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Interaction between α-Synuclein and Other Proteins in Neurodegenerative Disorders

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Protein aggregation is a common characteristic of many neurodegenerative disorders, and the interaction between pathological/toxic proteins to cause neurodegeneration is a hot topic of current neuroscience research. Despite clinical, genetic, and experimental differences, evidence increasingly indicates considerable overlap between synucleinopathies and tauopathies or other protein-misfolding diseases. Inclusions, characteristics of these disorders, also occurring in other neurodegenerative diseases, suggest interactions of pathological proteins engaging common downstream pathways. Novel findings that have shifted our understanding in the role of pathologic proteins in the pathogenesis of Parkinson and Alzheimer diseases have confirmed correlations/overlaps between these and other neurodegenerative disorders. The synergistic effects of α-synuclein, hyperphosphorylated tau, amyloid-β, and other pathologic proteins, and the underlying molecular pathogenic mechanisms, including induction and spread of protein aggregates, are critically reviewed, suggesting a dualism or triad of neurodegeneration in protein-misfolding disorders, although the etiology of most of these processes is still mysterious.

KEYWORDS: neurodegeneration, alzheimer disease, parkinson disease, protein interaction, coformer seeding, pathogenesis

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1. INTRODUCTION

Neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD), frontotemporal degeneration, prion, Huntington, and motoneuron diseases are increasingly being realized to have common cellular and molecular mechanisms including protein aggregation and inclusion body formation in selected areas of the nervous system. Therefore, these disorders are summarized as "proteinopathies" [1, 2]. The aggregations usually consist of insoluble fibrillary aggregates containing misfolded protein with β-sheet formation. The most probable explanation is that these inclusions and aggregates symbolize an end stage of a molecular cascade of complicated events, and that an earlier stage may be more directly tied up to the—hitherto unknown—pathogenesis of the disorder than the inclusions themselves, which may or may not represent diagnostic hallmarks. Small intermediates termed as "soluble oligomers" in the aggregation process may influence synaptic dysfunction, while large insoluble deposits might function as reservoirs of the bioactive oligomers that can lead to synaptic dysfunction, neuronal apoptosis, and brain damage [3, 4]. This is predominantly due to iron-related oxidative damage mediated by α-synuclein (αSyn) oligomerisation during the development of PD pathology [5]. Seeding induced by αSyn oligomers, the toxicity of which has been demonstrated *in vivo* [6], can induce intracellular αSyn aggregation, providing evidence for spreading of αSyn pathology [7] similar to that of prions [8]. Amyloid-β (Aβ) induces the neurodegenerative triad of spine loss, dendritic changes, and neuritic dystrophies through calcineurin activation [9], while soluble tau species rather than aggregated ones induce neurodegeneration [10]. Tau phosphorylation proceeds to tau aggregation that is favored by kinases like glucose-synthase kinase-3β (GSK-3β) [11], while inhibition of GSK-3β activity prevented not only tau phosphorylation but also tau aggregation in hippocampus [12]. Recent studies showed that caspase activation, observed in a tg mouse model overexpressing GSK-3β [13], precedes tangle formation [14]. Seeding of normal tau by pathological tau conformers further drives pathogenesis of neurofibrillary tangles (NFT) [15]. However, the mechanism by which oligomers trigger neurodegeneration still remains elusive. The aim of this paper is to review the molecular mechanisms and interactions between the various pathological proteins in neurodegeneration.

