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THE ROLE OF α-SYNUCLEIN IN NEURODEGENERATION – AN UPDATE

Kurt A. Jellinger*

Institute of Clinical Neurobiology
Kenyongasse 18, A-1070 Vienna, Austria

Abstract

Genetic, neuropathological and biochemical evidence implicates α-synuclein, a 140 amino acid presynaptic neuronal protein, in the pathogenesis of Parkinson's disease and other neurodegenerative disorders. The aggregated protein inclusions mainly containing aberrant α-synuclein are widely accepted as morphological hallmarks of α-synucleinopathies, but their composition and location vary between disorders along with neuronal networks affected. α-Synuclein exists physiologically in both soluble and membran-bound states, in unstructured and α-helical conformations, respectively, while posttranslational modifications due to proteostatic deficits are involved in β-pleated aggregation resulting in formation of typical inclusions. The physiological function of α-synuclein and its role linked to neurodegeneration, however, are incompletely understood. Soluble oligomeric, not fully fibrillar α-synuclein is thought to be neurotoxic, main targets might be the synapse, axons and glia. The effects of aberrant α-synuclein include alterations of calcium homeostasis, mitochondrial dysfunction, oxidative and nitric injuries, cytoskeletal effects, and neuroinflammation. Proteasomal dysfunction might be a common mechanism in the pathogenesis of neuronal degeneration in α-synucleinopathies. However, how α-synuclein induces neurodegeneration remains elusive as its physiological function. Genome wide association studies demonstrated the important role for genetic variants of the SNCA gene encoding α-synuclein in the etiology of Parkinson's disease, possibly through effects on oxidation, mitochondria, autophagy, and lysosomal function. The neuropathology of synucleinopathies and the role of α-synuclein as a potential biomarker are briefly summarized. Although animal models provided new insights into the pathogenesis of Parkinson disease and multiple system atrophy, most of them do not adequately reproduce the cardinal features of these disorders. Emerging evidence, in addition to synergistic interactions of α-synuclein with various pathogenic proteins, suggests that prion-like induction and seeding of α-synuclein could lead to the spread of the pathology and disease progression. Intervention in the early aggregation pathway, aberrant cellular effects, or secretion of α-synuclein might be targets for neuroprotection and disease-modifying therapy.

Keywords

α-synuclein • Neurodegeneration • Neuropathology • Synucleinopathies • Parkinson disease • Dementia • Multiple system atrophy • Biomarkers • Animal models

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Abbreviations

AD - Alzheimer disease
ad - autosomal-dominant
AGEP - advanced glycation endproduct
ALP - autophagy-lysosome pathway
ar - autosomal-recessive
AS - α-synuclein
Aβ - β-amyloid
BS - β-synuclein
CMA - chaperone-mediated autophagy
CNS - central nervous system
CSF - cerebrospinal fluid
CSPα - cystein string protein α
DA - dopamine
DDLB - diffuse dementia with Lewy bodies
DLB - dementia with Lewy bodies
DNA - desoxyribonucleic acid
Drp1 - dynamic-related protein 1
ER - endpoplasmic reticulum
f - familial
Fe - iron
GBA - glucocerebrosidase
GCI - glial cytoplasmic inclusions
GS - γ-synuclein
GSK-3β - glycogen-synthase kinase-3β
GWAS - genome wide association studies
Hsp - heat-shock protein
iLBD - incidental Lewy body disease
IMM - inner mitochondrial membrane
LB - Lewy body
LN - Lewy neurite
LRRK2 - leucine-rich repeat kinase 2
LVB/AD - Lewy body variant of Alzheimer disease
MAPK - mitogen-activating protein kinase
MAPT - tau protein gene
MBP - myelin basic protein
MPTP - 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mRNA - messenger ribonucleic acid
MSA - multiple system atrophy
MSA-C - multiple system atrophy with predominant cerebellar ataxia
MSA-P - multiple system atrophy with predominant parkinsonism
mtRNA - mitochondrial ribonucleic acid
NAC - non-amyloidogenic core
NCI - neuronal cytoplasmic inclusion
nDNA - nuclear DNA
NMR - nuclear magnetic resonance
NSF - N-ethylmaleimide-sensitive fusion protein
OMM - outer mitochondrial membrane
OPCA - olivopontocerebellar atrophy
OS - oxidative stress
p - phosphorylated

