Review

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# Tau as the Converging Protein between Chronic Stress and Alzheimer's Disease Synaptic Pathology

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**Key Words**
Alzheimer's disease · Environment · Tau · Stress · Glucocorticoids · Synapse · Missorting

**Abstract**
***Background:*** Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder with a complex physiopathology and still undefined initiators. Several risk factors have been suggested for AD with recent evidence supporting an etiopathogenic role of chronic environmental stress and glucocorticoids (GCs, stress hormones) in the development of the disease. Indeed, both AD and chronic stress are associated with neuronal atrophy, synaptic loss and cognitive impairment. Our previous studies have demonstrated the aggravating role of stress and GCs on AD pathology, including Tau hyperphosphorylation and aggregation and cognitive deficits in various AD models. In light of the suggested involvement of Tau missorting in AD synaptotoxity and the dual cytoplasmic and synaptic role of Tau, our recent studies focused on the possible role of Tau in the underlying cascades of stress/GC neuronal malfunction/atrophy in wild-type animals by monitoring the intracellular localization of Tau and its phosphorylation status in different cellular compartments. ***Summary:*** Biochemical, ultrastructural, behavioral and neurostructural analysis have helped demonstrate that prolonged GC administration leads to dendritic remodeling and spine atrophy and loss in the rat hippocampus triggering Tau missorting at hippocampal synapses with the participation of specific phosphorylated Tau isoforms in this synaptic accumulation. ***Key Messages:*** The above findings suggest that Tau plays an essential role in mediating the neurodegenerative effects of stress and GCs towards the development of AD pathology. In addition, they highlight the involvement of Tau missorting in mechanism(s) of synaptic atrophy, beyond AD adding to our limited knowledge of the mechanisms through which stress causes brain pathology.



## Tau Protein in and beyond Alzheimer's Disease

Improvements in life span over the last decades have, unfortunately, not been matched by improvements in the mental health span. The World Health Organization estimates that a leading cause of mental disability in the coming years will be Alzheimer's disease (AD), a disease that already affects more than 35 million people worldwide. To combat this brain disorder, clinical and basic research continues to strive to improve the mechanistic understanding of AD pathology which is characterized by: (i) the overproduction of amyloid-β (Aβ), a neurotoxic peptide which fibrillates and accumulates as senile plaques in the brain, and (ii) hyperphosphorylation of the cytoskel-



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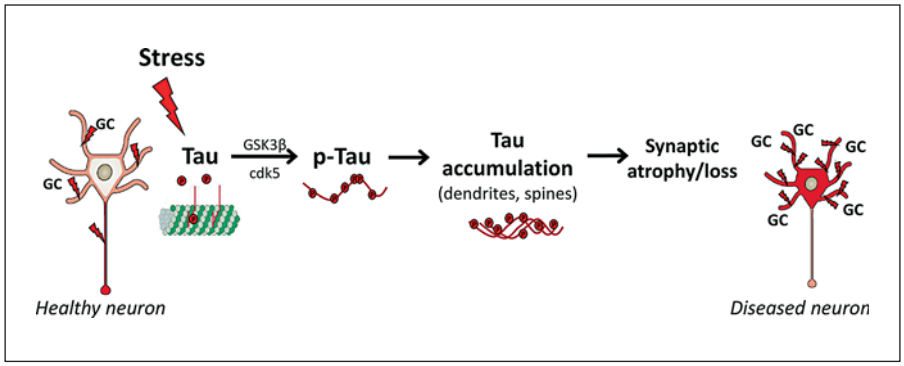


**Fig. 1.** The neurodegenerative potential of chronic stress and GCs may be mediated through Tau protein. Prolonged exposure to GCs and/or stress triggers the aberrant hyperphosphorylation of the cytoskeletal protein Tau (p-Tau; mainly localized in axons; red in the healthy neuron), through the activation of different kinases (e.g. GSK3-β and cdk5). This leads to the somatodendritic accumulation as well as synaptic missorting of Tau (red in diseased neuron), leading to neuronal malfunction and synaptic loss as well as cognitive impairment.

etal protein Tau which accumulates in neuronal soma as insoluble aggregates and neurofibrillary tangles [1, 2]. Sequential cleavage of the transmembrane protein amyloid precursor protein by β- and γ-secretases yields Aβ; this cellular pathway is called amyloid precursor protein (APP) misprocessing. Numerous studies have causally linked Aβ to synaptic malfunction, neuronal atrophy and synaptic loss. In addition, it has been suggested that Aβ also triggers the other neurodegenerative mechanism of AD, the abnormal Tau hyperphosphorylation, leading to the formation of Tau aggregates and neuronal atrophy and loss.

The potential key role played of Tau in AD gained recognition relatively recently, and the protein is now a target in several drug discovery programs aimed at AD [3]. There is now strong evidence that Tau mediates at least some of the neuro- and synaptotoxic effects of Aβ [4–7]. Accordingly, our own and other work has demonstrated that synaptic dysfunction and atrophy as well as memory impairments are accompanied by the accumulation of hyperphosphorylated Tau in synapses, implicating hyperphosphorylated tau in AD synaptic loss [8–10]. Interestingly, while it is generally known as an axonal protein with a role in microtubule stabilization and assembly, Tau was recently shown to be present at synapses where it acts as scaffold protein and interacts with various proteins/receptors that modulate synaptic signaling and plasticity [11, 12]; still, the exact role of Tau at synapses needs further investigation.

