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Role of Synucleins in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common causes of dementia and movement disorders in the elderly. While progressive accumulation of oligomeric amyloid-β protein (Aβ) has been identified as one of the central toxic events in AD leading to synaptic dysfunction, accumulation of α-synuclein (α-syn) resulting in the formation of oligomers has been linked to PD. Most of the studies in AD have been focused on investigating the role of Aβ and Tau; however, recent studies suggest that α-syn might also play a role in the pathogenesis of AD. For example, fragments of α-syn can associate with amyloid plaques and Aβ promotes the aggregation of α-syn in vivo and worsens the deficits in α-syn tg mice. Moreover, α-syn has also been shown to accumulate in limbic regions in AD, Down's syndrome, and familial AD cases. Aβ and α-syn might directly interact under pathological conditions leading to the formation of toxic oligomers and nanopores that increase intracellular calcium. The interactions between Aβ and α-syn might also result in oxidative stress, lysosomal leakage, and mitochondrial dysfunction. Thus, better understanding the steps involved in the process of Aβ and α-syn aggregation is important in order to develop intervention strategies that might prevent or reverse the accumulation of toxic proteins in AD.

Keywords Synuclein · Alzheimer's · Parkinson's · Amyloid · APP

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-β protein
α-syn	α-Synuclein
PD	Parkinson's disease

Introduction to the Pathogenesis of AD

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common causes of dementia and movement disorders in the elderly. While progressive accumulation of amyloid-β protein (Aβ) oligomers has been identified as one of the central toxic events in AD leading to synaptic dysfunction (Klein et al. 2001; Walsh and Selkoe 2004; Glabe 2005), accumulation of α-synuclein (α-syn) resulting in the formation of oligomers has been linked to PD (Giasson et al. 2000; Lee et al. 2001; Lashuel et al. 2002; Hashimoto et al. 2003b; Tsigelny et al. 2007). Alzheimer's disease and PD overlap in a heterogeneous group of disorders denominated Lewy body disease (LBD) (McKeith et al. 2005) where both Aβ and α-syn accumulate in the brain. Several lines of evidence now support a role for

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α-syn not only in PD but also in additional disorders including AD, multiple system atrophy (MSA), and others (Trojanowski et al. 1998).

Alzheimer's disease continues to be the leading cause of dementia in the aging population (Ashford 2004). Over 5 million people live with this devastating neurological condition and it is estimated that the US will experience an average 50% increase in patients with AD by the year 2025 (Hebert et al. 2004). Alzheimer's disease is a progressive neurodegenerative disorder that specifically damages limbic structures, the association neocortical pathways (Hof and Morrison 1991; Masliah et al. 1993; Braak and Braak 1994; Hof and Morrison 1994), and the cholinergic system (Perry et al. 1978; Perry 1995). Although the key neuropathological diagnostic features of AD are the presence of plaques—composed of amyloid-β (Aβ) peptides (Selkoe 1990)—and tangles containing the microtubule binding protein Tau (Trojanowski et al. 1993), the neurodegenerative process in AD probably initiates with damage to the synaptic terminals (Scheff et al. 1990; Terry et al. 1991; Masliah and Terry 1994). It has been postulated that the early synaptic pathology leads to axonal abnormalities (Goldstein et al. 2003), spine (Spires et al. 2005) and dendritic atrophy (Moolman et al. 2004), and eventually neuronal loss (Terry et al. 1991; Mucke et al. 2000). Therefore, disruption of the mechanisms involved in modulating synaptic plasticity might be responsible for the characteristic cognitive deficits in AD patients and as such represent an important target for treatment development.

Although the precise mechanisms leading to neurodegeneration in AD are not completely understood, several lines of investigation indicate that alterations in the amyloid precursor protein (APP), resulting in the accumulation of amyloid-β protein (Aβ) and APP C-terminal products, might play a key role in the pathogenesis of AD (Selkoe 1994a, b; Sisodia and Price 1995; Sinha et al. 2000; Kamenetz et al. 2003) (Fig. 1). Several products are derived from APP through alternative proteolytic cleavage pathways, and enormous progress has recently been made in identifying the enzymes involved (Selkoe 1999; Sinha et al. 1999; Vassar et al. 1999; Cai et al. 2001; Luo et al. 2001).