* *E-mail: kurt.jellinger@univie.ac.at*

PD - Parkinson disease
PDD - Parkinson disease-dementia
PK - proteinase K
ROS - reactive oxygen species
s - sporadic
Ser - serin
SN - substantia nigra
SNARE - soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptor
SNCA - α-synuclein gene
SNCB - β-synuclein gene
SNCG - γ-synuclein gene
SND - striato-nigral degeneration
Syn - synuclein
tg - transgenic
TH - tyrosine hydroxylase
TNF - tumor necrosis factor
TPPP - tubulin-polymerization-promoting protein
tTG - tissue transglutaminase
Ub - ubiquitin
UBA - ubiquitin-associated
UCHL1 - ubiquitin carboxy-terminal hydrolase L1
UPP - ubiquitin-proteasome pathway
UPR - unfolded protein response
UPS - ubiquitin-proteasomal system
WT - wild type

1. Introduction

α-Synuclein (AS) is implicated in the pathogenesis of Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [1-4]. PD is one of the most frequent neurodegenerative disorders, a progressive multisystem disease with variegated neurological and non-motor symptoms [5]. It is featured by degeneration of the dopaminergic nigrostriatal system, responsible for the core motor deficits [6], and multifocal involvement of the central, peripheral and autonomic nervous system and other organs, with widespread occurrence of presynaptic, intracytoplasmic, axonal, and dendritic depositions of fibrillary hyperphosphorylated AS protein that forms amyloid-like inclusions in selected neuronal populations [7-9]. Abnormal aggregates of AS occur in 3 major types of inclusions in a number of disorders that are collectively known as α-synucleinopathies [10,11]: (1) as intracellular and intraneuritic AS deposits (Lewy bodies /LB/ and Lewy neurites /LN/ in PD and DLB [3], (2) glial cytoplasmic inclusions (GCI) or Papp-Lantos bodies predominantly affecting oligodendroglia in MSA [12,13], and (3) in giant axonal swellings (spheroids) in these and other rare diseases [14-16] (see Table 1). These inclusions are widely accepted as diagnostic morphological hallmarks of α-synucleinopathies [17,18], although AS aggregates also affect both astroglia and microglia in PD, DLB and MSA [19,20]. Conversion of AS from soluble monomers to aggregated, insoluble forms is the key event in the pathogenesis of α-synucleinopathies. The question whether LBs and other AS aggregates are harmful or cytoprotective currently remains unresolved. Despite all aggregating AS protein in multiple systems, the solubility [21,22] and location of the protein varies between disorders along with neuronal populations affected [23]. The main clinical phenotypes of PD are related to diffuse progression of pathology and involvement of multiple neuronal networks and organs (see [9]), which has been suggested to result from a prion-like spreading of AS inducing its transmission and propagation of the disease [24-28]. In dementia syndromes variable clinical features are due to different pathologies (Parkinson disease-dementia / PDD/, pure DLB, and DLB with Alzheimer-like pathology or LB variant of Alzheimer disease / LBV/AD); their differentiation may be difficult. MSA was originally viewed as 3 different clinical phenotypes (Shy-Drager syndrome, striatonigral degeneration/SND or MSA-P, and sporadic olivopontocerebellar atrophy /sOPCA or MSA-C) due to different anatomical distribution of the pathological lesions associated with AS-positive glial inclusions [29,30]. The etiology of synucleinopathies seems to be complex, with variable contributions of both genetic and environmental risk factors, but in most cases, nongenetic factors play a role probably in interaction with susceptibility genes [31-34], although familial components may indicate genetic factors [35,36]. The recognition of the heterogeneity within synucleinopathies – as in other neurodegenerative disorders – is important for the classification of their phenotypes [37,38], probably related to genetic and environmental factors, as a basis for further therapy options.

