coenzyme Q10 to mice. Additionally, these mice were given the antioxidants methylene blue therapy, which reduced oxidative damage such tau hyperphosphorylation and damaged nucleic acids. Last but not least, vitamin E therapy or increased production of the antioxidative enzymes thioredoxin peroxidase significantly improved the neurodegenerative phenotype of transgenic flies [56,57].

Mechanisms of Oxidative Stress Regulation by Tau Protein

Microtubule Stabilization and Axonal Transport

Microtubule stabilization and axonal transport are critical mechanisms through which tau protein regulates oxidative stress within neurons, highlighting tau's multifaceted role in maintaining cellular homeostasis. Microtubules, part of the cytoskeleton, provide structural support to neurons and serve as tracks for the transport of organelles, vesicles, and other cellular components along axons. Tau binds to microtubules and promotes their assembly and stability, ensuring the proper functioning of neuronal transport systems. In a healthy state, tau's regulation of microtubules facilitates efficient axonal transport, which is essential for the distribution of mitochondria, the primary source of ROS and energy production in cells. By ensuring the proper localization and function of mitochondria, tau indirectly regulates the production of ROS, thereby helping to maintain cellular redox balance and mitigate oxidative stress

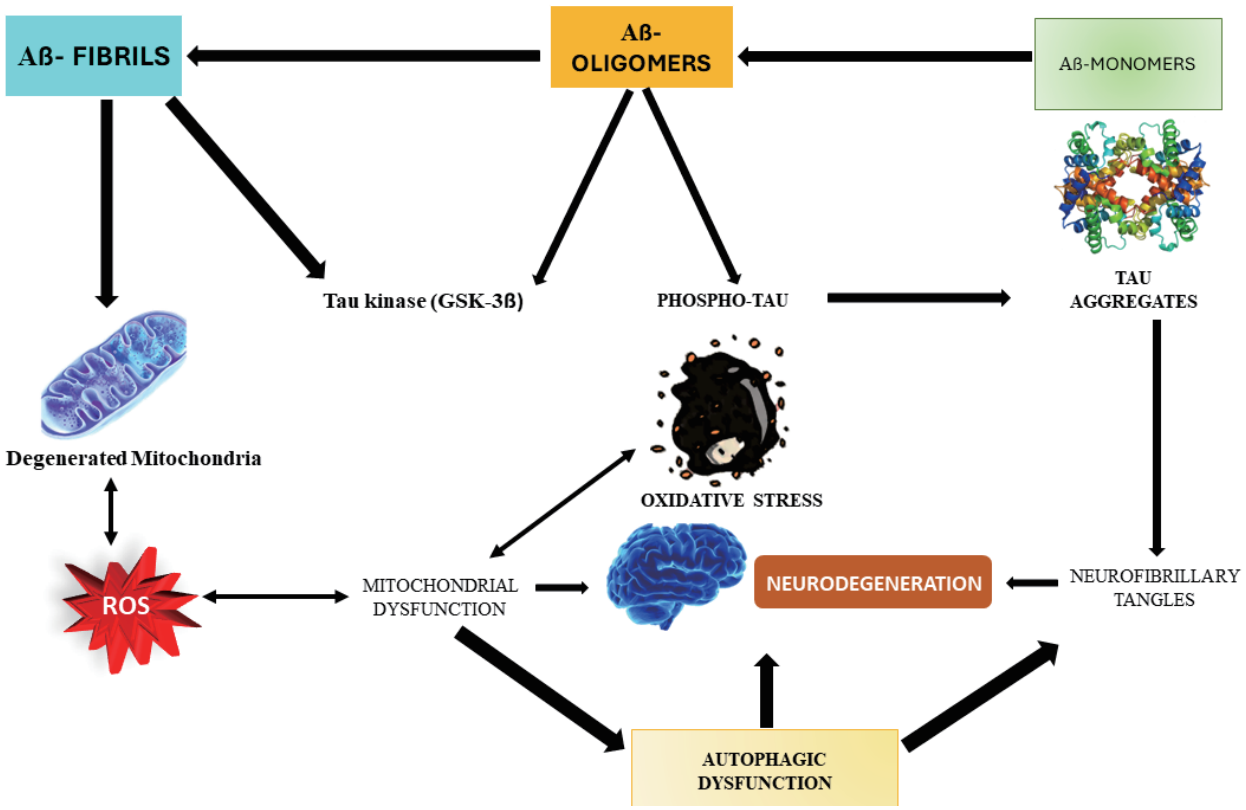

Figure 3: Antioxidant properties of curcumin and potential in inhibiting neurodegenerative diseases

[57]. However, when tau is hyperphosphorylated, as seen in neurodegenerative diseases like Alzheimer's, its affinity for microtubules decreases. This leads to microtubule destabilization and impaired axonal transport, causing a cascade of detrimental effects. The disintegration of microtubules disrupts the delivery of essential components, including antioxidants and metabolic enzymes, to regions of the neuron where they are needed most [58]. Understanding the intricate relationship between tau, microtubule stability, and axonal transport provides valuable insights into the mechanisms by which tau protein regulates oxidative stress, highlighting potential targets for therapeutic intervention [59-63].

Mitochondrial Dysfunction

