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PATHOGENESIS OF SYNAPTIC DEGENERATION IN ALZHEIMER'S DISEASE AND LEWY BODY DISEASE

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Abstract

Considerable progress has been made in the past few years in the fight against Alzheimer's disease (AD) and Parkinson's disease (PD). Neuropathological studies in human brains and experimental *in vivo* and *in vitro* models support the notion that synapses are affected even at the earliest stages of the neurodegenerative process. The objective of this manuscript is to review some of the mechanisms of synaptic damage in AD and PD. Some lines of evidence support the notion that oligomeric neurotoxic species of amyloid β, α-synuclein, and Tau might contribute to the pathogenesis of synaptic failure at early stages of the diseases. The mechanisms leading to synaptic damage by oligomers might involve dysregulation of glutamate receptors and scaffold molecules that results in alterations in the axonal transport of synaptic vesicles and mitochondria that later on lead to dendritic and spine alterations, axonal dystrophy, and eventually neuronal loss. However, while some studies support a role of oligomers, there is an ongoing debate as to the exact nature of the toxic species. Given the efforts toward earlier clinical and preclinical diagnosis of these disorders, understanding the molecular and cellular mechanisms of synaptic degeneration is crucial toward developing specific biomarkers and new therapies targeting the synaptic apparatus of vulnerable neurons.

INTRODUCTION

The past few years have witnessed considerable progress in the fight against Alzheimer's disease (AD), with the introduction of the revised clinical [1] and neuropathological [2] criteria for the diagnosis of AD, identification of new biomarkers [3–5], better characterization of the poly-genetic aspects of AD [6, 7], and a more clear understanding of the contribution of neurotoxic aggregates of amyloid β (Aβ) [8–10] and microtubule associated protein τ (Tau) [11, 12], to the pathogenesis of neurodegeneration in AD. Likewise, in disorders with parkinsonism and dementia such as Parkinson's disease (PD), PD with dementia (PDD) and dementia with Lewy bodies (DLB) (jointly denominated Lewy body disease [LBD]) [13] dramatic progress has been made in identifying new genes involved in familial [14] and sporadic [15] forms, several of them possibly converging on the α-synuclein (α-syn) pathway [16, 17].

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In 2013 an estimated 5.2 million Americans of all ages have AD and 1 million have PD [18]. This year an estimated 450,000 people in the US will die with AD, making AD the sixth-leading cause of death in the US [18]. Without a cure, the number of cases of AD, as defined by the 1984 and DSM-IV criteria, will double by the year 2050, with western states experiencing the highest rates [18]. The new criteria published in 2011 proposed three stages of the disease, namely preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD [1]. The 2011 criteria proposes that AD begins before the development of symptoms and that new positron emission tomography (PET) and cerebral spinal cord fluid (CSF) biomarkers are able to identify brain alterations before the onset neurological alterations [1]. However, the predictive value of such biomarkers is not yet proven in sporadic preclinical cases [19]. If AD can be detected earlier, as defined by the 2011 criteria, the number of people reported to have AD will be much larger than 5 million.

In 2011 a workgroup of experts was organized to revise the 1997 neuropathological criteria for the diagnosis of AD and related disorders [2]. The 1997 criteria required a history of dementia [20], while the new criteria disentangle the clinico-pathologic term “Alzheimer’s disease” from *AD neuropathologic change* [2]. Using the new criteria, AD neuropathologic change would be ranked along three parameters (Amyloid, Braak, CERAD) to obtain an “ABC score”. For this purpose a modified version of Thal phases of Aβ plaque accumulation was proposed [21], adapted to a four-point scale, continued use of the staging scheme for neurofibrillary tangles as described by Braak [22], reduced to four stages that improves inter-rater reliability, and continued use of CERAD protocol for neuritic plaque scoring [23]. The new criteria provided guidance on clinico-pathologic correlations for pathologists reporting autopsy findings based on the literature and analysis of the National Alzheimer’s Coordinating Center (NACC) database. The new criteria also emphasized the importance of assessing non-AD brain lesions in recognition of commonly co-morbid conditions in cognitively impaired elderly. Among the co-morbid conditions, synucleinopathies such as PD, PDD and DLB, are important given that over 75% of patients with AD display LB’s in the amygdala [24, 25] and about 25% of patients with AD develop parkinsonism [26].