2. The synuclein protein family

AS is an illustrative member of the rapidly growing family of natively unfolded proteins that lack a typical secondary structure [14,39]. The synucleins are small (127-140 amino acids) natively soluble unfolded proteins, which are highly charged and have low hydropathy [40,41]. The family includes AS, a 140 residue neuronal protein encoded by the 6-exon SNCA (PARK1) gene (OMIM 163890) coded on chromosome 4q.21 [42,43], β-synuclein

Table 1. α-Synucleinopathies.

1. Invariable forms (consistent occurrence of αSyn)
Sporadic Parkinson disease
Familial PD (αSyn-, PARKIN mutations)
Incidental Lewy body disease (preclinical PD)
REM sleep behaviour disorder (RSD)
Parkinson disease and dementia (PDD)
Dementia with Lewy bodies "pure" form (no or little AD-pathology), LB variant of AD (LBV/AD)
Pure autonomic failure
Lewy body dysphagia
Multiple system atrophy
Pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz syndrome)
2. Variable forms (inconsistent occurrence of αSyn)
Alzheimer disease (sporadic, familial)
Aging brain (with/without dementia)
Down syndrome
Frontotemporal lobe degeneration
Pick disease
Amyotrophic lateral sclerosis
Guamanian ALS-dementia complex
Progressive supranuclear palsy
Other tauopathies
Subacute sclerosing panencephalitis
Ataxia telangiectasia
Meige syndrome
Gerstmann-Sträussler-Scheinker disease
Gaucher disease
Traumatic brain lesions

(BS) and γ-synuclein (GS) [14], encoded by other distinct genes (chromosome 5 and 10, respectively [3,44]), that share significant sequences at the amino acid level [45]. A typical structural feature of synucleins (Syn) is the presence of a repetetive, degenerative amino acid motif KTKEGV throughout the first 87 residues and acidic stretches within the C-terminal region [46]. AS is characterized by 6 repeat sequences predicted to form 5 helices on the N-terminal half [41,47-49] and an acidic, glutamate-rich C-terminal region (Figure 1). Alternative SNCA splicing gives rise to 3 major isoforms (AS 140, 126, and 112) [51]. Human AS was originally described as the precursor protein for the non-amyloid component (NAPC) in Alzheimer disease (AD) amyloid plaques [52,53]. SNCA has 2 paralogous genes named SNCB (OMIM 602569) and SNCG (OMIM 602998), with which it shares a highly-conserved N-terminal domain [54], while BS lacks many amino acid residues in the NAC region [41]. GS, initially described as breast cancer associated protein 1 (BCSG1 [55]), is smaller than AS and BS protein due to a shorter C-terminal region, but contains much of the NAC region [41]. The most prominent feature of AS is the hydrophobic NAC domain, lacking in the other Syn proteins, which seems to be important for AS to form aggregates or fibrillary structures present in LB disease, MSA, etc [56]. Thus, apparently only human AS is pathogenetically associated with PD and related disorders [45]. While two studies suggested that AS occurs physiologically as a helically folded tetramer that resists aggregation [57,58], others showed that it predominantly exists as a disordered monomer [59]. Preformed fibrils generated from full-length and truncated recumbinant AS enter neurons, via endocytosis, and promote recruitment of soluble endogenous AS into insoluble deposits [60].

