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TAU-MEDIATED SYNAPTIC DAMAGE IN ALZHEIMER'S DISEASE

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Abstract

Synapses are the principal sites for chemical communication between neurons and are essential for performing the dynamic functions of the brain. In Alzheimer's disease and related tauopathies, synapses are exposed to disease modified protein tau, which may cause the loss of synaptic contacts that culminate in dementia. In recent decades, structural, transcriptomic and proteomic studies suggest that Alzheimer's disease represents a synaptic disorder. Tau neurofibrillary pathology and synaptic loss correlate well with cognitive impairment in these disorders. Moreover, regional distribution and the load of neurofibrillary lesions parallel the distribution of the synaptic loss. Several transgenic models of tauopathy expressing various forms of tau protein exhibit structural synaptic deficits. The pathological tau proteins cause the dysregulation of synaptic proteome and lead to the functional abnormalities of synaptic transmission. A large body of evidence suggests that tau protein plays a key role in the synaptic impairment of human tauopathies.

Keywords

• Alzheimer's disease• Synaptic loss• Tau protein• Neurofibrillary degeneration• Tauopathies• Tau mislocalization• Transgenic models

Introduction

Cognitive functions such as learning and memory depend on synaptic efficiency in certain regions of the brain [1]. In human neurodegenerative diseases, synapses are exposed to pathologically modified proteins aggregated in the intracellular and extracellular space. The protein aggregates may induce the loss of synaptic connections in vulnerable brain areas. The recurrent dysregulation of synaptic proteins [2], rapid *N*-methyl-D-aspartate receptors (NMDAR) endocytosis and regression of dendritic spines [3] are the forerunners in imposing synaptic impairment in these disorders.

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder with an estimated 35 million people affected worldwide [4]. The risk factors for AD include lower mental and physical activity during old age, head trauma, cardiovascular diseases, diabetes, obesity and smoking [5]. Histological examinations of an AD brain uncover two classical hallmarks, namely neurofibrillary tangles - composed of tau protein and senile plaques consisting of amyloid-beta (Aβ) protein [6, 7]. A very small proportion of AD cases have genetic dispositions which are categorized as familial AD [8]. However, the majority of AD cases are idiopathic, meaning that the cause of the illness is unknown. [9]. Despite scientific and pharmaceutical advancements, AD still poses as an epidemiological challenge for the future [10]. Therapeutic intervention for a neurodegenerative disease is best performed before irreversible memory loss and tissue damage occurs [11]. Therefore, investigating and understanding early pathological changes in AD would prove to be beneficial.

It has been suggested that AD may represent a synaptic disorder [12-14]. Synaptic impairment occurs very early in AD and correlates well with the severity of dementia [15-18]. Furthermore, at least certain components of the synaptic loss in AD occur regionally and are disproportionately large in the hippocampus [2].

Several studies have demonstrated that the degree of synaptic impairment and loss is linked with tangle pathology [19-21]. Therefore, studies on the involvement of tau protein in synaptic damage have received increased importance in recent years [22]. Identification of the molecular mechanisms underlying tau mediated synaptic damage in AD signifies an important step in the development of therapeutic agents that can prevent or delay the onset or progression of the disease.

Tau physiology and function

Tau protein belongs to the family of microtubule-associated proteins (MAP). It is localized mainly in the neurons of both vertebrates and certain invertebrates. In the human brain, tau proteome consists of six isoforms ranging from 352 to 441 aa [23]. The tau proteins are further classified by the presence of three repeat (3R) or four repeat (4R) regions in the C-terminal and the presence or absence of one (29 aa) or two (58 aa) inserts in the N-terminal region [24-26]. It is suggested that the repeat regions aa 244-368 of tau bind to microtubules directly [27] and the aa domains 151-243 and 369-400 surrounding the repeat region enhance the affinity of microtubule binding of tau.

Tau is involved in retrograde and anterograde transport by differential interaction with dynein and kinesin motor proteins [28]. Tau interacts with actin and spectrin proteins, this allows microtubules to interconnect with other cytoskeletal components and restrict the flexibility of the microtubules [29]. Furthermore,

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the N-terminal domain also interacts with the SRC homology 3 (SH3) domain of phospholipase C-γ (PLC-γ) and mediates the generation of arachidonic acid [30]. These results suggest that tau may modulate microtubule flexibility and also alter cell shape and structure. It is reported that the phosphorylation of tau protein in early developmental stages is slightly upregulated to provide optimal flexibility to the growth cones [31]. In addition, tau interacts with embryonic ectoderm development (Eed) protein to facilitate nuclear transport of Eed suggesting a possible role of tau in embryonic development [32]. Studies also suggest a role of tau protein in metabolic rate depression in hibernating animals [33].