The main purpose of this manuscript is to review evidence supporting the synapse failure hypothesis of AD and LDB and the role of Aβ, α-syn, and Tau accumulation in the pathogenesis of this process. We conclude that synaptic dysfunction occurs early, followed by pre-synaptic and spine loss, axonal dystrophy and eventually neuronal loss. We focus on synapses because Aβ is released at the synaptic terminal [27] and α-syn localizes to the synaptic vesicles [28] where they can effect synaptic transmission. However, a number of other cellular substrates play an equal important role (e.g.: neuro-inflammation, vascular, glial) and deserve close consideration. For example, a recent GWAS study highlighted the association of AD with innate immune response [29–33].

SYNAPTIC DAMAGE AND Aβ IN EARLY ALZHEIMER’S DISEASE

For several years the classical definition of neurodegeneration in disorders such as AD and PD was limited to the finding of selective neuronal loss and astrogliosis. This concept has now been expanded to include synaptic loss and neuro-inflammation. Synaptic damage can be detected at the earliest stages of AD. Patients with MCI demonstrate loss of pre-synaptic proteins such as synaptophysin, VAMP2, and SNAP25 and post-synaptic markers such as PSD95 and Shank1 [34]. Likewise ultrastructural [35] and confocal microscopy studies [36] have shown progressive alterations of synapses in early stages of AD and in APP tg models [37]. This has been confirmed in experimental APP transgenic models [38], as well as after acute injection of Aβ oligomers [39]. These studies have shown more severe loss of glutaminergic terminals but not GABAergic terminals in the hippocampus [40, 41].

Consistent with the neuropathological and structural studies, recent gene array investigations have shown that in early AD there is altered expression of genes involved in synaptic vesicle trafficking and release, neurotransmitter receptors and receptor trafficking, postsynaptic density scaffolding, cell adhesion regulating synaptic stability, and neuromodulatory systems [42–45]. The memory impairment in patients with AD is related to synaptic loss in the neocortex and limbic system [46–48]. In contrast, cognitive impairment does not correlated with Aβ plaques in the brain. The loss of synapses in AD is greater than the extent of the neuronal loss in the cortex. This suggests that synaptic damage precedes the loss of neuronal cell bodies. This is why synapses are a good correlate to cognitive deficits [43, 46, 47, 49–52]. The remaining synapses appear to be enlarged representing a possible compensatory mechanism [47, 53, 54].

The mechanisms of synaptic loss in AD might involve axonal transport defects, oxidative stress, mitochondrial damage, and neuroinflammation among others [55]. Increasing levels of $A\beta_{1-42}$, the proteolytic product of APP metabolism are also suspected to be centrally involved in the pathogenesis of synaptic damage in AD [56–60] (Fig 1A). Accumulation of Aβ in AD is the result of an imbalance in the mechanisms of synthesis, aggregation, and clearance (Fig 1B). Increased synthesis and aggregation has a prominent role in familial AD, and altered clearance including degradation and autophagy has a role in sporadic AD [61, 62]. The mechanisms through which accumulation of Aβ and other APP metabolites might lead to synaptic damage and neurodegeneration are under investigation. More specifically, the potential role of neurotoxic Aβ oligomers has emerged as a topic of considerable interest in recent years [63–66] (Fig 1).

Monomeric Aβ can aggregate to form amyloid fibrils, protofibrils, annular structures [67], Aβ-derived diffusible ligands (ADDLs) [68] and smaller order oligomeric species (for reviews, see [69–74]). Oligomers of Aβ can organize into dimers, trimers, tetramers, and higher order arrays that can form annular structures [75]. Smaller oligomers are divided into those generated from synthetic peptides and those purified from cells, transgenic (tg) mice, or AD human brains [8, 69, 76]. However, it is worth noting that there is great heterogeneity in the Aβ arrays accumulating in the brain of AD patients, and more recent studies have highlighted that there is uncertainty around the pathological significance of some of these oligomeric species [76].