While most research has been centered at investigating the role of APP/Aβ and Tau in the pathogenesis of AD, however, recent studies suggest that α-syn might also play a role in the pathogenesis of this neurodegenerative disorder (Iwai et al. 1995a; Iwai 2000) (Fig. 2).

The Synuclein Family of Proteins in Health and Disease

α-Synuclein is an abundant presynaptic molecule (Iwai et al. 1995b) that plays a role in modulating vesicular synaptic release (Murphy et al. 2000). Synucleins belong to a family of related proteins including α-, β-, and γ-syn. α-Synuclein belongs to a class of so-called naturally unfolded proteins (Lansbury 1999; Wright and Dyson 1999) (Fig. 3). α-Synuclein contains a highly amyloidogenic hydrophobic domain in the N-terminus region (aa 60–95) (Fig. 3) which is partially absent in β-syn and might explain why β-syn has a reduced ability to self-aggregate and form oligomers and fibrils (Hashimoto et al. 2001; Uversky et al. 2002). Moreover, previous studies have shown that β-syn interacts with α-syn and is capable of preventing α-syn aggregation and related deficits both in vitro and in vivo (Hashimoto et al. 2001). Overall, synucleins are believed to be involved in regulation of synaptic plasticity and dopamine neurotransmitter release (Murphy et al. 2000).

α-Synuclein plays a role in synaptic adaptations, including synaptic plasticity during development, learning (Clayton and George 1998), and regulation of synaptic vesicle mobilization at nerve terminals (Cabin et al. 2002). Additionally, previous studies have shown that α-syn may have important non-synaptic physiological functions that occur through interactions with other molecules such as the scaffolding protein Sept4 (Ihara et al. 2007) and the synaptic vesicle protein cysteine-strong protein-α (CSPα)

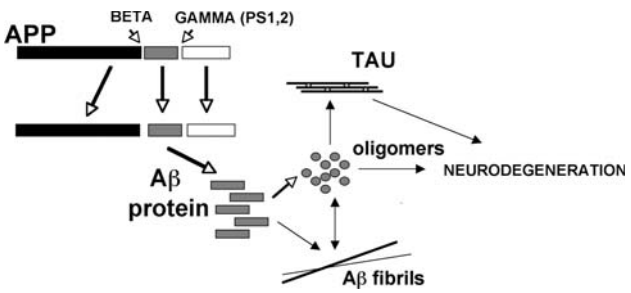

Fig. 1 Schematic representation of the metabolism of APP and the formation of Aβ aggregates

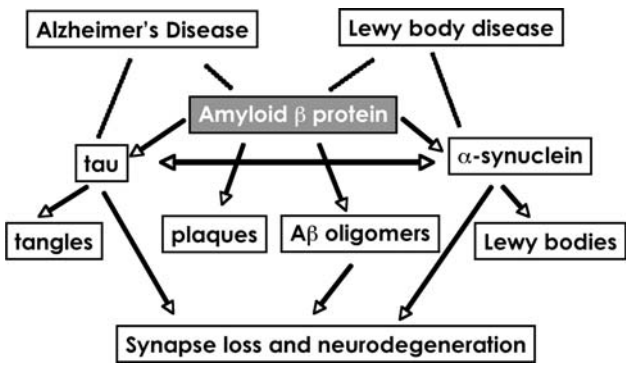

Fig. 2 Role of the interactions between Aβ, α-syn, and Tau in the pathogenesis of AD and LBD