2. INTERACTION BETWEEN αSyn, Tau, AND AMYLOID-β IN PARKINSON DISEASE

Intracytoplasmic proteinaceous inclusions, primarily composed of tau and/or αSyn, are predominant pathological features of AD and PD, respectively [16]. However, the coexistence of these and other pathological proteinaceous aggregates like Aβ is identified in many neurodegenerative disorders [17–19]. The cooccurrence of both αSyn and tau or other pathologic proteins highlights the interface between them [20]. They may be coaggregated in the same brain or even in the same region or in the same cell in human brains [18, 21, 22] and transgenic mice [23]. Whereas αSyn can spontaneously polymerize into amyloidogenic fibrils, *in vitro*, tau polymerization requires an inducing agent [24]. Cellular models, various transgenic and other experimental PD models, provided novel insights into the role of αSyn in the hyperphosphorylation of tau protein observed in disease [24–32]. These data suggest that oxidatively modified αSyn is degraded by the proteasome and plays a proaggregatory role for tau [31], and that αSyn is an *in vivo* regulator of tau protein phosphorylation at Ser (262). Toxic interactions with αSyn may lead to hyperphosphorylation of tau and eventually to the deposition of both proteins in the disease [33]. E46K human αSyn tg mice develop Lewy-like and tau pathology associated with age-dependent motor impairments, supporting the notion that αSyn is involved in the pathogenesis of human diseases [34].

Recent postmortem studies showed increased accumulation of tau protein phosphorylated at Ser 262 and 396/404 in the striata of PD patients and in the A53T αSyn mutant mouse model of PD [27, 35]. This is related to increased activity of GSK-3β [26, 29], a major kinase that hyperphosphorylates tau to produce pathologic forms of tau [36] and may be a possible link between Aβ and tau [37, 38]. Dopamine D1 receptor activation induces tau phosphorylation via cyclin-dependent kinase 5 (cdk5) and GSK-3β

signaling pathways [39]. Expression of both GSK-3β and microtubule-associated protein/microtubule affinity-regulating kinase 2 inhibited the formation of αSyn-induced tau aggregation [24]. Reduced 19S and 20S proteasomal subunit activites in PD striata suggest that they account for the abnormal disposal of αSyn and phosphorylated tau (p-tau). The small decrease in proteasomal activity in PD striata is consistent with other studies that showed no significant changes of these proteins in PD striata but lower activity in substantia nigra (SN) [40]. In an MPTP model and in MPP+ cellular models, αSyn has been shown to induce GSK-3β-catalyzed tau phosphorylation [41–43]. PD-associated risk factors such as environmental toxins and αSyn mutations promote tau phosphorylation at Ser 262, causing microtubule instability, which leads to neuronal degeneration [30]. Rotenon exposure may also induce αSyn and Aβ aggregation as well as increased hyperphosphorylation of tau, although high concentrations of the pesticide lead to cell death before protein aggregation [32].

Tau in MPTP models and in human postmortem PD striata is hyperphosphorylated at the same sites (Ser 202, 262, and 396/404) as in AD [35], whereas phosphorylation of soluble tau differs in AD and Pick disease brains [44]. Tauopathy in PD striata is restricted to dopaminergic neurons, whereas degeneration in the inferior frontal cortex, associated with increased tau deposition because of diminished proteasomal activity in the absence of oxidative stress and pGSK-3β activity, is not associated with tauopathy [35]. In the αSyn overexpressing mouse model of PD tauopathy, along with microtubule destabilization, exists primarily in the brainstem and striatum, the two major brain regions known to express high levels of αSyn and undergo the highest levels of degeneration in human PD. Thus, tauopathy in PD may have a restricted pattern of distribution [28], which differs from its generalized affection in AD. Whether there are differences in the 3- and 4-repeat tau pathology between these disorders is not yet fully understood and needs further investigation.

There is strong interaction between αSyn, tau, and Aβ, particularly in their oligomeric forms, which might synergistically promote their mutual aggregation and vice versa [33, 45, 46]. Cross-seeding between dissimilar proteins that share β-sheet structures has been described, for example, of Aβ and αSyn [47], tau and αSyn [48], and prion protein and Aβ [49]. *In vivo* interactions between αSyn and tau are supported by genetic studies [50, 51], and in familial PD, fibrillation of αSyn and tau is caused by the A 53T mutation [48]. A family with early onset dementia was pathologically characterized by widespread appearance of LBs and NFTs, but no amyloid deposits [52]. Recent studies gave evidence that prions trigger hyperphosphorylation of tau in genetic, sporadic, and transmitted forms of prion diseases in the absence of amyloid plaques [53].