An example of a naturally occurring oligomer specie is Aβ*56 derived from the brains of APP tg mice, which has been shown to promote age-dependent memory deficits [77]. Aβ*56 and Aβ trimers secreted by cultured cells could turn out to share common synaptotoxic properties [69]. The Aβ dimers, trimers, and higher order oligomers secreted by cultured neurons inhibit LTP, damage spines, and interfere with activity-regulated cytoskeleton associated protein (Arc) location [64, 65, 69, 78, 79]. Additional studies have shown that Aβ dimers extracted from human CSF disrupt synaptic plasticity and inhibit hippocampal LTP *in vivo* [80] (Fig 1). Together, these studies indicate that Aβ oligomers, ranging in size from 2–12 subunits, might be responsible for the synaptic damage and memory deficits [81]. A number of recent studies have begun to investigate the possibility that Aβ oligomers might interfere with synaptic function by altering synaptic proteins such as post-synaptic density-95 (PSD95) [82–85], Shank1 [34], and glutamate receptors [86].

Although the neurotoxic effects of the Aβ have been widely studied in experimental models, less is known about the characteristics of the oligomers across the spectrum of AD and how this correlates with cognition and synaptic proteins. We have previously utilized immunoblot analysis to investigate the relationship between levels of Aβ oligomers and synaptic proteins in fractions from the brains of AD patients and APP tg mice. Our studies show that Aβ oligomers, in particular dimers and pentamers, progressively accumulate in the

brains of AD patients, as well as in APP tg mice. This was accompanied by reductions in the levels of synaptic scaffold proteins such as PSD95, Shank1 and Shank3 [34].

While accumulation of Aβ oligomers at the synaptic site have been proposed to be an important trigger in the pathogenesis of AD, this hypothesis has been challenged by the lack of a unified description of the toxic oligomer [76] and by recent negative results from clinical trials using Aβ vaccines [87]. Alternative explanation as to why the vaccine trials showed little or no efficacy include that patients treated were at late stages of the disease and that the antibodies did not target specific Aβ oligomers [88].

DOWNSTREAM MECHANISMS OF SYNAPTIC DEGENERATION IN ALZHEIMER'S DISEASE

As described in the previous section, synaptic degeneration occurs early in the progression of AD involving neocortical and limbic system circuitries. Upstream of the cascade is the accumulation of Aβ oligomers at the synaptic sites. The process of synaptic damage could involve a multistep process beginning with dysregulation of glutamate receptors [89, 90] and scaffold molecules such as PSD95 and Shank1 [34] that results in alterations in the axonal transport of synaptic vesicles and mitochondria that later lead to dendritic and spine alterations, as well as axonal dystrophy (Fig 2). Therefore, in the early stages synaptic and network dysfunction [91, 92] might be the norm and actual loss of pre-synaptic terminals and dendritic spines will occur later as synapses become more damaged (Fig 2). Some studies have suggested that at the early stages of the disease progression, aberrant synaptic sprouting might occur as a compensatory mechanism [44]. This is followed by axonal degeneration, while neuronal loss occurs in the later stages of the disease.

Downstream to the accumulation of Aβ oligomers at the synaptic sites there are a number of receptors and signaling cascades involved that converge on abnormal Tau phosphorylation, aggregation and mis-localization from the pre-synaptic to the axonal site (Fig 2). Several Aβ oligomers receptors have been identified including mGluR5 [93], ephrin (ephR2) [94], prion protein (PrP) [95] and others. Extracellular Aβ oligomers bound to lipid-anchored PrP(C) activates intracellular Fyn kinase to perturb synapses (Fig 1) [96–98]. Moreover, recent studies have shown that co-expression of the metabotropic glutamate receptor, mGluR5, allowed PrP(C)-bound Aβ to activate Fyn. PrP(C) and mGluR5 interact physically, and cytoplasmic Fyn forms a complex with mGluR5, resulting in eEF2 phosphorylation and dendritic spine loss [99].

Once bound to synapses, Aβ oligomers can dysregulate the activity and reduce the surface expression of both N-methyl-D-aspartate (NMDA) and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)-propanoic acid (AMPA) types of glutamate receptors, impairing signaling pathways involved in synaptic plasticity [100, 101]. Another interesting finding is that the glutamate receptor system involved in synaptic loss in AD is represented by extracellular NMDARs (eNMDARs). Recent studies have shown that Aβ induces the release of astrocytic glutamate, which in turn activates extrasynaptic NMDA receptors on neurons [102]. This eNMDAR activity leads to synaptic transmission, tau phosphorylation, and caspase-3 activation, each of which is implicated in spine loss. Nitromemantine, which blocks eNMDARs activity, protects synapses from Aβ oligomer toxicity [102] (Fig 1).