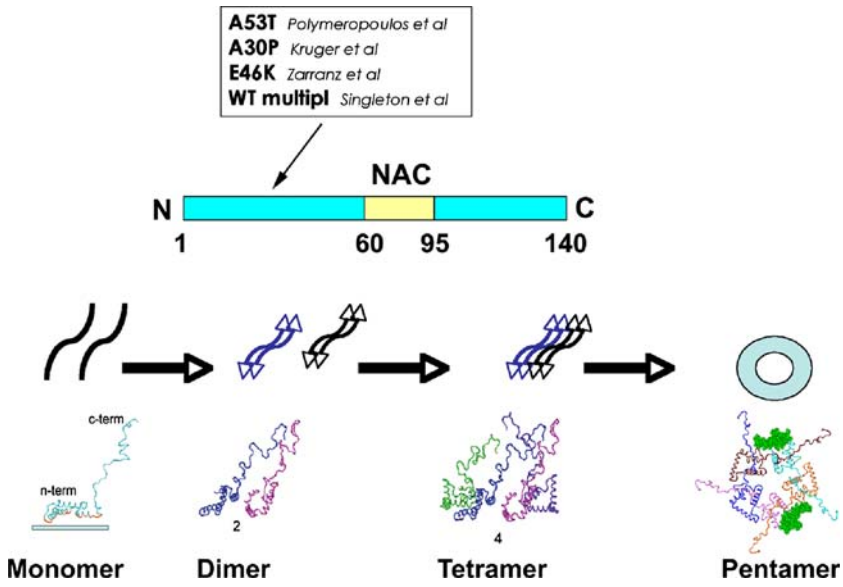

Fig. 3 Molecular dynamics of α-syn structure and progressive aggregation leading to the formation of toxic oligomers

(Chandra et al. 2005). α-Synuclein has been implicated in the pathogenesis not only of LBD (Trojanowski et al. 1998; Hashimoto and Masliah 1999) but also of other disorders with parkinsonism, including MSA (Spillantini et al. 1998; Wakabayashi et al. 1998b; Wakabayashi et al. 1998a). These disorders are collectively referred to as synucleinopathies (Hardy and Gwinn-Hardy 1998) and might share common pathogenic pathways that promote toxic conversion of α-syn.

Various lines of evidence support the contention that abnormal aggregates arise from a partially folded intermediate precursor that contains hydrophobic patches. It has been proposed that the intermediate α-syn oligomers form annular protofibrils and pore-like structures (Ding et al. 2002; Volles and Lansbury 2002; Lashuel et al. 2003; Rochet et al. 2004; Tsigelny et al. 2007) (Fig. 3). The mechanisms through which monomeric α-syn converts into a toxic oligomer and later into fibrils is currently under intense investigation. Recent studies suggest that α-syn oligomerization might occur on the membrane and involves interactions between hydrophobic residues of the amphipathic α-helices of α-syn (Zhu et al. 2003). These studies indicate that the hydrophobic lipid-binding domains in the N-terminal region might be important in modulating α-syn aggregation (Conway et al. 1998; Lansbury 1999; Uversky et al. 2001; Jao et al. 2004).

Molecular modeling and molecular dynamic simulations showed that α-syn homodimers could adopt non-propagating (head-to-tail) and propagating (head-to-head) conformations (Tsigelny et al. 2007) (Fig. 3). Propagating α-syn dimers on the membrane incorporate additional α-syn molecules, leading to the formation of pentamers and hexamers, which form rings suggestive of pore-like structures (Tsigelny et al. 2007) (Fig. 3). Oligomers form complexes in the membranes of neurons that facilitate abnormal calcium currents that might disturb synaptic and neuronal function leading to neurodegeneration (Danzer et al. 2007).

In conclusion, it is likely that α-syn oligomers might be responsible for the neurodegenerative process in LBD/PD. The Lewy bodies (LBs), which primarily contain α-syn fibrils, might represent a cellular mechanism to isolate more toxic oligomers. The α-syn oligomers most likely associate with the neuronal membranes and synapses, interfering with neurotransmission and plasticity. Thus, better understanding the steps involved in the process of α-syn aggregation is important in order to develop intervention strategies that might prevent or reverse α-syn oligomerization and toxic conversion.

Disease Models, Knockouts, Assays

APP tg Animal Models of AD

The main focus of the following sections in AD will be on models involving amyloid deposition and Tau hyperphosphorylation. In AD, mutations in PS1 and 2 and polymorphisms in apolipoprotein E (ApoE) have been also linked with AD and as such are important targets. Recently developed tg animal models have shown that it is possible to reproduce certain aspects of AD pathology over a shorter period of time (Masliah et al. 1996b; Games et al. 1997; Price et al. 2000). In one such model, the platelet-derived growth factor (β chain) (PDGF-β) promoter drives an alternatively spliced human APP (hAPP) minigene (PDAPP) encoding mutated V → F hAPP695, 751, 770 (Games et al. 1995; Rockenstein et al. 1995). This confers

a high ratio of mRNA encoding mutated hAPP versus wt mouse APP (Rockenstein et al. 1995) that promotes development of typical amyloid plaques, dystrophic neurites, loss of presynaptic terminals, astrocytosis, and microgliosis (Games et al. 1995; Masliah et al. 1996b; Games et al. 1997).