3. Structure, regulation and function of α-synuclein

3.1. Structure of α-synuclein

The structure of AS contains 3 main modular protein domains: (1) a highly conserved amino acid lipid binding α-helix (residues 1-60); (2) a non-amyloidogenic core (NAC) domain (residue 61-95), the central hydrophobic/amyloidogenic part of the molecule and the building block of AS aggregates [56,61], responsible for the conformational change from random coil to β-sheet (protofibril and fibril formation) [62], with critical residues for its aggregation or fibrillation (residues 66-74) [56]; (3) a variable carboxy terminal acidic tail (residues 95-140) that appears critical for the chaperone-like activity of AS [63] (Figure 1). The carboxy-terminus inhibits β-sheet and fibril formation [62,64]. AS contains several phosphorylation sites for protein kinases [54]. Over half of the molecule (amino acids 7-87) is composed of 7 motifs with a KTKEGV sequence, which are part of 11-residue repeats forming 5 amphipathic helices on the amino-terminal half responsible for its lipid affinity [14,54,63], although this has recently been debated [17]; helix 5 is responsible for protein-protein interactions [65]. While the hydrophobic NAC region remains dynamically disordered, the SL1 binding mode (residues 3-2) is prone to intermolecular interactions which progress toward oligomers and fibrils [66].

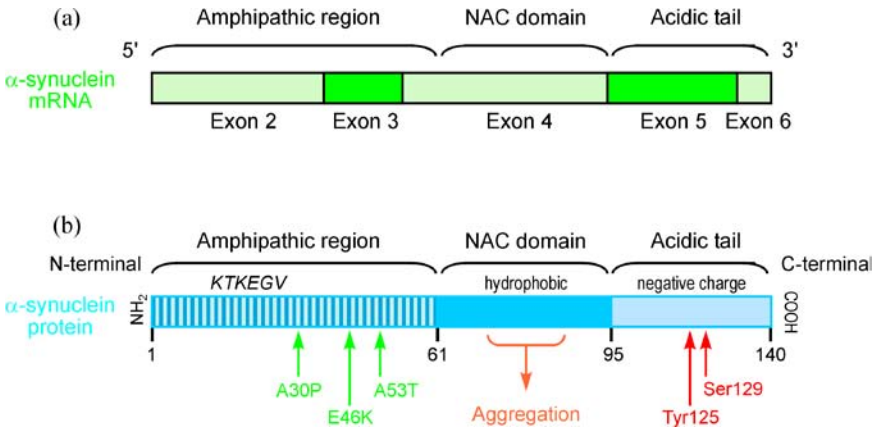

Figure 1. Schematic representation of human α-synuclein, depicting (a) SNCA mRNA and (b) protein domains (modified after [50]).

The predominant physiological species of AS are a helically folded tetramer or a disordered monomer with a low propensity to aggregate into fibrils [57-59,67]. It is potentially prone to misfold and has a strong tendency to self-aggregate *in vivo* [68], resulting in toxicity [69]. Wild-type (WT) AS is monomeric and intrinsically/natively unfolded at low concentration but adopts an α-helical conformation when bound to membranes [70,71]. AS is an intrinsically disordered protein but a very dynamic molecule that can adopt different conformational states depending on conditions and cofactors [72,73]. The helical membrane-bound AS forms a partially-folded stage that is the key intermediate in aggregation and fibrillation; it provides the seeds responsible for accelerated deposition of the less aggregation prone and disordered free cytosolic form [44,74,75]. Upon binding to membranes or synaptic vesicles it assumes an α-helical structure [49]. Folding and misfolding of AS occurs on membranes [76]. The misfolded isoform of the protein may lose the ability to bind membranes after the translation and accumulates as free AS in the cell.

Fibrils generated *in vivo* from AS show similar features characteristic of amyloid fibrils and include an antiparallel β-sheet structure [62,77]. Recent nuclear magnetic resonance (NMR) studies of full-length AS fibrils showed that the core extends with a repeated structural motif, thus disagreeing with their previously proposed fold [78]. The secondary structure of AS is determined by its environment and implies that the conformation of endogenous AS depends upon whether it is cytoplasmic or membran-bound [79]. Rapid exchange of AS between bound and unbound states provides mechanisms to ensure that stable cellular structures remain dynamic and susceptible to regulation.