Finally, recent work has also found that Aβ oligomers are ligands with nanomolar affinity to paired immunoglobulin-like receptor B (PirB) in murines and its human ortholog, leukocyte immunoglobulin-like receptor B2 (LilrB2). The extracellular domains of PirB and LilrB2 mediate this role, leading to cofilin signaling. The synapto-toxic effects of Aβ oligomers

require PirB, and in a transgenic model of AD, PirB not only contributed to memory deficits present in adult mice, but also mediated loss of synaptic plasticity the cortex [103].

Downstream to Aβ, recent studies suggests an emerging role for Tau at the synapse (Fig 2). Even in the absence of tangles, mice over-expressing human Tau display significant synaptic degeneration, suggesting that soluble, oligomeric Tau is the synaptotoxic species [104]. Aggregated or hyperphosphorylated Tau is able to interact with post-synaptic signaling complexes, regulating glutamatergic receptor content in dendritic spines [105], and influencing axonal mitochondrial transport [106, 107]. Interestingly, reducing Tau by genetic means [106] or with immunotherapy reduces behavioral deficits, synaptic dysfunction and network degeneration [108] (Fig 2).

Recent studies suggest that the abnormal localization of Tau to the dendrites might play a role in AD [109]. In support of this possibility, a study showed that Tau translocation to dendrites is mediated by spastin, a microtubule (MT)-degrading enzyme. Spastin is recruited by MT polyglutamylation, induced by Tau mis-sorting, triggering translocalization of TTLL6 (Tubulin-Tyrosine-Ligase-Like-6) into dendrites. Consequences of this translocation include spine loss, as well as mitochondria and neurofilament mislocalization. Adding Tau to Tau-deficient neurons reestablishes Aβ-induced toxicity, which requires phosphorylation of Tau's KXGS motifs. Transgenic mice overexpressing Tau show TTLL6 translocalization into dendrites and decreased MT stability [110].

Another interesting downstream pathway includes α1-takusan, which was previously identified as a protein that enhances synaptic activity via interaction with PSD-95 and mitigates oligomeric Aβ-induced synaptic loss. In contrast, knockdown of takusan results in enhanced synaptic damage. α1-Takusan interacts with Tau either directly or indirectly, and prevents Aβ-induced Tau aggregation and mitochondrial pathology. α1-Takusan protects synapses from Aβ-induced insult via interaction with PSD-95 and Tau [111].

In addition to the indirect interactions between Aβ and Tau mediated by receptors and signaling pathways, recent studies suggest that monomeric and oligomeric Aβ directly interacts with tau in neurons affected by AD. These interactions progressively increased with the disease process damaging synapses, leading to cognitive decline in AD patients [112].

In between the Aβ oligomer receptors and Tau, a number of studies suggest the role for abnormal activation of signaling cascades including GSK3β, CDK5 and Fyn kinase (Fig 1). Pharmacological interventions targeting the interactions between Aβ oligomer and receptors as well as blocking these kinases have been proposed for the treatment of AD. A number of reviews deal with this subject in greater detail [113–116].

SYNUCLEIN ACCUMULATION IN SYNAPTIC DEGENERATION IN LEWY BODY DISEASE

Lewy body diseases (LBDs) form a heterogeneous group of disorders including PD, PDD and DLB [13]They are often referred to as synucleinopathies as the accumulation of the presynaptic protein α-syn is what characterizes LBDs. α-Syn is a highly abundant protein at the pre-synaptic terminals [117–119], where it is associated with the distal reserve pool of synaptic vesicles [120–122] and has a role in the regulation of neurotransmitter release, synaptic function and plasticity [123, 124] (Fig 3). Various mutations (A53T, A30P, and E46K) [125–127] and multiplications of [128] within the gene encoding of α-syn (*SNCA*) leads to dominant familial parkinsonism (Fig 3A). Furthermore, certain polymorphisms in SNCA are associated with elevated risk levels for sporadic PD [129]. An increasing group of

evidence from animal models, as well as data from genetic, biochemical and biophysical studies support the hypothesis that the processes of α-syn oligomerization [130, 131] and fibril growth [132, 133] have central roles in the pathogenesis of PD and other synucleinopathies [134–136] (Fig 3A).