Other models have expressed mutant hAPP under the regulatory control of either the human or murine (m)Thy-1 promoter (Andra et al. 1996; Sturchler-Pierrat et al. 1997; Moechars et al. 1999; Bornemann and Staufenbiel 2000) or the protease-resistant prion protein (PrP) promoter (Hsiao et al. 1996; Borchelt et al. 1997). Amyloid deposition begins at 12 months of age; however, co-expression of mutant PS1 accelerates amyloid deposition, beginning at 4 months of age (Borchelt et al. 1996; Borchelt et al. 1997; Holcomb et al. 1998). Another more recently developed model, where APP is also expressed under the control of the PrP promoter, displays even earlier onset of amyloid deposition, starting at 3 months and progressing to mature plaques and neuritic pathology from 5 months of age, accompanied by high levels of $A\beta_{1-42}$ (Chishti et al. 2001). While the PrP promoter has provided several models that mimic aspects of familial AD (FAD), other promoters targeting expression of APP to neurons provide alternative models demonstrating pathology that recapitulate similar and additional aspects of FAD. In this regard, we have generated lines of tg mice expressing hAPP751 cDNA containing the London (V717I) and Swedish (K670M/N671L) mutations under the regulatory control of the murine (m)Thy-1 gene (mThy1-hAPP751) (Rockenstein et al. 2001). Therefore, while expression of mutant hAPP under the PDGF-β promoter results in the production of diffuse (and some mature) plaques (Games et al. 1995; Mucke et al. 2000), tg expression of mutant hAPP under the mThy-1 (Andra et al. 1996) and PrP (Hsiao et al. 1996; Borchelt et al. 1997) promoters favors the formation of mature plaques in the hippocampus and neocortex. This suggests that the differential patterns of Aβ deposition might be dependent on the specific neuronal populations selected by the promoter, levels of expression and topographical distribution of the transgene, and levels of $A\beta_{1-40}$ and $A\beta_{1-42}$. Consistent with this, in FAD and Down syndrome, production of high levels of $A\beta_{1-42}$ results in early plaque formation (Citron et al. 1997). This suggests that early age of onset and plaque formation depends on high levels of $A\beta_{1-42}$ production (Rockenstein et al. 2001).

More recent models have been focused toward modeling the role of Aβ protofibril generation and other mutations in APP in the pathogenesis of AD. Of them, the most interesting are those expressing APP bearing the Arctic mutation. These mice rapidly develop extensive plaque formation (Cheng et al. 2004). For a review of these and additional tg models of neurodegenerative disease, please visit the Alzheimer's Forum website at: http://www.alzforum.org/res/com/tra.

α-Synuclein Transgenic Models of PD and LBD

Since progressive intraneuronal aggregation of α-syn has been proposed to play a central role in the pathogenesis of PD and related disorders (Hashimoto and Masliah 1999; Trojanowski and Lee 2000; Volles and Lansbury 2002), most tg models have been focused at investigating the in vivo effects of α-syn accumulation utilizing neuron-specific promoters. Several recent reviews have been published addressing this subject (Hashimoto et al. 2003a; Fernagut and Chesselet 2004). Among these models, overexpression of wt α-syn under the regulatory control of the PDGF-β promoter has been shown to result in motor deficits, dopaminergic loss, and formation of inclusion bodies (Masliah et al. 2000). Mice with the highest levels of expression (line D) showed intraneuronal accumulation of α-syn that started at 3 months of age and was accompanied by the loss of tyrosine hydroxylase (TH) fibers in the caudoputamen region and synapses in the temporal cortex. Although no apparent neuronal loss was detected in the substantia nigra (SN), measurements of dopamine levels in the caudoputamen region showed a 25–50% reduction at 12 months of age. Consistent with these results, tg mice showed mild to moderate motor deficits in the rotarod, particularly in mice with the greatest loss of dopamine, indicating that more substantial deficits (>75%) of this transmitter might be necessary for more overt deficits to appear. In mThy-1-hαsyn tg mice, this protein accumulated in synapses and neurons throughout the brain, including the thalamus, basal ganglia, SN, and brainstem (Rockenstein et al. 2002; Fleming et al. 2004).