3.2. Localization and regulation of α-synuclein

In normal brain, AS is predominantly expressed in CNS neurons, especially in the neocortex, hippocampus, striatum, thalamus, and cerebellum, where it is localized in the cytosol and at presynaptic terminals [3,80,81]. From there it is to be delivered to the neuronal perikarya by axonal transport. Recently, AS has been observed in neuronal mitochondria in different brain regions [82,83]. AS was also found in olfactory receptor neurons and the olfactory epithelium [84], and at low levels in skeletal muscle, cells of the neuromuscular junction [85,86], and oligodendrocytes [87]. It is localized outside of the nervous system in multiple organs suggesting that its function is not only exclusive to the brain and related diseases, but may also be associated with non-neurological disorders. BS is expressed in brain, spinal cord [88] and astrocytes [89], but heavily in cells of the peripheral nervous system [86] and in retina [54]. GS or persyn occurs in cell bodies and axons of sensory neurons, sympathetic neurons and in brain [90]. GS overexpression can induce a neurodegenerative phenotype in mice [91].

AS has been reported to be restricted to axon terminals [92-95], which led to the acceptance that it was a cytoplasmic, presynaptic protein [79]. However, it was also detected in the perikarya within several brainstem structures [56]. AS/Syn-1 expression occurs in human and rat brain somata, dendrites, and glia [96-98] that are susceptible to cellular AS aggregation (see [19,20]. Endogenous AS is normally distributed in both cytosolic and membrane-bound forms, contradicting the assertion that is is exclusively a cytoplasmic protein. Expression and aggregation of both soluble and lipid-associated forms were found in wild type (WT) and mutant transgenic (tg) mouse brain [99].

Levels of AS are regulated by a balance of synthesis, degradation, and secretion. The ubiquitin-proteasomal system (UPS) and the autophagy-lysosome pathway (ALP) are the two major control systems postmitotic neurons use to maintain intracellular proteostasis [100-102]. Proteasomal dysfunction results in the accumulation of SUMOylated AS; these post-translational modifications contribute to inclusion formation [103], while sumoylation of AS promotes protein solubilization and suggests that deficits in sumolysation may contribute to AS aggregation [104]. Cathepsin D expression level affects AS processing, aggregation and toxicity *in vivo* [105]. AS aggregates may be fragile and lack the cohesion characteristics of the insoluble cellular inclusions formed *in vivo*, while in other conditions, they are insoluble [79]. Membrane-bound α-helical AS does not contribute to aggregation/fibrillization [106], while soluble folding intermediates may be essential for its aggregation by a cascade comprising initially soluble oligomers, then insoluble oligomers, and finally fibrils present in inclusions [67,107-109].

Two pathogenic mechanisms have been suggested to induce, accelerate and/or aggrevate protein aggregation (Figure 2): (1.) β-sheet conformation by itself further promotes or accelerates aggregation of AS. (2.) Increased iron levels either directly or via iron-increased levels of oxidative stress (OS) catalyze the conversion of α-helical AS conformation into β-pleated conformation, which is found in LBs and GCIs [108,110-112]. On the other hand, metal-catalyzed oxidation of AS inhibits formation of filaments with increased formation of β-sheet rich oligomers or protofibrils [113]. Advanced glycation endproducts (AGEP) and iron interact with AS aggregation [114,115], which is further promoted by increased calcium [116]. Hsp90 modulates assembly of AS in an ATP-dependent manner by restricting conformational fluctuations [117].

The mechanism that causes post-translational changes of AS includes phosphorylation at residue serin (Ser)129 by kinases [118-121] (promoting fibril formation *in vitro* [122]), C-terminal truncation and ubiquitination [123], being a common feature in synucleinopathies [124]. In a mouse model overexpressing AS enhanced phosphatase activity reduced the phosphorylation and aggregation of AS [125], but the mechanisms for degradation of pAS are unclear. The ubiquitin (Ub)-independent proteasome pathway or a Ub-dependent pathway after dephosphorylation have both been implicated [126].