Neurofibrillary tau pathology is modulated by genetic variations of αSyn [54]. Tau phosphorylation is found in synapse-enriched fractions of frontal cortex in PD and AD [55] and in brainstems of αSyn mice [56]. Other links between αSyn and tau are suggested by the colocalization of both proteins in both NFTs and Lewy bodies (LBs), especially in neuronal populations vulnerable for both aggregates [21, 57–59], in the olfactory bulb in AD with amygdaloid LBs [57], and in neuronal and glial cytoplasmic inclusions in multiple system atrophy (MSA) [60, 61]. Between 15 and 60% of AD brains show numerous αSyn lesions in the amygdala, even in the absence of subcortical LBs [62, 63]. AD with amygdala LBs is considered a distinct form of α-synucleinopathy [64]. In AD patients with clinical extrapyramidal symptoms, between 50 and 88% of the patients showed extensive αSyn pathology co-localized with p-tau in SN, tau and less αSyn pathology in brainstem significantly increasing with higher neuritic Braak stages [65–67].

In conclusion, genetic, pathologic, and biochemical evidence support a role for tau in the pathogenesis of PD [33], and concurrence of tau, αSyn, and TDP-43 pathology in brains of AD and LB disease provide a better understanding of the pathogenic pathways in these disorders [17]. It has been suggested that the process of LB formation is triggered, at least in part, by Alzheimer pathology [18, 68], while the interaction between αSyn and tau in MSA awaits further elucidation [61, 69]. Recent data suggest that PD and AD could be linked by progressive accumulation of p-tau, activated GSK-3β, and αSyn [27, 35, 70, 71], while activation of caspase and caspase-cleft Δtau may represent a common way of abnormal intracellular accumulation of both tau and αSyn, promoted by Aβ deposition, unifying the pathology of AD and LB diseases

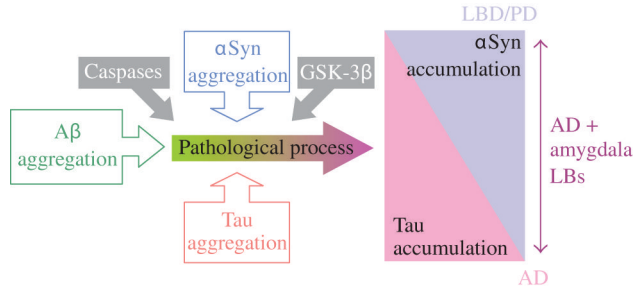

FIGURE 1: Hypothetic diagram unifying pathologic processes in Alzheimer and Lewy body diseases. PD: Parkinson disease; LBD: Lewy body disease; LBs: Lewy bodies; AD: Alzheimer disease.

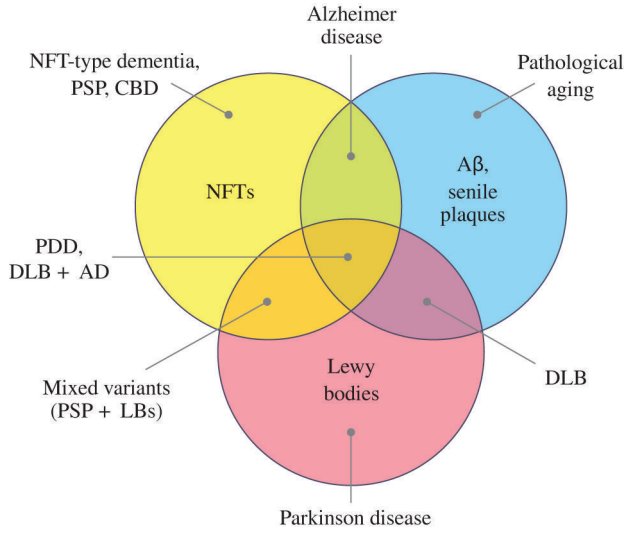

FIGURE 2: Morphologic interrelations of synucleinopathies, tauopathies, and amyloidopathies. NFTs: neurofibrillary tangles; PSP: progressive supranuclear palsy; CBD: corticofrontal degeneration; PDD: Parkinson disease dementia; DLB: dementia with Lewy bodies; AD: Alzheimer disease; LBs: Lewy bodies.