Because previous studies have shown that mutations associated with familial parkinsonism accelerate α-syn aggregation and oligomerization (Conway et al. 1998; Narhi et al. 1999), we compared the patterns of neurodegeneration, α-syn aggregation, and neurological alterations in tg mice expressing wt or mutant (A53T) hα-syn at comparable levels under the PDGF-β promoter. Remarkably, we found that mice expressing low levels of mutant hα-syn developed progressive motor deficits and neurodegeneration associated with hα-syn accumulation in synapses and neurons, but very few or no inclusions were found (Hashimoto et al. 2003a). Similarly, mice expressing high levels of mutant A53T, but not wt or A30P mutant, α-syn developed a severe and complex motor impairment leading to paralysis and death (Giasson et al. 2002; Lee et al. 2002; von Coelln et al. 2006). In contrast to our model expressing low levels of mutant α-syn, animals expressing higher levels of A53T α-syn developed age-dependent intracytoplasmic neuronal α-syn inclusions

paralleling disease onset, and the α-syn inclusions recapitulated features of human disorders. Moreover, immunoelectron microscopy revealed that the α-syn inclusions contained 10–16 nm wide fibrils similar to human pathological inclusions. These mice demonstrate that A53T α-syn leads to the formation of toxic filamentous α-syn neuronal inclusions that cause neurodegeneration (Giasson et al. 2002).

This spectrum of α-syn-associated neurodegenerative phenotypes in various tg models can be partially attributed to the different effects conferred by expressing mutant versus wt α-syn. Another important factor is the promoters selected to drive α-syn expression, which regulate both expression levels and cell-type specificity. For example, under the mThy-1 promoter, expression of either wt or mutant α-syn (van der Putten et al. 2000) results in extensive insoluble α-syn accumulation throughout the CNS including, in some cases, in the SN or motor neurons (Rockenstein et al. 2002). Under the mouse PrP promoter, expression of mutant A53T α-syn enhanced the accumulation of aggregation-promoting C-terminally truncated species of α-syn (Li et al. 2005). Under the rat TH promoter, expression of double mutant hα-syn adversely affects the integrity of dopaminergic terminals and leads to age-related declines in motor coordination and dopaminergic markers (Richfield et al. 2002).

Further studies to investigate the role of α-syn mutations and selective neuronal vulnerability in the SN have been performed in rats utilizing lentiviral and adeno-associated-viral vectors (Kirik et al. 2002; Klein et al. 2002; Lo Bianco et al. 2002). In contrast to tg mice models, a selective loss of nigral dopaminergic neurons associated with a dopaminergic denervation of the striatum was observed in animals expressing either wt or mutant forms of hα-syn. This neuronal degeneration correlates with the appearance of abundant α-syn-positive inclusions and extensive neuritic pathology detected with both α-syn and silver staining. Rat α-syn similarly leads to protein aggregation but without cell loss, suggesting that inclusions are not the primary cause of cell degeneration in PD (Lo Bianco et al. 2002).

In summary, these in vivo models support the contention that α-syn-dependent neurodegeneration is associated with abnormal accumulation of detergent-insoluble α-syn (probably representing oligomeric forms) rather than with inclusion formation representing fibrillar polymeric α-syn. The specific accumulation of detergent-insoluble α-syn in these tg mice recapitulates a pivotal feature of LBD (Kahle et al. 2001) and it is of significant importance in the future development and evaluation of novel treatments.