Mitochondrial dysfunction plays a significant role in the regulation of oxidative stress and is intimately connected with tau protein pathology in neurodegenerative diseases. Tau protein, crucial for stabilizing microtubules and facilitating intracellular transport, also influences mitochondrial function through its interactions with the cytoskeleton. In healthy neurons, tau supports mitochondrial transport along microtubules, ensuring their proper distribution and function. Mitochondria are essential for generating ATP, the energy currency of the cell, and play a central role in buffering ROS produced during oxidative phosphorylation. Proper mitochondrial function relies on effective transport systems, which are maintained by tau's stabilization of microtubules. By facilitating the movement of mitochondria to areas of high energy demand, tau helps regulate cellular energy metabolism and manage oxidative stress. However, when tau becomes hyperphosphorylated and forms neurofibrillary tangles, its ability to stabilize microtubules is compromised. This destabilization disrupts mitochondrial transport, leading to impaired distribution and function of mitochondria within neurons. As a result, mitochondria can become dysfunctional, reducing their capacity to produce ATP and increasing the production of ROS. Elevated ROS levels exacerbate oxidative stress, leading to further mitochondrial damage and a vicious cycle of increased ROS production and oxidative damage [64]. The accumulation of damaged mitochondria, coupled with impaired transport, results in localized areas of oxidative stress that contribute to neuronal dysfunction and degeneration. Furthermore, tau aggregates themselves can contribute to mitochondrial

dysfunction. Mitochondrial dysfunction associated with tau pathology can lead to a reduction in cellular antioxidant defences, further exacerbating the impact of oxidative stress on neuronal health. The interplay between tau, mitochondrial function, and oxidative stress highlights the importance of maintaining mitochondrial integrity and effective tau function for neuronal health. Therapeutic strategies aimed at stabilizing tau, enhancing mitochondrial function, or improving mitochondrial transport could potentially mitigate the detrimental effects of mitochondrial dysfunction and oxidative stress [65-69].