α-Syn aggregates that might play a role in LBD include oligomers, protofibrils, and fibrils. The Lewy bodies, which are the hallmark of LBD, contain mostly fibrillar forms of α-syn [137, 138]. As is the case with Aβ for AD [76], there is no consensus as to the precise α-syn aggregates that are responsible for the synaptic damage in LBD [135]. However, there is indirect evidence supporting the existence of oligomeric α-syn intermediates *in vivo* under pathophysiological conditions[120, 131, 139–141].

A number of oligomeric intermediates of different morphologies, including spherical, chain-like, and annular oligomers have been described prior to fibril formation by α-syn [142]. Studies suggest that α-syn oligomers can be divided into small (~2–5 mers), medium (~5–15 mers), and large (~15–150 mers)[143, 144]. It is unclear which of these aggregates are physiological and which ones represent toxic species. A couple of studies have reported a stable native α-syn tetramer [145, 146] while other studies suggest the monomer as the native structure [147]. A more recent study suggests that most of the native α-syn is a monomer with a small fraction as trimers and tetramers that prevent non-membrane-bound monomers from aggregating [148]. In vitro studies suggest that the oligomers that undergo a conformational change leading to PK-resistant species might be more toxic [143].

The levels of α-syn is regulated through the balance between rates of α-syn synthesis, aggregation, and clearance [149] (Fig 3B). Dysfunction of one or more of the pathways that balance these rates can lead to anomalous and, therefore, toxic levels of α-syn. For example, in certain forms of familial parkinsonism, multiplication of SNCA leads to elevated accumulation of α-syn due to the increase in the protein expression levels [128], whereas in other forms, SNCA mutations enhance the propensity of α-syn to aggregate [130]. A genome-wide association study (GWAS) linked certain variations in the SNCA gene to higher risk for developing PD [15]. A representative example of such a polymorphism is known as Rep1. Rep1 occurs in the promoter region of *SNCA* and could increase the susceptibility to PD by increasing the expression of α-syn [150]. Clearance of α-syn monomers and aggregates takes place via direct proteolysis (i.e., by neurosin or matrix metalloprotease 9 (MMP9)) [151], binding to molecular chaperones (for example, heat shock proteins (HSPs)) [152], the proteasome [153–155], and autophagy (related to the activity of the lysosome) [149, 156–158]. In some isolated forms of PD and DLB, inability of the autophagy pathways to eliminate oligomers might facilitate α-syn-mediated toxicity [157]. It has been shown that chaperone-mediated autophagy [121] of mutant α-syn is impaired. In PD and DLB, regulation of the levels of key autophagy molecules such as ATG7, a ubiquitin-like modifier-activating enzyme, and mTOR, a serine–threonine-protein kinase, are impaired [159].

Accumulation of protease K (PK)- resistant α-syn aggregates at the synaptic site results in early degeneration in selected circuitries in PD, PDD and DLB [160]. Degeneration in DLB cases is more closely associated with synaptic accumulation of PK-resistant α-syn than to Lewy bodies [161]. By confocal microscopy there is an average 30–40% loss of synapses in the frontal and temporal cortex in patients with DLB. Synapse loss in the frontal-temporal cortex in DLB patients correlates well with the cognitive impairment [162].

In addition to the direct damage to the synaptic membrane, α-syn oligomers might also trigger synaptoxicity by damaging mitochondria [163], lysosomes [164], or disrupting microtubules [165]. Moreover, a recent study showed that α-syn aggregates might interfere

with the axonal transport of synaptic proteins, such as synapsin-1 [123]. Therefore in the early stages of the process of synaptic degeneration in synucleonopathies, there is a failure of synaptic function due to altered transport of vesicles, synaptic proteins, and mitochondria (Fig 2). This then leads to pre-synaptic terminal loss, dendritic damage, axonal dystrophy and eventually degeneration of selective neuronal populations within the striato-nigral and cortico-limbic systems among others (Fig 2).

Similarly to what has been described in the previous sections for AD and Aβ oligomers [93], in PD/DLB α-syn accumulating at the synapses might interact with several receptors including mGluR5 [166]. Activation of glutamate receptors could lead to excitotoxicity and activation of signaling pathways that target Tau aggregation and phosphorylation [167–170] (Fig 2). However it is possible that downstream of α-syn and signaling pathways, targets other than Tau might also be involved because knocking down Tau in α-syn tg mice does not completely rescue the deficits associated [171].