Disease Targets and Ligands for Combined AD and PD

α-Synuclein as a Target in Combined AD/PD

α-Synuclein was originally identified in AD plaques as the precursor protein of the non-Aβ component (NAC) of AD amyloid (Fig. 4a) and thus was called non-amyloid component of plaques (NACP) (Ueda et al. 1993; Iwai et al. 1995a; Masliah et al. 1996a; Iwai 2000). NAC, a highly hydrophobic 35-amino acid domain within the α-syn molecule, may be involved in amyloid formation (Iwai et al. 1995a) (Fig. 3). NAC is highly amyloidogenic and aggregates to form fibrils under oxidative conditions (Hashimoto et al. 1997; Hashimoto et al. 1999), and NAC also interacts with Aβ and promotes Aβ aggregation (Yoshimoto et al. 1995).

Remarkably, several studies have now confirmed that the pathology of AD and PD overlap in a heterogeneous group of conditions denominated jointly LBD (McKeith 2000; Lippa et al. 2007). Approximately 25% of all cases of AD develop parkinsonism and about 50% of all cases of PD develop AD-type dementia after 65 years of age (Hansen et al. 1990). Moreover, 70% of patients with

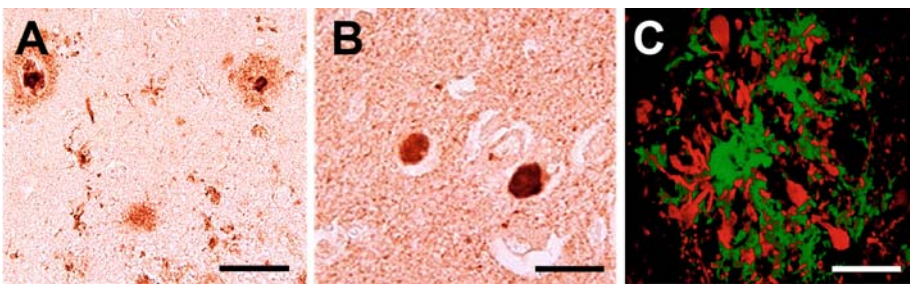

Fig. 4 Characteristics of α-syn aggregates and inclusions in the brains of AD patients. **a** Representative section from the brain of an AD patient immunostained with an antibody against the NAC region of α-syn. The staining shows characteristic plaques composed of Aβ protein. **b** Representative section from the brain of an AD patient immunostained with an antibody against α-syn that detected Lewy body-like inclusions in the neocortex. **c** Representative section from the brain of an AD patient double immunolabeled with antibodies against Aβ and α-syn shows co-localization of the two signals in plaques. Scale bar, 20 μm (**a**), 10 μm (**b**, **c**)

sporadic AD display the formation of α-syn-positive LB-like inclusions in the amygdala and limbic structures (Lippa et al. 1998; Trojanowski et al. 1998; Hamilton 2000) and by the time of autopsy, approximately 90% of patients with probable LBD also meet the Reagan pathologic criteria for AD (Hyman and Trojanowski 1997; McKeith et al. 2005). Similarly, in patients with FAD and Down's syndrome, LB-like pathology and parkinsonism have been reported (Lippa et al. 1999). Interestingly, the brains of patients with DLB and PDD display very similar pathology, with the exception that recent studies have shown extensive deposition of Aβ and α-syn in the striatum and hippocampus in DLB compared to only α-syn in PDD cases (Duda et al. 2002; Jellinger and Attems 2006). Furthermore, previous studies provide extensive support for an interaction between pathogenic pathways in AD and PD, in particular FAD cases with presenilin mutations that present with significant LB pathology (Rosenberg 2005; Snider et al. 2005; Leverenz et al. 2006). The amyloidogenic fragment, NAC, of α-syn is found in the amyloid plaque (Hashimoto et al. 2000) (Fig. 4a), although some controversy has emerged in this respect (Culvenor et al. 1999). The dystrophic neurites in the plaques from AD patients display intense α-syn immunoreactivity (Masliah et al. 1996a) (Fig. 4), α-syn-positive aggregates are found in limbic regions in AD (Lippa et al. 1999) (Fig. 4b) and the overall levels of α-syn are abnormal in the early stages of AD (Iwai et al. 1996). Moreover, genetic polymorphisms in the α-syn gene have been shown to regulate the susceptibility to AD (Xia et al. 1996; Tsigelny et al. 2008).