Impaired Antioxidant Defence

Antioxidant defences, including enzymatic antioxidants like SOD, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants such as glutathione, vitamins C and E, work to neutralize ROS and protect cells from oxidative damage [70]. Tau facilitates the transport of these critical antioxidants to their sites of action, helping to sustain a balance between ROS production and elimination. However, in neurodegenerative conditions where tau becomes hyperphosphorylated and forms neurofibrillary tangles, its function in stabilizing microtubules is compromised. This disruption impairs the intracellular transport of essential components, including antioxidants and their precursors. The consequent reduction in antioxidant levels exacerbates the impact of oxidative stress, as cells become less equipped to counteract the damage caused by elevated ROS. Furthermore, tau aggregates can directly interfere with antioxidant systems by sequestering antioxidant enzymes or disrupting their activity. For instance, hyperphosphorylated tau has been shown to impair the function of glutathione, a crucial antioxidant, by affecting its synthesis and regeneration. The impairment of antioxidant defences in the presence of pathological tau leads to an accumulation of oxidative damage, further promoting tau hyperphosphorylation and aggregation. This creates a feedback loop where oxidative stress exacerbates tau pathology, and tau pathology, in turn, worsens oxidative stress. Understanding the relationship between tau, oxidative stress, and antioxidant defences provides valuable insights into the development of effective treatments aimed at preserving neuronal health and function [71-75].

Inflammatory Responses

When tau becomes hyperphosphorylated and aggregates into neurofibrillary tangles, it triggers a cascade of inflammatory responses that exacerbate oxidative stress. Activated microglia, the resident immune cells in the brain, respond to tau pathology by releasing pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines further activate the inflammatory response, leading to the production of ROS and reactive nitrogen species (RNS), which can cause widespread oxidative damage to neurons and other brain cells. The inflammatory response initiated by pathological tau also involves the activation of the nuclear factor kappa B (NF-κB) signaling pathway, a key regulator of inflammation [76, 77]. NF-κB activation leads to the transcription of various inflammatory mediators and enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), which contribute to increased ROS and RNS production. This heightened oxidative stress can damage cellular components, such as lipids, proteins, and DNA, and further propagate tau hyperphosphorylation and aggregation, creating a detrimental feedback loop [78, 79].

Calcium Homeostasis

Proper calcium homeostasis is maintained through a delicate balance of calcium influx through channels and pumps, and calcium sequestration by organelles such as the endoplasmic reticulum (ER) and mitochondria. However, tau pathology, particularly tau hyperphosphorylation and aggregation into neurofibrillary tangles, disrupts this balance [80]. Hyperphosphorylated tau impairs the stability of microtubules, leading to alterations in cellular calcium dynamics. One significant consequence is the disruption of calcium transport and signaling pathways. For instance, tau pathology can affect the function of calcium channels, such as voltage-gated calcium channels and NMDA receptors, leading to dysregulated calcium influx. Elevated intracellular calcium levels can activate various enzymes, including phospholipases and proteases, which contribute to increased oxidative stress by generating ROS and RNS [80, 81]. Therapeutic strategies that aim to restore calcium balance, enhance tau function, or protect mitochondria from calcium-induced damage may help mitigate the impact of tau pathology and associated oxidative stress. For example, calcium channel blockers, mitochondrial protectants, or agents that stabilize tau could potentially alleviate the negative effects of disrupted calcium homeostasis. Understanding the intricate mechanisms by which tau influences calcium regulation and oxidative stress

provides valuable insights into developing targeted interventions to preserve neuronal function and address tau-related neurodegenerative diseases [82-85].

Recent studies on tau protein for regulation of oxidative stress

Tau Protein Phosphorylation as the Correspondence Between Connectivity Failure, Mitochondrial Dysfunction, and Oxidative Stress [86]