The association of AS with membranes affects bilayer structure, stability, and fibril formation [127]. Membrane-bound AS can aggregate spontaneously [128], but it does not require membranes to form protofibrils and fibrils [129], and α-helical conformation correlates inversely with fibril formation [106]. Membrane binding may, therefore, prevent AS self-association [130]. Regulation of AS by activity and the relationship between membrane binding and aggregation have been summarized recently [51,131,132].

Overexpression of wild type (WT) AS lacking the central hydrophobic non-amyloid component domain in *Drosophila melanogaster* abolishes the aggregation and mitigates its neurotoxic effects [133]. However, the observation of aggregated AS by and of itself does not prove that aggregation is important; all available date prove that deposition of AS occurs, not that it is causal [134].

The mechanism of AS degradation remains unclear. Some suggest that monomeric AS can be degraded by the Ub-proteasome pathway (UPP) [135,136], while others found that only a small portion of soluble-cell-derived intermediates as oligomers, not

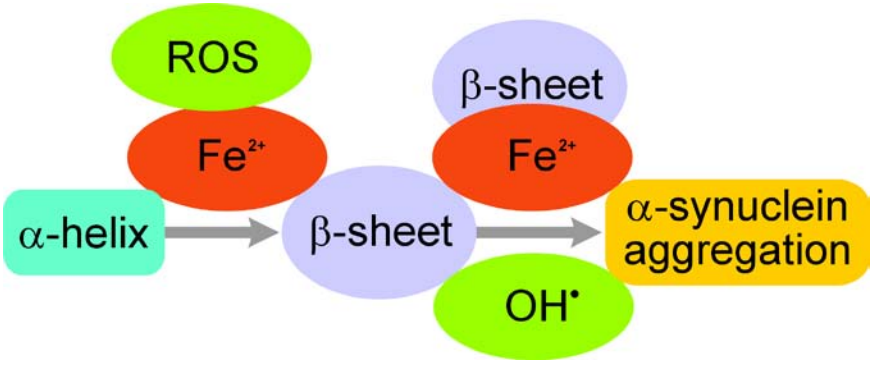

Figure 2. Pathogenic mechanisms to induce α-synuclein aggregation.

including monomeric AS, is targeted to the 26S proteasome for degradation [137]. By contrast, total AS concentrations increase after lysosomal inhibition [136,138-140]. There are distinct roles *in vivo* for the UPS and the ALP in the degradation of AS [141,142] and two separate lysosomal pathways – chaperone-mediated autophagy (CMA) and macroautophagy or the endosomal-lysosomal system - may be the initiating factors in AS degradation [136,143,144]. Dysregulation of the autophagy pathway has been observed in the brains of PD patients and in animal models of PD [145]. Macroautophagy itself is blocked by AS via Rab1a dysregulation [146]. WT AS but not mutant forms, is degraded by CMA [138,140,147], whereas all forms are degraded by macroautophagy [136,147].

3.3. General functions of a-synuclein

The physiological function of AS is incompletely understood. However, general consensus is that it is a multifunctional protein implied in many cellular processes that coordinates nuclear and synaptic events, neuronal plasticity [88,95,148-150], modulation of synaptic transmission, vesicle fusion and recycling, synaptic integrity, neuronal differentiation and regeneration [151]. It interacts with presynaptic membranes and regulates synaptic vesicle pools [95,152], while others found no effect of overexpressed AS on synaptic efficacy [153]. AS has functions on lipid metabolism, signal transduction, axonal transport of synaptic vesicles [73], microtubule and membrane and regulation of endoplasmic reticulum (ER) and Golgi vesicle trafficking [45,154].