Underlying interactions between α-syn and Aβ play a fundamental role in the pathogenesis of LBD (Lippa et al. 1998; Hashimoto et al. 2000; Masliah et al. 2001; Pletnikova et al. 2005). Specifically, Aβ worsens the deficits associated with α-syn accumulation (Pettegrew 1989; Lippa et al. 1998; Lippa et al. 2005; Pletnikova et al. 2005; Deramecourt et al. 2006; Mandal et al. 2006; Lippa et al. 2007), and Aβ promotes the oligomerization and toxic conversion of α-syn (Masliah et al. 2001; Mandal et al. 2006) (Fig. 5), suggesting that Aβ and α-syn might directly interact in vitro and in vivo. In support of this possibility, under pathological conditions, both aggregated Aβ and α-syn might associate with membranes and accumulate in caveolae (Soto et al. 1994; Bouillot et al. 1996; Eliezer et al. 2001; Fortin et al. 2004; Kubo et al. 2005; Bar-On et al. 2006; Kim et al. 2006; Bar-On et al. 2008; Williamson et al. 2008). Consistent with these findings, our recent studies have shown that Aβ and α-syn co-localize in membrane and caveolar fractions, and Aβ stabilizes α-syn multimers that might form channel-like structures in the membrane (Tsigelny et al. 2008). Moreover, lipid rafts in the membrane have been postulated to play a role in oligomerization of misfolded proteins (Soto et al. 1994; Kazlauskaite and Pinheiro 2005; Kim et al. 2006) including α-syn (Fortin et al. 2004; Bar-On et al. 2006; Bar-On et al. 2008) and Aβ (Soto et al. 1994; Kim et al. 2006; Williamson et al. 2008) and might represent a suitable site for the abnormal interactions between aggregated forms of α-syn and Aβ. Furthermore, highly amyloidogenic intraneuronal Aβ (Wilson et al. 1999) has been shown to accumulate in the endoplasmic reticulum (Cook et al. 1997; Hartmann et al. 1997), Golgi apparatus (Xu et al. 1997; Xia et al. 2000), and the endosome–lysosome system (Koo and Squazzo 1994), and these organelles may provide additional sites for interaction between Aβ and α-syn. In support of this possibility, aggregated forms of Aβ and α-syn have been independently described in several intracellular membranous structures (Bahr and Bendiske 2002; Hashimoto et al. 2003b; Lee et al. 2005; Nixon and Cataldo 2006); (Tsigelny et al. 2007).

Mechanisms of Neurodegeneration and Interactions Between α-syn and Aβ in Combined AD/PD

The aggregates of α-syn might independently contribute to the neurodegenerative process in AD or via interactions with Aβ. Most studies have investigated the formation of toxic oligomeric species derived from homologous monomers. We have recently investigated the interactions between heterogeneous proteins that can form toxic hybrid oligomers, showing that Aβ and α-syn can interact in vivo and in vitro (Tsigelny et al. 2008). Supporting these findings, Aβ and α-syn co-immunoprecipitated in the brains of patients with LBD as well as in double APP/α-syn transgenic (tg) mice. Furthermore, molecular modeling studies showed that these interactions promoted the formation of

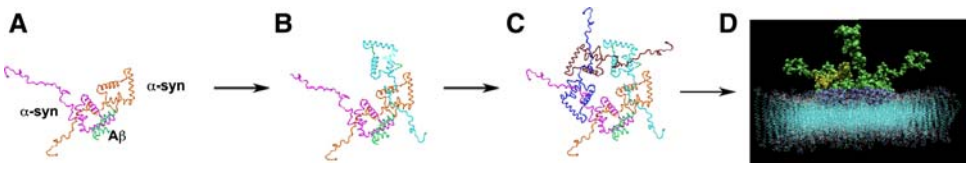

Fig. 5 Molecular dynamics of α-syn and Aβ interactions leading to the formation of hybrid pores in the membrane. **a** Conformation of α-syn dimer in the presence of one molecule of Aβ. **b** Conformation of α-syn trimer with the Aβ monomer. **c** Conformation of α-syn pentamer with the Aβ monomer and the formation of a central pore-like channel. **d** Space-filled model showing the pore-like α-syn pentamer with the Aβ monomer embedded in a membrane

highly stable ring-like oligomers composed of both Aβ and α-syn and these species dock in the membrane (Fig. 5). Similarly, in vitro studies confirmed that both freshly solubilized as well as aggregated Aβ and α-syn can directly interact and form hybrid ring-like structures.