The study by Siddhartha Mondragón-Rodríguez et al. examines the phosphorylation of tau protein as a crucial link between oxidative stress, mitochondrial dysfunction, and connectivity failure, with significant implications for AD. The researchers highlight that tau hyperphosphorylation is a critical pathological hallmark in AD, contributing to the disruption of neuronal function. Their results reveal that hyperphosphorylated tau impairs mitochondrial function by disrupting the electron transport chain, leading to increased production of ROS. This oxidative stress further exacerbates tau pathology, creating a vicious cycle of mitochondrial dysfunction and oxidative damage. The study also underscores the impact of tau-induced oxidative stress on synaptic connectivity, noting that the accumulation of phosphorylated tau in axons and dendrites disrupts synaptic function and plasticity. This connectivity failure is particularly detrimental in AD, where synaptic loss is strongly correlated with cognitive decline. The study suggests that therapeutic strategies aimed at modulating tau phosphorylation or enhancing mitochondrial resilience could provide dual benefits by addressing both tau pathology and oxidative stress. Additionally, the researchers highlight the need for further investigations into the specific kinases and phosphatases involved in tau phosphorylation, as well as the signaling pathways linking tau, mitochondria, and oxidative stress. This study's findings reinforce the central role of tau in AD and provide a compelling argument for developing treatments that target the molecular interplay between tau phosphorylation, mitochondrial health, and oxidative stress.

Alzheimer's disease and glycated tau protein: a mechanism for oxidative stress induction [87]

This study provides critical insights into how glycation of tau protein contributes to oxidative stress in AD. Their research indicates that glycated tau, formed through the non-enzymatic attachment of sugar molecules to the tau protein, significantly enhances tau's propensity to aggregate. It was elaborate on the dual role of glycated tau in AD pathology. This cycle is characterized by the production of ROS, which further promotes tau glycation and aggregation. The study highlights the potential of targeting tau glycation as a therapeutic strategy to mitigate oxidative stress and its deleterious effects in AD. By preventing glycation or enhancing cellular antioxidant defences, it might be possible to reduce the accumulation of glycated tau and the subsequent oxidative damage. It was also suggested that understanding the molecular pathways involved in tau glycation could provide new therapeutic targets. Furthermore, the study emphasizes the interplay between glycated tau and other AD pathologies, such as amyloid-beta plaques and neuroinflammation, proposing that a multifaceted approach addressing these interconnected pathways could be more effective in treating AD. Overall, this research provides a compelling argument for the significance of tau glycation in AD and underscores the need for further studies to explore therapeutic interventions targeting this process to combat oxidative stress and neurodegeneration. The results reveal that glycated tau proteins are more prone to aggregation compared to non-glycated tau, leading to the formation of neurofibrillary tangles, a hallmark of AD pathology.

The Crucial Vicious Circle in Neurodegenerative Tauopathies: Tau Hyperphosphorylation and Oxidative Stress [88]?

In this research results demonstrated a significant interaction between tau hyperphosphorylation and oxidative stress, highlighting a detrimental feedback loop that exacerbates neurodegeneration in tauopathies like AD. The study revealed that hyperphosphorylated tau impaired mitochondrial function, leading to an increase in ROS production. This mitochondrial dysfunction was marked by reduced electron transport chain activity, diminished mitochondrial membrane potential, and decreased ATP production. As a result, oxidative stress levels were elevated, with heightened markers of oxidative damage such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) detected in brain tissues. The discussion emphasized that oxidative stress not only contributed to further tau hyperphosphorylation by activating kinases such as glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) but also intensified the pathological effects of tau. The

authors proposed that this bidirectional relationship between tau hyperphosphorylation and oxidative stress created a vicious circle, exacerbating neuronal damage and disease progression. They suggested that breaking this cycle could be crucial for therapeutic strategies, including the use of antioxidants to mitigate oxidative stress and kinase inhibitors to prevent tau phosphorylation.

Alzheimer Disease-Related Events, Oxidative Stress, and Tau Phosphorylation Are Linked by p38 Kinase Activation [89]

In this research article the results elucidated a critical interplay between tau phosphorylation, oxidative stress, and cell cycle-related disruptions in AD. The study found that activation of p38 mitogen-activated protein kinase (p38 MAPK) played a pivotal role in this pathological network. Elevated p38 MAPK activity was associated with increased tau hyperphosphorylation, which contributed to the formation of neurofibrillary tangles, a hallmark of AD. Additionally, the research showed that p38 MAPK activation exacerbated oxidative stress by enhancing the production of ROS and reducing the efficacy of cellular antioxidant defences. The discussion emphasized that the p38 MAPK pathway served as a crucial mediator connecting tau pathology with oxidative stress and cell cycle abnormalities. Overall, the study provided significant insights into the molecular mechanisms linking tau phosphorylation with oxidative stress and cell cycle events, underscoring the potential of targeting p38 MAPK in the development of AD therapies.