[72–74] (see Figure 1). In addition, emerging evidence suggests that prion-like spreading, evolving secreted proteins such as Aβ, and cytosolic proteins such as tau and αSyn are spreading by cell-to-cell transmission, thus unifying the pathogenesis of many neurodegenerative disorders [8, 75], but is not fully understood whether they are due to similar protein aggregation and misfolding mechanisms. Combined determination of αSyn, tau, and Aβ concentrations in cerebrospinal fluid (CSF) show differential patterns in these neurodegenerative disorders [76]; in particular tau/αSyn ratios can contribute to the discrimination of PD [77].

Other studies have suggested that Aβ is more likely to promote the deposition of αSyn than tau [78], and Aβ is known to initiate hyperphosphorylation of tau [79]. Cortical αSyn load is associated with Aβ plaque burden in a subset of PD patients [80]. Aβ peptides enhance αSyn accumulation and neuronal deficits in a tg mouse model [81], and αSyn-induced synapse damage is enhanced by Aβ 1-42 [82]. Both can be linked by separate mechanisms driven by a common upstream component [83]. Recent studies showed that Aβ 1-42 tightly binds to tubulin polymerization promoting protein (TPPP/p25) and causes aberrant protein aggregations inhibiting the physiologically relevant TPPP/p25-derived microtubule assembly, the interaction of TPPP/p25 and Aβ can produce pathologic aggregates in AD and LB diseases [84]. These lesions represent a collision of two or more processes, but it is unclear whether there is a common underlying final pathology leading to neuronal degeneration (see [85]) (Figure 2).

3. AMYLOID-β AND Tau IN ALZHEIMER DISEASE

The brains in patients with AD, in addition to nerve and synapse loss, are characterized by two hallmark lesions, Aβ-containing plaques and NFT, which are composed of hyperphosphorylated forms of microtubuli-associated protein tau [86]. Progression of NFT pathology throughout the brain correlates with disease progression [87], and loss of synapses is one of the earliest events that has been associated with functional impairment [88]. Although both Aβ and tau have been extensively studied with regard to their separate modes of toxicity (see [89]), more recently new light has been shed on their possible interactions and synergistic effects in AD, linking Aβ and tau [90, 91]. Moreover, the interaction between tau and Aβ mediated by FIN kinase should be considered, since it is an interesting link between the two pathogenic hallmarks of the disorders [36–38].

According to the amyloid cascade hypothesis, Aβ formation is the critical step in diving AD's pathogenesis [92]. Support for this concept stems from the identification of pathogenic mutations in patients with familial AD linked to Aβ formation and a higher frequency of AD in people with trisomy 21, who carry an additional APP allele [93].

Although Aβ and tau exert toxicity through separate mechanisms [94], evidence from both *in vitro* and *in vivo* models suggest that there are three possible models of interaction between the two. (1) Aβ drives tau pathology, supported by induction of tau hyperphosphorylation by Aβ formation in APP tg mice [95], induction of neuronal tau hyperphosphorylation by Aβ oligomers [96] and, together with neuritic degeneration, by soluble Aβ-protein dimers isolated from Alzheimer cortex [97], or by Aβ-rich brain extracts [98], and aggravation of NFT pathology by intracranial injection of synthetic Aβ into mutant tau tg mice [99]. On the other hand, a single-dose intraventricular injection of an Aβ antibody in 4-month-old mice cleared intraneuronal Aβ pathology and reduced early cognitive deficits [100], and inhibition of GSK-3β attenuated Aβ-induced tau phosphorylation *in vitro* and can reduce tau pathology *in vivo* [12, 101]. Other data suggest induction of NFT formation by amyloidogenic peptides rather than specifically by Aβ [102]. While the 3xtg AD mouse model, based on early intraneuronal accumulation of Aβ played an important role in supporting the "intraneuronal Aβ hypothesis" [100], recent evidence claims that these mice early and age-dependently accumulate AβPP instead of Aβ within neurons [103, 104], thus challenging this hypothesis. (2) Synergistic effects of Aβ and tau by impairment of mitochondrial respiration in triple tg mice that display both Aβ and tau pathologies [105]. This indicates the convergence of Aβ and tau on mitochondrial deterioration and establishes a molecular link in AD pathology *in vivo* [106, 107]. (3) Tau mediates Aβ toxicity supported by the observation that tau $-/-$ neurons are protected from Aβ induced cell death in cell culture [108–110]. Tau reduction also prevents Aβ-induced defects in axonal transport of mitochondria and other cargoes [111], which may link the "tau hypothesis" to other ones, the axonal transport impairment hypothesis, according to which tau induces failure of axonal transport [112, 113], and the "oxidative stress hypothesis" according to which mitochondria are functionally impaired, resulting in the production of reactive oxidative species [114]. Astrocytes have been shown to be important mediators of Aβ-induced neurotoxicity and tau hyperphosphorylation in primary cultures [13].