Recent studies demonstrate the role of tau protein in long term potentiation [34] and long term depression [35, 36]. Tau to dendrite conglomeration is also necessary for targeting of fyn kinase to the postsynaptic compartment [37] and subsequent phosphorylation of NMDAR subunit NR2B in dendrites [38], and in the initiation of myelination [39]. To sum up, tau protein plays a diverse role in neuronal activity including cytoskeleton organization, signaling and synaptic plasticity.

Neurofibrillary tangles and tau protein

In 1906, Alzheimer first reported the presence of neurofibrillary tangles (NFT) in a woman suffering from dementia [40]. These structures are observed mainly in the glutamatergic pyramidal neurons of the hippocampus and the entorhinal cortex, supra and infragranular layers of association cortical areas, cholinergic neurons of nucleus basalis of Meynert and noradrenergic neurons in the locus coeruleus [6, 23]. Electron microscopy images of NFT were first studied by Kidd and were referred to as longitudinally arranged fibrillar bundles [41]. Additionally, diffraction pattern revealed the presence of a double helical stack of cytoskeletal protofilaments [42]. NFT predominantly composed of paired helical filaments (PHF) are morphologically described as helical ribbons being 8-24 nm in width, with 80-nm periodic twists in AD [43]. Several decades later it was established that tau was one of the main components of NFT [44-47]. However, it was not until 1988 that tau protein was proved to be the major and integral part of the PHFs in AD [48, 49].

Tau is an intrinsically disordered protein [50]. In diseased brains, tau protein undergoes numerous pathological alterations leading to aberrant conformational modifications which liberate tau from the microtubules [51-53]. Although tau phosphorylation is observed in normal human brains, the degree and extent of tau phosphorylation is severe in AD [54, 55]. Phosphorylation is one of the crucial post-translational modifications of tau protein in AD brains [24]. In AD, tau protein is hyperphosphorylated at 19 aa residues [56]. Numerous studies have reported the phosphorylation of tau in the binding domain, which hinders tau binding to microtubules such as Ser 262 [57], Thr 231 [58], Thr 212 and Ser 214 [59]. The liberated tau proteins then aggregate into PHF and deposit intracellularly into NFT. Studies have further shown that isolated PHF exhibit either α-helical or β-sheeted structures in various conditions [60, 61] and intermediary conformations during structural transition [62].

Truncation of tau transforms physiological tau to pathological forms that are vulnerable to oligomerization [63]. Biochemical characterization of PHF revealed a 12 kDa pronase resistant fragment decorated by antibody MN423 [64]. Epitope mapping suggests that MN423 recognizes truncated tau at Glu391 of the PHF core, suggesting that tau truncation is a disease associated process [65]. Later it was shown that the truncation at Glu391 enhanced the rate of tau filament formation [66]. Furthermore, it was also shown that truncation of tau may be involved in the evolution of NFT in AD brains [67-69].

Tau proteome in human tauopathies

Biochemical and proteomic studies demonstrate the existence of different pathological tau compositions in tauopathies. Based on the type of tau isoforms involved, tauopathies are classified into several classes [70]. In class I tauopathies, the aggregation of all 6 tau isoforms in equal ratios is observed [70, 71]. Biochemically, tau triplets of 60, 64 and 69 kDa, and additional minor bands of 72/74 kDa are characteristic for AD, some cases of frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP 17), Niemann-Pick disease, type C, Down syndrome and dementia pugilistica [70].

In class II tauopathies, insoluble tau doublets of 64 and 69 kDa predominantly composed of 4R tau isoforms are observed. This class includes progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and some specific cases of FTDP-17 [72, 73]. Class III tauopathies are characterized by the presence of pathological tau doublets of 60 kDa and 64 kDa with predominant 3R tau isoforms (lacking the exon 10) [70]. Pick's disease is the sole neurodegenerative tauopathy assigned to this class [72]. Class IV tauopathy is represented by a single neurological disorder – myotonic dystrophy of type I or Steinert's disease (DM1), in which a major insoluble tau band of 60 kDa, and minor 64 and 69 kDa bands are identified.