In addition to the role of α-syn accumulating at the synaptic site, recent evidence suggests that under pathological conditions, toxic α-syn oligomers could be released from neurons [172–174] (Fig 3B). Failure of the intracellular clearance pathways, such as autophagy, might contribute to the pathological release of α-syn [157, 175]. Extracellular α-syn aggregates can then transfer from neuron to neuron or from neuron to glial cell [176] where they can nucleate further intracellular aggregation and/or trigger neuro-inflammation and exacerbate the synaptic pathology and neuronal loss [157, 177]. We have recently found that extracellular α-syn released from neuronal cells is an endogenous agonist for Toll-like receptor 2 (TLR2), which activates inflammatory responses in microglia. The TLR2 ligand activity of α-syn is conformation-sensitive; only specific types of oligomer can interact with and activate TLR2. This paracrine interaction between neuron-released oligomeric α-syn and TLR2 in microglia suggests that both of these proteins are novel therapeutic targets for modification of neuroinflammation in PD and related neurological diseases [178]. It is likely that similar to Aβ oligomers, there are several other neuronal and glial receptors for oligomeric α-syn.

Supporting a potential role of extracellular α-syn in the synaptopathology in LBD, previous studies have shown accumulation of α-syn in fetal grafted neurons in patients with PD [179], as well as in grafted neuronal precursor cells in the hippocampus [157] and basal ganglia [180] in mouse models. Interestingly, α-syn has also been shown to ectopically accumulate in oligodendroglial cells in multiple system atrophy (another synucleinopathy) [181] and in astroglial cells in PD [176, 181]. Moreover, the ascending distribution of the Lewy body pathology in LBD, as described by Braak [182] and recent studies published by the group of Dr. V. Lee showing prion-like propagation of α-syn after intra-cerebral injection of seeds [183], which has been interpreted to support the dissemination of α-syn from subcortical to cortical brain regions. Hardy has recently reviewed this topic and identified the caveats of using terminology such as “prion” to describe PD and suggests the use of the term “templating” [184].

In summary, Aβ, α-syn, and Tau aggregates might play a role in synaptic damage in AD and LBD. At the earliest stages, it has been proposed that oligomers might interfere with the transport of synaptic vesicle proteins and glutamate receptors resulting in functional deficits that are potentially reversible; however, further investigation as to the precise nature of the toxic oligomers is necessary. Later on signaling pathways and Tau might be engaged in association with axonal transport defects of trophic factors and mitochondria that in turn lead to synaptic loss and oxidative stress. This could be followed by axonal alterations and eventually neuronal loss and neuroinflammation, resulting in irreversible damage (Fig 2). Given the efforts toward earlier and preclinical diagnosis of AD, PD, and related disorders,

understanding the molecular and cellular mechanisms of synaptic degeneration is crucial to developing specific biomarkers and new therapies targeting the synaptic apparatus of vulnerable neurons.