Although knowledge about the roles of tau and its interactions with Aβ is increasing (see [1, 115]), many questions about the scaffolding partners for tau in its interaction with Aβ are still unanswered. While this phenomen may result from direct cross-seeding of tau by aggregated Aβ [116, 117], indirect pathways such as Aβ-induced tau phosphorylation, inflammation, and/or disruption of proteostasis [37, 91, 118] have not been ruled out.

As we gain a deeper understanding of the different cellular functions of tau, the focus shifts from the axon, where tau has a principal role as microtubule-associated protein, to the dendrite, where it mediates Aβ toxicity [91]. On the other hand, according to several data, tau aggregates may be a consequence rather than a cause of neurodegeneration [14, 119]. Therefore, the effects promoted by Aβ and tau should be analyzed more specifically to identify the mechanisms that underlay Aβ and tau toxicity and/or neuroprotection in order to find appropriate therapeutic targets.

4. INDUCTION AND SPREAD OF PROTEIN AGGREGATES IN NEURODEGENERATIVE DISEASES

Increasing evidence implicates the importance of disease-specific proteins and their interrelations in various neurodegenerative disorders [1–4, 16]. In PD, αSyn-rich lesions that typify Lewy body pathology, first arise in the lower brainstem and in the anterior olfactory nucleus and olfactory bulb; they subsequently appear in a predictable sequence in mesencephalic and neocortical regions [120–122], although their reliability of Lewy pathology staging in sporadic PD has been a matter of discussion [123–126]. The concept that αSyn lesions ramify within the CNS by a seeding-like process is supported by the observation that fetal dopaminergic transplants in the striatum of a subset of PD patients surviving more than 5 years may develop αSyn-positive Lewy bodies [127–129]. These data imply for a host-to-graft propagation of αSyn, but the effects of LBs in the grafted neurons are unclear [129], although neuron-to-neuron (interneuron) transmission or transsynaptic spread of αSyn appears a likely interpretation for the propagation of the disease [8, 129]. It has been suggested that LBs develop in transplanted dopaminergic neurons in a fashion similar to that in the host SN [130]. On the other hand, LB pathology in grafted neurons does not necessarily mean their functional impairment. Similar accumulation of αSyn occurs in stem cells transplanted into transgenic mice [8]. Secreted αSyn can recruit endogenous αSyn in the recipient cells, act as a permissive template, and promote misfolding in small aggregates [131]. Some of the uptake of αSyn from the extracellular space appears to occur via endocytosis, although additional mechanisms might also contribute [131, 132]. It is probable to trigger the formation of large LB-like aggregates in cultured cells, when artificial methods, bypassing physiologic uptake mechanisms, are used to promote the entry of misfolded αSyn. *In vivo* approaches in cell cultures could not discriminate between a prion-like mechanism—host-derived, misfolded αSyn inducing misfolding of αSyn generated in the graft—versus simple translocation of aggregated synuclein from the host to the graft. Thus, in cell culture all the mechanisms needed for prion-like behavior of misfolded αSyn appear to be in place [131, 133, 134]. These and other data suggest that αSyn pathology could be induced in cells and may spread by a prion like mechanism involving the transmission of conformationally altered αSyn [135–138]. Thus, the prion-like propagation of αSyn lesions has been demonstrated as has the induction of proteinaceous lesions associated with other neurodegenerative diseases, such as aggregates of superoxide dismutase 1 (SOD1) [139, 140], aggregates of polyamine [141], which typify Huntington disease and spinocerebellar ataxias, or cytosolic aggregates of TDP-43 [142], which are present in ALS and frontotemporal lobar degeneration with TDP-43-positive inclusions (FTDL-TDP). The capability of passing between living cells is not limited to prions and those cited above; it was also shown for aggregates of truncated tau, consisting of the microtubule-binding region and a fluorescent protein tag that can leave and enter cells in culture and promote the aggregates and fibrillization of normal tau within them [115, 143–146]. The recent demonstration of tau-positive pretangle material in the locus ceruleus before involvement of the transentorhinal region of the cerebral cortex in young individuals [147] suggests a progression of tau pathology via neuron-to-neuron transmission and transsynaptic transport of tau protein aggregates [148], since seeding of neuronal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles [15]. These data may indicate that the currently used neuropathological stages of AD [149–151] will have to be reclassified. Mutant P201S tau, as found in frontotemporal dementia with parkinsonism (FDTP-19), is capable of spreading through the cortex of an Alz 17 tg mouse expressing the human wild type protein and induce an NFT-like pathology that consists of human tau in brain areas distant from the injection site [145]. These and other data raise the possibility that neurodegenerative pathologies could spread within the brain via a mechanism analogous to prion-like self-propagation, although alternative mechanisms, such as disruption of basic cellular proteostasis by exogenous aggregates, cannot be excluded [152]. Furthermore, tau and αSyn are present in blood and CSF in both monomeric and oligomeric forms, suggesting release of these normally intracellular proteins *in vivo* [77, 153–155]. The intercellular transfer of cytosolic protein aggregates may also occur through nanotubes, exosomes, or microvesicles [135]. Like other pathogenic proteins, Aβ can be taken up, modified, and secreted by cells *in vitro* [108, 156], and it is also present in the CSF [157].