Tau synaptic proteome

The localization of tau in the axonal and somatodendritic compartments has drawn considerable interest in the last decade. It has been suggested that tau protein is localized mainly in the axons [74] due to the presence of an axonal targeting sequence [75]. However, some recent studies indicate a wide spread distribution of tau protein in other compartments including the nucleus [76] and dendrites [37, 77]. Interestingly, tau protein has been detected in the total synaptosomes isolated from a rat brain [38]. Our study demonstrated that tau protein in the rat brain was mainly distributed in presynaptic fractions while in postsynaptic densities it was almost absent [78] (Fig. 1). Isolation and evaluation of synaptic fractions from human and dogs also revealed identical patterns of tau protein distribution (Fig. 1). These results suggest that tau is mostly located in the presynaptic component, which supports the notion that tau is predominantly distributed in axonal compartment.

On the other hand, it has been shown that tau protein migrates to dendrites following

synaptic activation and is phosphorylated at various sites [38, 79]. In synapses, tau protein interacts with actin [80], microfilaments [81], postsynaptic density protein 95 (PSD-95), NMDAR [38] and kinases such as fyn [37]. Likewise, tau protein is necessary for dendritic targeting of fyn kinase [37]. Besides, the loss of tau protein in dendrites resulted in a decreased spine density [82]. Independent results from tau knockout mice show that tau protein is essential for NMDA-dependent long term potentiation (LTP) [34] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-dependent long term depression (LTD) [35, 36]. Furthermore, selective phosphorylation of tau protein was observed following NMDAR activation which in turn regulates tau interaction with fyn kinase [38]. These results establish a profound role of tau protein in the neuronal dendrites.

Synaptic impairment in Alzheimer's disease

In AD, cognitive decline best correlates with synaptic loss and synaptic failure [6, 12, 83-85]. Synaptic degeneration is a slow process, which begins as a reversible functionally-responsive stage marked by deregulation of synaptic function, and then culminating into irreparable loss of synapses [86]. Furthermore, the degree of synaptic reorganization in AD is also perturbed due to defective microtubule re-organization, impaired actin dynamics, and re-entry into the cell cycle [87-89].

Loss of synapses in the limbic cortex is the basis for cognitive deficits in AD brains [12, 13]. It is suggested that dementia in AD is a combined manifestation of the disruption of neuritic substructures and the loss of synaptic terminals in neocortical and subcortical regions in the brain [90]. Initial investigations in the field of synaptic impairment in AD involved morphological studies for synaptic loss and damage in various brain areas [16], both in early and late stages of AD [2, 91-95]. During early stages, an increase in glutamatergic and cholinergic synapses was observed [96, 97]. However, as the disease progressed there was a rampant change in the density of these synapses. Synaptic loss occurs in early

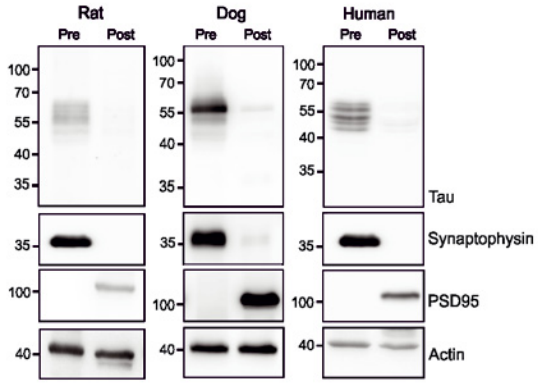

Figure 1. Tau synaptic proteome in physiological conditions. Pre- and postsynaptic fractions were isolated as previously published [78]. Synaptic fractions from rat, dog and humans show that tau protein is predominantly distributed in the presynaptic fraction (pre), while in postsynaptic fraction is observed in traces (post).

pathological stages with almost 45% fewer synapses in mild AD [18, 98]. A significant decrease in the synapses/ neurons ratio by up to 48% in hippocampus and 56% in cerebellum was reported [99]. In AD brains, synaptic loss is seen in the cortical areas [13, 100], predominantly in the frontal (45% reduction) and temporal cortex (25-36% reduction) [15, 90, 101]. Furthermore, the entorhinal cortex and locus coeruleus also display a loss of synapses [18, 90, 102-104]. In addition, cognitive disabilities in mild cognitive impairment were associated with decreased levels of glutamatergic synapses [97, 105]. The levels of glutamatergic synapses strongly correlated with clinical dementia in patients with mild and severe AD [97]. Interestingly, an enlarged average area of surviving synapses in AD was also observed [99]. However, this increase led to an overall reduction in synaptic surface per μm^3 of tissue indicating that structural changes and concomitant functional changes play a crucial role in synaptic pathology in AD.