Phosphorylation prevents the proteasome from turning over tau protein: the role of RCAN1 and oxidative stress [90]

This study investigated how tau protein phosphorylation affects its degradation by the proteasome and the role of oxidative stress and RCAN1 (Regulator of Calcineurin 1) in this process. The results demonstrated that tau hyperphosphorylation significantly inhibited its turnover by the proteasome, leading to an accumulation of tau in neurons. This accumulation was associated with reduced proteasomal activity, which was further exacerbated by oxidative stress. The study revealed that oxidative stress, characterized by elevated levels of ROS, impaired proteasomal function and thus contributed to the failure of tau degradation. Elevated RCAN1 levels were associated with increased tau accumulation and impaired proteasomal activity, indicating that RCAN1 exacerbated the negative effects of tau hyperphosphorylation and oxidative stress on protein turnover. In the discussion, the authors emphasized that the inhibition of tau degradation by the proteasome due to phosphorylation creates a feedback loop that contributes to tau pathology and neurodegeneration. The study suggested that targeting RCAN1 or improving proteasomal function could be potential therapeutic strategies to address tau accumulation and related neurodegenerative processes. Overall, the findings provided valuable insights into the molecular mechanisms underlying tau pathology and offered potential targets for therapeutic intervention in neurodegenerative diseases.

Alzheimer's disease's neurofibrillary pathology and tau protein [91]

In the study, the results elucidated the pivotal role of tau protein in the development of neurofibrillary tangles (NFTs), a hallmark of AD. Goedert's research demonstrated that abnormal hyperphosphorylation of tau protein leads to its detachment from microtubules and subsequent aggregation into paired helical filaments (PHFs) and NFTs within neurons. This pathological process disrupted the normal microtubule dynamics essential for axonal transport, ultimately resulting in impaired neuronal function and cell death. The study highlighted that the extent and distribution of NFTs correlated strongly with the severity of cognitive decline in AD patients, reinforcing the critical contribution of tau pathology to the disease's progression. Goedert also explored the molecular mechanisms underlying tau hyperphosphorylation, identifying key kinases such as glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) that were implicated in this process. In the discussion, it was emphasized that tau pathology, characterized by its abnormal phosphorylation and aggregation, plays a central role in the neurodegenerative process of AD. The study proposed that targeting tau hyperphosphorylation and aggregation could be a promising therapeutic strategy for AD. Potential approaches included the development of kinase inhibitors to prevent tau phosphorylation and immunotherapy to enhance the clearance of aggregated tau.

Alzheimer's disease: Tau Proteins and Tauopathies [92]

In this study, the researchers investigated the pathological role of tau proteins in AD and other related tauopathies. The results revealed that tau proteins, when abnormally hyperphosphorylated,

lose their ability to stabilize microtubules, leading to the formation of NFTs. The study demonstrated that hyperphosphorylated tau proteins aggregate and disrupt neuronal function by interfering with axonal transport and cellular signaling pathways. The researchers also identified several kinases, including GSK-3β and CDK5, that play crucial roles in tau hyperphosphorylation. Additionally, the study highlighted that oxidative stress and mitochondrial dysfunction contribute to the pathological phosphorylation and aggregation of tau, further exacerbating neuronal damage. In the discussion, it was emphasized that tauopathies, characterized by the abnormal aggregation of tau proteins, are central to the pathogenesis of AD and other neurodegenerative diseases.