Increasingly, Tau is being recognized to play a key role in brain physiology and pathology that goes beyond AD. For example, Tau has been suggested to be an essential mediator of different neuropathological processes beyond AD, e.g. excitotoxicity and epileptogenesis; hereby, Tau depletion blocks the neuronal malfunction damage and behavioral deficits [13–15]. Further, our previous work indicated that Tau may lie at the core of chronic stress-induced pathological aging of the brain [10, 16]. Those findings proposed that Tau hyperphosphorylation may be a critical mechanism through which chronic stress and glucocorticoids (GCs, stress hormones) initiate neuropathological events that precipitate AD pathology [17]. Together, the above findings highlight Tau as a potential key modulator of neuronal and synaptic function during healthy and pathological brain states.

## Chronic Stress and GCs as Precipitators of AD Pathology

Several factors that place individuals at risk for developing AD have been identified. Clinical evidence supports an etiopathogenic role for chronic stress and elevated GC levels in the development of AD pathology (fig. 1). Human studies suggest that exposure to chronic stress advances the onset of familial AD [18, 19] while high levels of GCs have been reported in the blood plasma, saliva and cerebrospinal fluid of AD patients [20–24]; the increased GC levels commonly associate with memory deficits in these patients [25, 26]. Since chronic elevation of GC levels is known to impair memory and other cognitive functions, it appears likely that GCs contribute to the progressive cognitive decline observed in AD. The hippocampus is a principal target of GC actions, and hippocampal neurons express the highest levels of GC receptors in the brain. The hippocampus is early affected in AD, and its dysfunction results in impairments in declarative, spatial and contextual memory. These facts, together with the important part played by the hippocampus in restraining GC secretion and, thus, regulating physiological mechanisms of stress response, have made this brain region a focus of research fields of both stress and AD raising the question of how high GC levels and chronic stress

impact the deterioration of hippocampal functions related to toxic Aβ and Tau hyperphosphorylation.

Previous studies from our own and other laboratories showed that exposure to chronic stress or prolonged treatment with the synthetic GC dexamethasone result in increased APP misprocessing and Aβ production in the hippocampus of AD animal models in parallel with memory deficits [27–29]. Further, we and others have shown that chronic stress and/or GC treatment trigger Tau hyperphosphorylation in neuronal somata in various animal models of AD; notably, these treatments hyperphosphorylated several Tau epitopes [10, 27] known to be associated with cytoskeletal pathology, synaptic loss and hippocampal atrophy as well as impairments of memory, speed of mental processing, and executive functions in AD patients (e.g. pSer262, pThr231) [30–35]. Our own work also demonstrated that GC treatment and chronic stress increased Tau accumulation by affecting turnover of the protein [10, 16], indicating that GCs may reduce Tau degradation through dysregulation of molecular chaperones responsible for tau proteostasis (e.g. heat-shock proteins Hsp90 and Hsp70) [36]. Interestingly, Hsp90 and Hsp70 serve to maintain GC receptors in a high-affinity state, thus suggesting a point at which GC/GC receptor signaling and Tau degradation machinery can intersect. The reduced Tau degradation could also facilitate the increased aggregation of Tau into insoluble forms triggered by stress in P301L-Tau Tg mice (mice expressing human tau carrying the most common Tau mutation P301L) [36]. In this last study, chronic stress was shown to promote C-terminal truncation of Tau by caspase-3 and abnormal conformation of Tau in the hippocampus of P301L-Tau Tg mice. Together with Tau hyperphosphorylation, both truncation and abnormal conformation of tau precede its aggregation and formation of neurofibrillary tangles [37–39], thus serving as early markers of disease.

## Tau Accumulation: Linking Stress with Synaptic Pathology and AD?

Recent human and animal studies suggest that mislocated Tau, due to missorting in dendritic spines and synapses, underpins the synaptic pathology found in AD [8, 40–42]. This could possibly explain the known correlation between Tau hyperphosphorylation and synaptic loss and memory impairment in experimental animals [9, 40], and such a mechanism could also possibly explain how stress results in synapse and memory loss. These hypotheses are indeed supported by very new studies in our laboratory that implicate Tau missorting in GC-triggered hippocampal pathology in wild-type animals [43]. We demonstrated, both by biochemical (subcellular fractionation) and ultrastructural (electron microscope) analysis, that prolonged GC administration in wild-type animals led to cytosolic and dendritic Tau accumulation in the rat hippocampus and triggered Tau hyperphosphorylation in epitopes related to its malfunction (Ser396/404) and cytoskeletal pathology (e.g. Thr231 and Ser262). In addition, we show that chronic GC administration also increased Tau levels in the synaptic compartment related to dendritic remodeling and synaptic loss exhibiting a preferential subcellular accumulation of different Tau isoforms in different intracellular compartments [43]. Overall, these recent findings from our laboratory support a role for Tau and its missorting in GC-induced dendritic remodeling and synaptic loss.

This brief review highlights the essential role of Tau protein in the neurodegenerative potential of chronic stress and GC towards the development of AD. It also summarizes the emerging evidence that Tau missorting may be a common mechanism in both AD and stress-related disorders of the brain adding to our knowledge about the poorly understood cellular cascades of stress-related brain pathology.

## Disclosure Statement

The authors have no conflicts of interest to declare.

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