The mechanisms of synaptic damage in AD are still unclear. It is suggested that abnormal processing of growth associated proteins may be responsible for synaptic damage in CNS of AD brains [106, 107]. Ultrastructural investigations revealed pathological accumulation of cytoskeletal proteins and lysosomal structures in the synapses of AD patients [106, 108, 109]. Additionally, accumulation of both Aβ and tau protein in the synaptosomes from AD brains [110] present cues for synaptic pathogenesis and its possible relation to either the abnormal function of synaptic proteins or direct toxic effects at the synaptic sites or both [111]. Several factors may be attributed to the changes in the synapses of AD brains: 1) decreased mRNA levels of synaptic proteins [85, 112]; 2) selective degradation of proteins; for example, the presence of caspases was observed in synaptosomes isolated from AD brains [110, 113]; 3) decreased transporter proteins in the synapses [114]; 4) abnormal function of synaptic proteins [111,115]; 5) abnormal deposition of proteins leading to diminished synaptic activity; for example, tau protein was shown to interact with synaptic proteins *in vivo* [37, 38].

Role of tau protein in synaptic pathology

Several studies have focused on Aβ as the trigger for synaptic damage in AD and suggest that tau protein is downstream of Aβ in AD pathology [7, 116, 117]. Interestingly, it was shown that the loss of neocortical synaptic inputs in AD brain could be independent from amyloid deposits [107,118]. In addition, neurodegeneration in AD is not a direct result of extracellular Aβ neurotoxicity [119]. Therefore, Aβ pathology may or may not be a direct causal agent for synapse loss in AD [120]. Conversely, limited studies focusing on tau as the candidate mediating synaptic protein loss and damage have been reported. Several factors point towards a prominent role of tau

protein in mediating synaptic pathology: 1) the progression of tau pathology correlates well with the cognitive decline in human AD [121]; tangle pathology also showed stronger correlation with synapse density and Blessed score of cognitive impairment in AD [122], 2) synapse loss parallels tangle formation and occurs in the same regions in AD brains [13, 15, 20, 21], 3) higher tangle count is associated with lower levels of presynaptic proteins in AD [91]; furthermore, neurons containing NFT are responsible for selective synaptic deficits [123], 4) NFT-bearing neurons demonstrated a 35-57% reduction in synaptophysin mRNA in AD brain [85], and even more importantly 5) synaptic deficits are observed in frontotemporal lobar degeneration (FTLD), PSP, and Niemann-Pick disease type C (NP-C), which are independent of any Aβ pathology [124-128]. All these evidences suggest a well-established relationship between synaptic damage and tau pathology.

Insights on tau mediated pathology in synapses from tau transgenic models

Tau transgenic models have been widely used to examine disease pathogenesis of tau protein. Behavioral and cognitive functional deficits can be easily studied in these animals due to the availability of lab scale methodologies such as Morris maze test, object recognition test and many others neurobehavioral tests [129]. Transgenic models used for the study of the tau neurodegenerative cascade express human wild-type tau, mutant tau linked to FTDP-17 or structurally modified tau species derived from AD [130]. Tau transgenic lines are driven by constitutive or inducible promoters to regulate the expression of the exogenous protein [131, 132]. Several of these tau transgenic models exhibit deregulation in synaptic proteome, impairment of synaptic transmission, loss of synapses and dendritic loss (Table 1).