5. CONCLUSIONS

Interaction between αSyn, tau, and Aβ may be a molecular mechanism in the overlapping pathology of LB disease and AD, possibly representing a complex continuum, characterized by variable amounts of pathologic proteins, and Aβ is suggested to promote accumulation of both αSyn and tau; the procession from Aβ to neurite pathology in the cerebral cortex of AD and DLB may be unifiable [73, 74]. DLB-3xtg-AD mice exhibit accelerated formation of αSyn and LB-like inclusions in the cortex and enhanced increase of p-tau deposits immunoreactive for antibody AT8 in the hippocampus, and neocortex provide further evidence that tau, αSyn, and Aβ interact *in vivo* to promote accumulation of each other and accelerate cognitive dysfunction, although accumulation of αSyn alone can significantly disrupt cognition [158, 159]. Polymorphic tau and Aβ-tau aggregates may be due to repeated sequences, which are prone to variable turn locations along the tau repeats, suggesting that synergistic interactions between repeats in tau protein and Aβ may be responsible for accelerated aggregation via polymorphic states [117]. These changes and common inflammatory mechanisms in these disorders [160] could be generated by the same stimulus, with the outcome possibly having an inverse relationship depending on genetic backgrounds and environmental factors. Although recent data documented colocalization of αSyn and tau in LBs [57], of Aβ and p-tau in synaptosomes [161], synaptic terminals [162], and in triple transgenic mice [105], why tau, Aβ, and αSyn pathologies are so intimately associated remains one of the major questions of the pathogenesis of neurodegeneration in selected/vulnerable brain regions that are typical for different disease processes (double or triple amyloidoses). It has been suggested that these pathologies represent a common final pathway leading to or preventing neuronal damage [23, 70, 71, 85]. The basic molecular mechanisms (presumed regional differences in proteasomal, caspase, GSK-3β activities, oxidative stress in the presence of αSyn deposition, etc.) need further elucidation, and the molecular basis of the synergistic effects of αSyn, p-tau, Aβ, and other pathologic proteins, suggesting a dualism or triad of neurodegeneration, are a major challenge for modern neuroscience. Improved understanding of these mechanisms may not only improve our insight into the pathogenesis of proteinopathies, but also have an impact on diagnostic and therapeutic possibilities.

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