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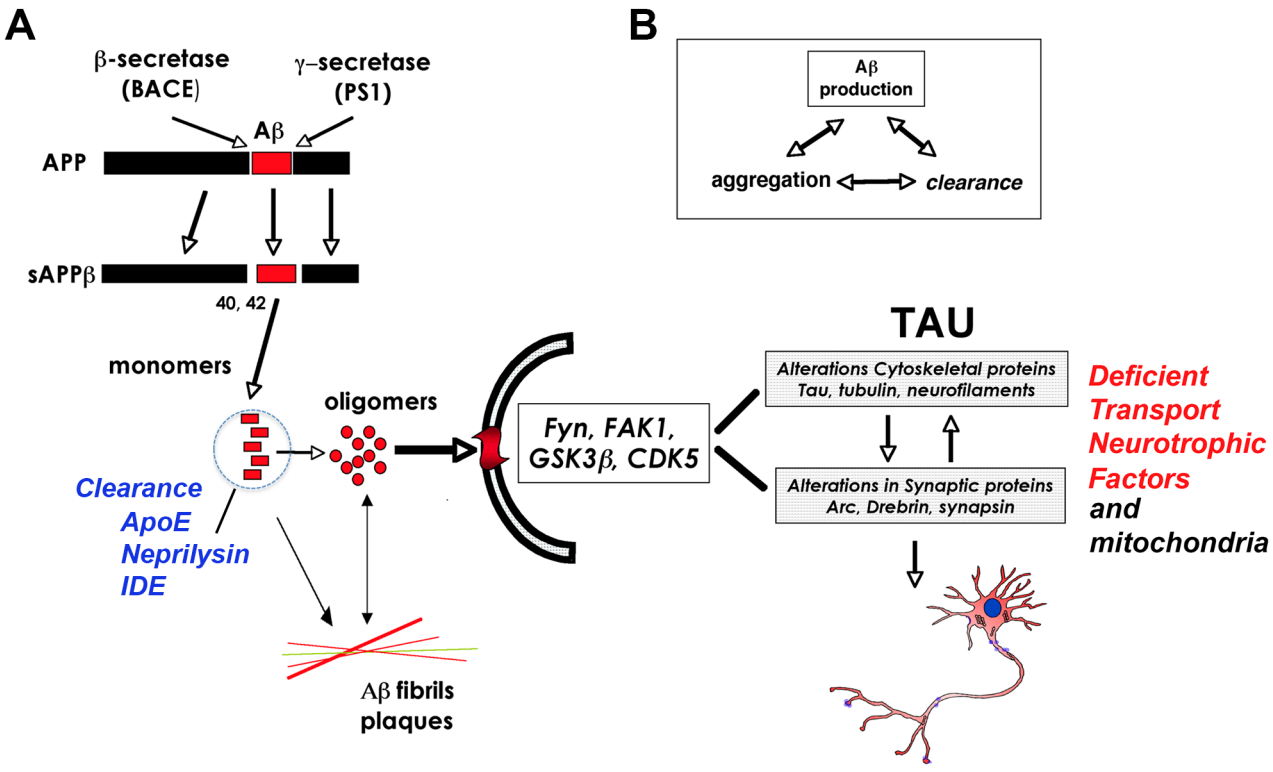

Figure 1.

Schematic diagram showing the processing of APP, the formation of Aβ oligomers, and its interaction with Tau in the mechanisms of synapse loss. A) APP is cleaved by β and γ-secretases to form sAPPβ. Monomeric Aβ42 can form Aβ oligomers that can be cleared by ApoE and proteases such as neprilysin and IDE. Both Aβ monomers and oligomers progress to fibrils and plaques, while Aβ oligomers interact with surface receptors that in turn activate various kinases to alter Tau, leading to loss of axonal transport of neurotrophic factors and impaired mitochondrial function, culminating in neurotoxicity. B) Aβ production is dependent on both Aβ clearance, aggregation and synthesis.