Structural alterations and electrophysiological changes

Transgenic tauopathy models recapitulate several AD like morphological changes in the synapses. Transgenic tau lines expressing human 6 tau isoforms or human full length tau protein (hTau2N/4R) display loss of synapses and mushroom spines [133- 135]. More specifically, mice lines expressing 6 human tau isoforms in tau knockout background exhibit more thin spines rather than mushroom like spines [135]. Interestingly, an initial decline in mushroom spine volume at 3 months of age was reversed after 6 months, indicating a certain degree of compensatory mechanism [135]. Despite an increase in mushroom spine volume, the older animals still displayed diminished LTP and spatial memory deficits [136]. Interestingly, the effect of htau40 in spine reduction was rescued by double transfection of the cells with MARK2 (phosphorylates tau in repeat region KXGS) indicating that phosphorylation of tau at this site is crucial for tau release from microtubules [137].

Several mice models expressing FTDP-17 tau mutations have been developed which demonstrate synaptic deficiency. For instance, mice expressing P301S mutation show hippocampal synaptic loss [138], mainly in the CA3 region [139]. More specifically, a progressive loss of spines in layer V of the neocortex along with reduced LTP was observed in these mice [140]. Similarly, mice expressing human mutant tau with P301L mutation also exhibit loss of synapses in this subset of neurons [141-143] and a loss of dendritic spines [77]. In addition, remnant dendritic spines exhibit deficits in dendritic diameter and length [144,145]. Finally, synaptic hyperexcitability in the form of increase in depolarization, action potential and synaptic excitatory postsynaptic potentials (sEPSP) were observed in these animals [146]. Comparable effects were also observed in other mice strains expressing P301L mutant tau with a different genetic background (JNPL13) [147], mainly as increases in long-phase LTP [148]. The animals also exhibited improved learning and memory processes. Interestingly, mice models expressing P301L mutated tau protein residing solely in the entorhinal cortex (rTgTauEC) exhibited loss of synaptic vesicles [149]. In contrast, the presynaptic alteration enhanced axonal excitability in these animals, but reduced LTP [150]. However, signs of cognitive insufficiency were absent or mild in these animals. Interestingly, in early stages the P301L tau mutant mice showed elevated levels of dendritic spine when compared to wild type mice (tau-P301L mice) [143]. The P301L tau mutant mice also exhibited increased levels of vesicular glutamate transporter 1 (vGLUT1) indicating a compensatory mechanism [151]. Although in older animals the deleterious repercussions of P301L mutant tau expression are widely noted.

Unlike previously reported tau lines, young mice expressing G272V/P301S double mutant tau showed no overt synaptic pathology [152]. However, older animals displayed a decrease in excitatory postsynaptic potentiation (EPSP) [153]. Organotypic sections from THY-Tau22 mice (G272V and P301S mutations) showed that the reduction in synaptic activity is induced by brain-derived neurotrophic factor [154]. Likewise, the double mutated tau mice model expressing K257T/P301S also displayed impairment in sustenance of LTP [155].

Sydow *et al*. [156] generated on/off mouse model ($Tau^{RD\Delta PP}$ (244-372) ΔK280 mice) expressing the tau repeat domain with pro-aggregant mutation (where point mutation at lysine 280 drives aggregation of tau). The mice showed aggregation of endogenous and recombinant tau, tau missorting into the dendrites and synaptic loss [157]. Moreover, organotypic slides from mice showed marked reduction in synaptic boutons, diminished dendritic density and altered morphology [158-159]. Furthermore, diminished calcium influx after membrane depolarization was observed suggesting altered calcium dynamics in these neurons. Transgenic mice also showed marked deficits in LTP in CA1 and CA3 hippocampal regions [156, 160].

Studies from transgenic tau models clearly show that tau protein can damage the structural and functional properties of synapses leading to the impairment of LTP and/or LTD.

Proteomic changes in tau transgenic models

The synaptic impairment in AD is mainly characterized by the dysregulation of synaptic proteins at proteomic and transcriptomic levels [91, 161, 162]. Massive loss in components of the synaptic and dense core vesicles is

Table 1. A summary of transgenic tauopathy models, form of tau protein expressed and their effect on synapse structure and function.