In agreement with this possibility, a previous study showed that Aβ promotes the aggregation of α-syn in vivo and worsens the deficits in α-syn tg mice (Masliah et al. 2001). Moreover, α-syn has also been shown to accumulate in the brains of APP tg (Yang et al. 2000) and APP/presenilin-1 (PS1) double tg mice that produce large amounts of Aβ (Kurata et al. 2007). In addition, as described in the previous section, several studies have now shown that in the brains of LBD patients, Aβ contributes to the levels and state of α-syn aggregation and LB formation (Pettegrew 1989; Lippa et al. 1998; Lippa et al. 2005; Pletnikova et al. 2005; Deramecourt et al. 2006; Mandal et al. 2006; Lippa et al. 2007). Taken together, these studies in tg mice and human brains support the contention that Aβ and α-syn interact in vivo and that these interactions are of significance in the pathogenesis of the disease.

Aβ might promote α-syn aggregation by directly interacting with α-syn molecules bound to the membrane and therefore facilitating the formation of more stable oligomers. However, Aβ might promote α-syn aggregation through other pathways, including increased oxidative stress, calpain activation with C-terminal cleavage of α-syn (Mishizen-Eberz et al. 2005; Dufty et al. 2007), and aberrant phosphorylation induced by secreted forms of Aβ.

The hybrid multimers of Aβ and α-syn might embed in the membrane (Fig. 5d) of mitochondria, lysosomes, and the plasma membrane, leading to the formation of nanopore-like structures resulting in abnormal ion conductance (Tsigelny et al. 2008). Previous studies have shown that Aβ penetrates in the membrane and aggregates to form channels that facilitate the abnormal trafficking of cations such as Ca^{2+} and K^{+} (Arispe et al. 1993; Arispe et al. 1996; Lin et al. 2001; Mattson 2007). Studies of α-syn aggregation by atomic force microscopy have shown that the oligomers form heterogeneous pore-like structures that might induce cell death via disruption of calcium homeostasis (Quist et al. 2005; Danzer et al. 2007).

Next Frontiers in Drug Discovery

Alterations in the balance between factors promoting aggregation, clearance, and synthesis of Aβ and α-syn might be centrally involved in the formation of oligomers and the pathogenesis of neurodegeneration. Clearance of Aβ and α-syn oligomers occurs primarily via degrading enzymes (neprilysin), chaperone molecules (β-syn, HSP27, 70), and lysosomal pathways (autophagy). Immunotherapy approaches might reduce α-syn accumulation by stimulating autophagy. Gene therapy approaches using viral vectors can be used to target these pathways involved in Aβ and α-syn clearance. For example, delivery of neprilysin, an Aβ-degrading enzyme, into the brains of APP tg mice results in amelioration of the behavioral deficits, improved synaptic formation, and decreased Aβ accumulation. Since Aβ also promotes the aggregation of α-syn, gene therapy delivery of neprilysin has also been shown to reduce the α-syn pathology and deficits in tg mice expressing both APP and α-syn. Another important clearance mechanism amenable for manipulation by gene therapy is the autophagy pathway. For this lysosomal degradation system, the oligomers are targeted to the chaperone-mediated system or to the macroautophagy pathway. In both AD and PD the autophagy pathway is abnormal. Therefore increasing autophagy with mTor antagonists and gene therapy to promote autophagy might be of therapeutical value. Such pro-clearance properties might also provide a novel strategy for the treatment of other neurodegenerative disorders.

Conclusions

In combined AD/PD, both Aβ and α-syn might directly interact under pathological conditions leading to the formation of toxic oligomers and nanopores that increase intracellular calcium. Other mechanisms involved include oxidative stress, lysosomal leakage, and mitochondrial dysfunction. Thus, better understanding the steps involved in the process of Aβ and α-syn aggregation is important in order to develop intervention strategies that might prevent or reverse the toxic conversion in AD.

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