Tau protein, both total and phosphorylated, functions as a biological marker for Alzheimer's [93]

In this research, the investigators focused on evaluating the levels of total tau (t-tau) and phosphorylated tau (p-tau) proteins as potential biomarkers for the early diagnosis and progression monitoring of AD. The results indicated that both t-tau and p-tau levels were significantly elevated in the cerebrospinal fluid (CSF) of AD patients compared to healthy controls and individuals with other neurological conditions. Elevated t-tau levels reflected the extent of neuronal damage and degeneration, while increased p-tau levels were associated with the formation of NFTs and the pathological phosphorylation of tau. The study showed that the measurement of these biomarkers could differentiate AD from other dementias with high sensitivity and specificity. Moreover, the combination of t-tau and p-tau levels provided a more robust diagnostic tool compared to using either marker alone. Longitudinal analysis revealed that rising levels of these tau markers correlated with cognitive decline and disease progression, suggesting their utility in tracking the severity of AD. In the discussion, it was emphasized the clinical significance of t-tau and p-tau as biomarkers for AD. The integrating t-tau and p-tau measurements with other biomarkers, such as amyloid-beta levels and imaging techniques, could enhance diagnostic accuracy and provide a comprehensive understanding of AD pathology. Furthermore, the study underscored the importance of standardizing tau measurement techniques to ensure consistency and reliability across clinical settings.

Immunotherapy Specifically Targeting Pathological Tau Protein in Tauopathies Associated with Alzheimer's Disease [94]

In the study, researchers investigated the efficacy of immunotherapeutic approaches aimed at reducing pathological tau aggregates in the brain. The results demonstrated that both active and passive immunization strategies significantly reduced the levels of hyperphosphorylated tau and tau aggregates in animal models of AD. The study found that these immunotherapies facilitated the clearance of tau aggregates by microglia, the brain's resident immune cells, thereby reducing the burden of NFTs. It was highlighted that by specifically targeting pathological tau, these therapies could address a key aspect of AD pathology that is not directly targeted by amyloid-beta therapies. The discussion noted that the reduction in tau pathology correlated with functional improvements in the treated animals, underscoring the therapeutic relevance of tau clearance. The study concluded that while there are hurdles to overcome, immunotherapy targeting pathological tau holds significant promise for altering the course of AD and related tauopathies, potentially providing a new avenue for treatment that could improve patient outcomes and quality of life.

Alzheimer's disease and other tauopathies: hyperphosphorylation and aggregation of tau proteins, and potential neuroprotective approaches [95]

In this research, the results highlighted that tau protein hyperphosphorylation was a critical factor in the pathogenesis of AD and other tauopathies. Researchers observed that hyperphosphorylated tau proteins aggregated into NFTs, which disrupted microtubule stability and led to neuronal dysfunction and cell death. This pathological process was linked to cognitive decline and other symptoms of tauopathies. The study also investigated potential neuroprotective strategies, including pharmacological inhibitors of tau kinases, antioxidants to counteract oxidative stress, and agents aimed at enhancing tau clearance. Results showed that these strategies could effectively reduce tau hyperphosphorylation and aggregation in preclinical models, leading to improved neuronal health and cognitive function. The discussion emphasized the therapeutic potential of targeting tau pathology, suggesting that while current treatments focus on amyloid-beta, addressing tau hyperphosphorylation and aggregation could offer a more direct approach to treating AD. It was noted the promise of kinase inhibitors and antioxidants, as well as the potential benefits of immunotherapy to

enhance tau clearance. It was highlighted the need for further research to optimize these strategies, ensure their efficacy in clinical settings, and assess their long-term safety. Overall, the study provided significant insights into tau pathology and suggested that targeted neuroprotective strategies could play a crucial role in managing tau-related neurodegenerative diseases.