Tau type	Host	Human Tau form	Line	Structural changes	Electrophysiological abnormalities	Proteomic changes	Reference
Normal	Mice	6 tau isoforms	hTau mice			↓ Synaptophysin, synaptojanin, mGluR, synaptobrevin, syntaxin, PSD-95, TrkB	173
					↓ HFS-induced LTP in Schaffer collateral fibers		136
		Tau 2N/4R isoform	Wtau-Tg	↓ Synapse density		↓ PSD-95	133
			Tau.4R mice	↓ Length of mushroom spines, ↑ spine density			134
			JNPL3	↓ Density of synaptic boutons, synaptic stripping			147
				↑ Late phase-LTP			148
			Tau-4R-P301L mice	↓ Length of mushroom spines, ↑ spine density			134
Mutated				↓ Dendritic complexity and length, ↓ spine density			144
		Tau 40 with P301L mutation	rTg4510	↓ Dendritic diameters, ↓ cortical spine	↑ sEPSC		145
				↓ Mushroom spines, dendritic regression	↑ Action potential firing rates, ↑ sEPSC		146
						↓ AMPAR and NMDAR	77
				↓ Apical dendritic spines, ↓ synapses			141
				↓ Synapses, ↓ dendritic spines			142
						↑ Hippocampal vGLUT1, GLT-1	151
			rTgTauEC	↓ Synaptic vesicles		↓ Synaptophysin, synapsin, spinophilin	149
					↑ Axonal excitability, ↓ PTP		150
		Tau 40 with P301S mutation	PS19 mice	↓ Hippocampal synapse	↓ LTP		138
				↓ Synapse density in CA3		↓ Glutamate levels in hippocampus and thalamus	139
			P301S Tau x YFP-H mice	↓ Spine density in cortical layer V			140
		Mutated Tau 43 K257T/P301S	DM-htau tg mice		↓ Maintenance of LTP in the dentate gyrus		155
		Tau 34 G272V/ P301S mutation	THY-Tau22		↓ EPSP		153
Deletion/ Truncated		Tau 40 with deletion of K280	hTau40DK280	↓ Dendritic spines			157
				↓ Dendritic spines	↓ Hippocampal LTP	↓ AMPAR, NMDAR, synaptophysin	174
		Δtau 244–372 with deletion of K280	RDTau (244-372) DK280		↓ LTP	↓ Synaptophysin, NMDAR1, PSD-95, drebrin	156
					↓ LTP		160
						↓ Spinophillin	132
				↓ Synaptic vesicles density	↓ LTP of the mossy fiber tract		158
		Δtau aa1-255	Δtau74			↓ Dendritic targeting of Fyn kinase	37
	Rat	Δtau 3R aa151-391	SHR24	↓ Synaptic vesicle density, microtubule bundling in the presynapses		↓ Synaptophysin, neurofilament H and M, ↑ tubulin proteins	78

Legends: 2N, 2 inserts; 3R, 3 repeat; 4R, 4 repeat; DM, AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; Double mutation; LTP, Long-term potentiation; EC, Entorhinal cortex; sEPSP, Synaptic excitatory postsynaptic potentials; GLT-1, Glutamate transporter 1 (ortholog of EAAT2); hTau, human tau; HFS, High frequency stimulation; NMDAR, *N*-methyl-D-aspartate receptors; PS1, Presenilin 1; PP, Perforant path; PSD-95, Postsynaptic density protein 95; PTP, Post-tetanic potentiation; YFP, Yellow fluorescent protein; vGLUT, Vesicular glutamate transporter.

prominent in AD [163, 164]. More specifically, proteins regulating synaptic plasticity are reduced in the AD brain [165]. Moreover, stage dependent decline in synaptic protein levels have also been observed [91].

Interestingly, synaptic fractions from human AD displayed elevated levels of tau protein in the postsynaptic density suggesting tau mislocalization and missorting [166]. Synaptic activity induced the physiological release of tau protein from synapses [167], a process which is aggravated in synaptosomes from AD brains [168], suggesting a massive deregulation in synaptic machinery in AD brains. Interestingly, C-terminally truncated tau was more prominent in the presynapses of AD brain (about 75-85%) with low levels of N- and C-terminal double truncated tau species [168]. Remarkably, predominant tau species in the synapses of AD brains were insoluble indicating tau aggregation. These results demonstrate that tau mislocalization and truncation exacerbate synaptic dysfunction in AD brains.

It is still uncertain how the tau isoforms in the synaptic compartments of diseased brain vary when compared to the healthy individuals. In murine neurons expressing human tau proteins, the three repeat tau isoform shows both neuronal body and synapse like distribution, while four repeat tau isoform was more "synapse like" in distribution [169]. However, based on these pieces of evidence, it is hypothesized that regional specific changes in the tau isoforms may contribute to pathogenesis of human tauopathies [169]. Therefore altered distribution of tau isoforms may be one of the causative factors for deficits in the synapses in the tauopathy brain.