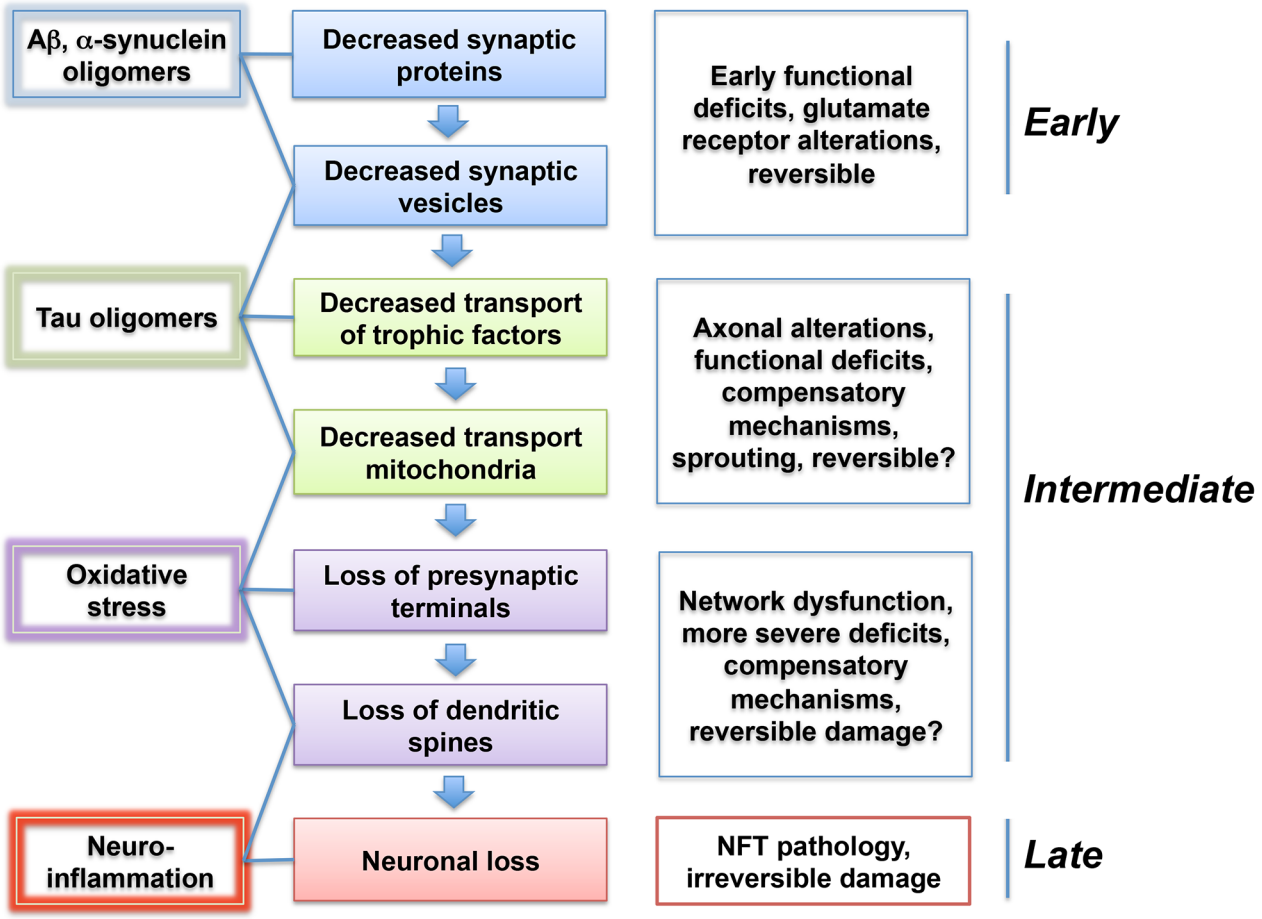

Figure 2.

Schematic representation of progression of the mechanisms of synaptic damage in AD and synucleinopathies. At the earliest stages, oligomers interfere with the transport of synaptic vesicle proteins and glutamate receptors resulting in functional deficits that are potentially reversible. Later on signaling pathways and Tau are engage in association with axonal transport defects of trophic factors and mitochondria that in turn lead to synaptic loss and oxidative stress. This is followed by axonal alterations and eventually neuronal loss, resulting in irreversible damage different neurotoxic insults, their effect on neuronal function, and stage with in the disease progression.

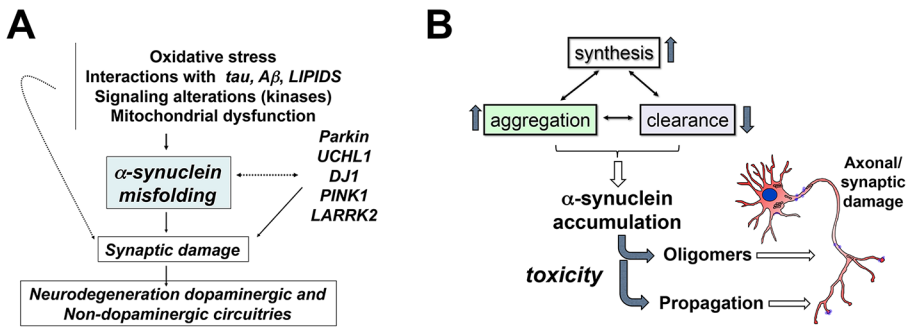

Figure 3.

Role of α-syn in the mechanisms of synapse loss in Lewy body disease. A) Neurotoxic events and genetic predisposition lead to α-syn misfolding and aggregation that in turn leads to synaptic damage and ultimately neurodegeneration of dopaminergic and non-dopaminergic circuits. B) Increased synthesis and aggregation, and/or decreased clearance of α-syn leads to α-syn accumulation causing toxicity via oligomers and propagation of the toxic species resulting in in axonal and synaptic damage.