Alzheimer's disease biomarkers include phosphorylated tau protein, total tau in CSF, and Aβ42 [96]

In this study, the results revealed that CSF levels of total tau (t-tau), amyloid-beta 42 (Aβ42), and phosphorylated tau (p-tau) were reliable biomarkers for diagnosing and monitoring AD. Researchers found that AD patients had significantly elevated levels of t-tau and p-tau, along with decreased levels of Aβ42, compared to healthy controls and individuals with other neurological disorders. These elevated t-tau and p-tau levels were associated with neuronal damage and neurofibrillary tangles, while lower Aβ42 levels indicated amyloid plaque deposition in the brain. The study demonstrated that the combination of these biomarkers provided high sensitivity and specificity in distinguishing AD from other dementias. It emphasized the clinical utility of these CSF biomarkers in early diagnosis and disease progression monitoring, highlighting their potential to facilitate timely intervention and improve patient outcomes. It also stressed the importance of standardizing measurement techniques and suggested that combining these biomarkers with imaging methods could enhance diagnostic accuracy and provide a comprehensive understanding of AD pathology. Overall, the findings supported the use of CSF t-tau, p-tau, and Aβ42 as robust biomarkers for Alzheimer's disease, aiding in both diagnosis and the development of targeted therapies.

Conclusion

A significant pathophysiological alteration in AD is oxidative stress, by causing mitochondrial malfunction, boosting metal toxicity, and creating vicious pathophysiological cycles, it is intimately related to amyloid pathology and tau pathology. Although it also offers as a potential therapeutic target, oxidative stress is indeed a crucial clinical hallmark of AD. The etiology of tauopathies appears to involve both oxidative stress & tau hyperphosphorylation as important components. Uncertainty still exists regarding the connection between tau hyperphosphorylation and intracellular ROS. Oxidative stress has been demonstrated to result from the build-up of hyperphosphorylated tau, while ROS have also been demonstrated to promote tau hyperphosphorylation. In this situation, a deeper comprehension of oxidative stress's role in various pathologies may be used to first identify novel disease markers and later create therapeutic approaches to slow, stop, or reverse illness progression. A vicious circle that plays a significant part in the pathological process in tau diseases, including AD, may also be formed by the intimate interaction between tau hyperphosphorylation & Oxidative Stress.

Abbreviations

MAPT: Microtubule associated protein tau;
CNS: Central nervous system;
MBDs: Microtubule binding domains;
NMR: Nuclear magnetic resonance;
PS-1: Presenilin-1;
SH3: SRC Homology 3;
PLC: Phospholipase C;
HDAC-6: Histone deacetylase-6;
KO: Knockout;
MAP1A: Microtubule associated proteins;
cDNA: Complementary DNA;
NFTs: Neurofibrillary tangles;
ROS: Reactive oxygen species;
AD: Alzheimer's disease;
RNS: Reactive nitrogen species;
mDNA: Mitochondrial DNA;
PUFAs: Poly-unsaturated fatty acids;
4-HNE: 4-hydroxynonenal;
MDA: Malondialdehyde;
MCI: Mild cognitive impairment;
F2-IsoPs: F2-isoprostane;
CSF: Cerebrospinal fluid;
8-OHdG: 8-hydroxy-2'-deoxyguanosine;
APP: Amyloid precursor protein;
Mn-SOD: Manganese superoxide d-imutase;
ROS: Reactive oxygen species;
Drp1: Dynamin related protein 1;
UCPs: Uncoupling protein;
MELAS: Mitochondrial encephalomyopathy, lactic acidosis with stroke-like events;
LHON: Lebar's hereditary optic neuropathy;
8-OHG: 8-hydroxy guanosine;
SOD-2: Superoxide dismutase-2;
CTE: Chronic traumatic encephalopathy;
SOD: Superoxide dismutase;
GPx: Glutathione peroxidase;
JNKs: C-Jun N-terminal kinases;
FTDP-17: Frontotemporal dementia & parkinsonism;
GSK3: Glycogen synthase kinase-3;
PC12: Pheochromocytoma

Conflict of interest

Authors declare that we have no Conflict of Interest.

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