Although several studies have evaluated the deregulation of synaptic proteins, less is known about the pathological tau proteome in the presynaptic and postsynaptic compartments. We evaluated the synaptic tau proteome in a rat model of tauopathy expressing human truncated tau [78]. Transgenic rat models fully recapitulate the human neurodegenerative tau cascade [170, 171]. Like humans, rats also express six tau isoforms in the CNS and can mimic changes in tau proteome as in humans [172]. Synaptic tau proteome was significantly altered in transgenic rats [78]. Tau protein in the presynaptic compartment was elevated in transgenic rats expressing human truncated tau (Fig. 2). In the postsynaptic fraction, expression of human truncated tau protein induced mis-sorting and mislocalization of endogenous tau (Fig. 2). These results are consistent with an earlier report showing mislocalization of tau in postsynaptic density of AD brains [166]. These results establish that physiological distribution of tau protein is perturbed in AD brains contributing to synaptic degeneration.

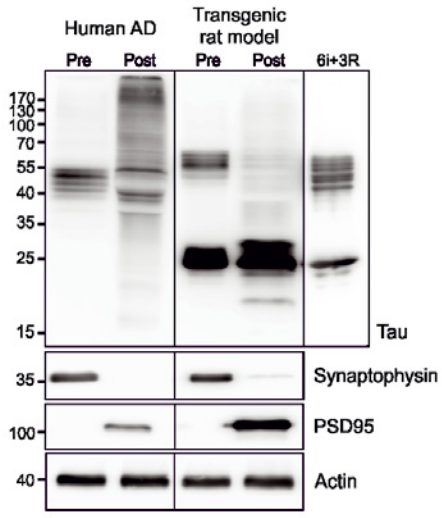

Figure 2. Tau mislocalization in disease conditions. In Alzheimer's disease (Human AD) and transgenic rat model expressing human truncated tau protein aa151-391 (Transgenic rat model) tau protein is mislocalized to the postsynaptic fraction (Post). Synaptic fractions were isolated as previously reported [78]. Recombinant 6 human tau isoforms (6i) and truncated 3 repeat tau protein (3R) were used as controls.

Evaluation of truncated tau proteome in the presynaptic compartments of transgenic rats revealed phosphorylation of human truncated tau at residues T205, S214, S262 and S356. Conversely, truncated tau in the postsynaptic compartment was phosphorylated mainly at T212. This pattern of tau distribution elicited specific pathological changes in these rats. Elevated levels of α- and β-tubulin proteins and specific increase in glutamylated and detyrosinated tubulin was observed in the presynaptic terminals of these animals. Electron microscopy revealed microtubule bundling and diminished levels of synaptic vesicles in the presynaptic terminals of these animals. In the postsynaptic compartment, expression of human truncated tau protein led to a decrease in neurofilament proteins. However, no change in the levels of tubulin or MAP 2B/2C was observed. These evidences suggest that different phospho-tau species elicits specific pathological effects in the presynaptic and postsynaptic compartments of transgenic rat model [78].

Deregulation of synaptic proteins is widely observed in transgenic models of tauopathies. Loss of synaptophysin, a synaptic vesicle protein, is commonly observed in tau transgenic models [78, 149, 173, 174]. In addition, other synaptic proteins synapsin, synaptojanin, synaptobrevin are reportedly decreased in these animals. Furthermore, expression of tau also deregulated dendritic proteins PSD95 and spinophillin suggesting postsynaptic deficits in these animals [132, 149]. In mice models, tau protein induces synaptic impairment by diminishing the trafficking of metabotropic glutamate receptors (mGluR) [156,173], AMPA and NMDA receptors [77], which contribute to LTP deficits.

Recent evidence speculates a role of tau protein in synaptic signaling and point towards functional reduction of tau within synaptic contacts in transgenic tau models. All of this evidence points to a more intricate role of tau protein in the synapses. Furthermore, synaptic tau proteome alterations may be one

of the key pathological steps in AD and other tauopathies.

Conclusion

Outcomes from numerous studies indicate a vital role of physiological tau protein in the synaptic biology including induction of LTP, LTD and dendritic activity (Fig. 3). Besides, cues from transgenic rodent tau models clearly demonstrate deleterious effects of pathological tau protein in the synapses (Fig. 3). A strong knowledge on tau driven synaptic damage will be essential in order to understand and intervene early pathological events in AD. We emphasize the role of disease modified tau protein in inducing synaptic impairment and comprehensively assemble multiple evidence of synaptic damage from transgenic tau models expressing various forms of tau protein. Put together, unlike previously assumed, tau protein may have a significantly larger role in imparting synaptic instability and cognitive deficits in AD and other tauopathies.

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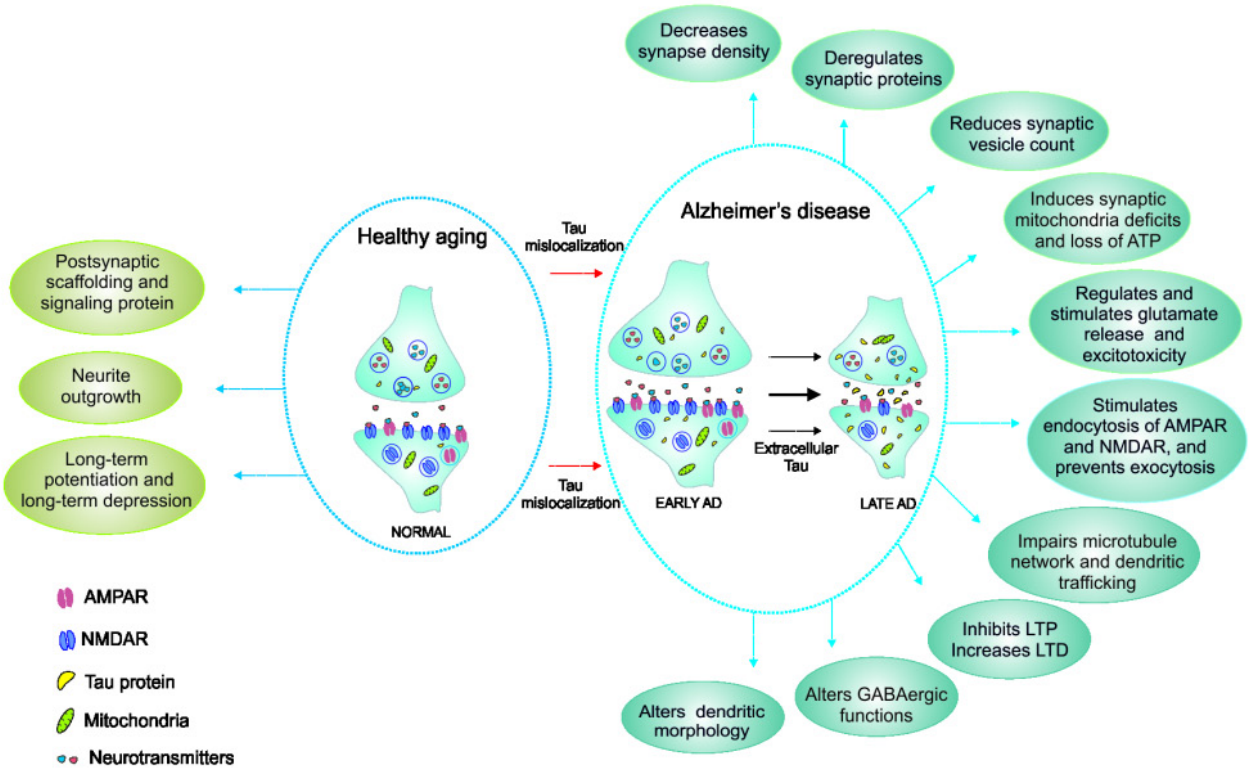

Figure 3. Tau protein in the physiology and pathology of neuronal synapses. Tau protein performs physiological functions in synapses (in light green). In diseased conditions, misfolded phosphorylated and truncated tau proteins impair several pre- and postsynaptic machineries to perturb synaptic function (dark green). Misfolded tau impairs synaptic vesicle transport and release, deregulates several synaptic proteins and alters synaptic and dendritic morphology. The cumulative effect of synaptic tau in disease condition results in reduction of synaptic plasticity and induction of excitotoxicity and postsynaptic long-term depression.

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