Of note is that knock-out mouse models of AS have no overt phenotype, suggesting that AS is not required for neuronal development and/or that compensatory pathways exist [155]. However, absence of AS is associated with striatal dopamine (DA)-dependent dysfunction [88,149,156], reduction in the reserve pool of synaptic vesicles, and defective mobilization of DA and glutamate [157]. AS is involved in vesicle and membrane trafficing, presynaptic DA recruitment [158], and neurotransmitter release [88,159-163], and in Golgi apparatus influencing protein traffic [164], but appears not necessary for synaptic development [41]. AS associates with mitochondrial membranes [165], phospholipid membranes [47,80,106,166-170], and co-localizes with synaptophysin, which suggests regulation of synaptic vesicle formation [149]. A recent study of Syn triple knock-out (TKO) mice demonstrated the fundamental role of AS in the control of presynaptic terminal size and synaptic structure. Complete loss of synucleins causes alterations in DA handling by presynaptic terminals, decreased chaperone activity, and age-dependent neuronal dysfunction [171-173]. Soluble overexpression of AS in mice impaired neurotransmitter release via defective synaptic vesicle recycling, in the absence of overt toxicity [160], and overexpression of AS, due to loss of synapsin, is involved in vesicle mobilization. AS further has a physiological role in ligand-stimulating receptor endocytosis and vesicle recycling [79,174]. Increased levels of WT or mutant AS could impair protein clearance, which could lead to further accumulation of the protein, ultimately leading to protein misfolding, toxic oligomers, aggregate formation, and cell death [175].

Mounting evidence indicates a protective role of AS at the synapse, where it has a non-classical chaperone activity by the carboxy-terminal region, facilitating the assembly of the soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptor (SNARE) complex important for folding and re-folding of synaptic proteins [151,153,176-179]. AS interacts with cystein string protein α (CSPα), also known as heat shock protein (Hsp) 40, a presynaptic molecular chaperone, which contributes to maintaining the integrity of synaptic nerve terminals, vesicle integrity, vesicle recycling, and neurotransmitter release [180,181]. Tg expression of AS has been shown to abolish the lethal phenotype in mice created by deletion of CSPα, manifesting in widespread age-dependent neurodegeneration [151], providing support for a protective role of CSPα against AS toxicity, misfolding and aggregation. This might protect against synaptic degeneration [160] that may precede overt PD-related pathology. AS has antioxidant function, and is a negative regulator for DA synthesis [50,159,171,182,183] by affecting the activity of its key enzyme, tyrosin hydroxylase (TH) [184]. Many other functions have been attributed to AS, including inhibition of phospholipase D 2 and of autophagy, participation in OS production, ubiquitination, nitration, glycolysation, phosphorylation, etc [132,163,185-187]. AS redistributes neuromelanin lipid in the SN in PD [188], it associates with many proteins [41] and regulates the activity of several enzymes, e.g. mitogen-activating protein kinases (MAPKs [189]). The GATA transcription factor of SCA directly regulates its transcription in lock-step with the rate limiting enzymes of heme-iron metabolism [190], but its actual role remains elusive [191,192].

3.4. The role of α-synuclein mutations

The most direct and compelling evidence for a functional role of AS in the pathogenesis of synucleinopathies is the causal relationship between genetic mutations and disease, and gene expression profiling of SN DA neurons gave further insight into PD pathology [193-196]. Approximately 7% of all PD cases result from a monogenic cause [35,197,198]. In PD, mutations in AS or multiplication of the SNCA gene encoding AS, result in a phenotype of cellular inclusions, cell death, and brain dysfunctions, and familial (f) PD mutations influence AS assembly [199,200]. So far, 18 PARK loci have been described, and 10 genes have been linked to PD [35,196,198,201-206] (Figure 3): Autosomal-dominant (ad) parkinsonism is caused by the genes encoding AS or LRRK2 (leucine-rich repeat kinase 2, dardarin/PARK 8), clinically comparable to sporadic (s) PD [207-209], but with variable neuropathology [210,211], suggesting an upstream role of LRRK2 in protein aggregation [212]. Mutations in the LRRK2 gene, being the most common form of fPD in the world, cause impairment of protein degradation pathways, in particular autophagy, which can lead to accumulation of AS and unbiquitinated proteins, accumulation of oxidized proteins, inflammatory response, and increased apoptosis [213] (Figure 4). While the distribution of AS levels in the cytosolic or membrane fractions is similar between the G2019S (the most prevalent

LRRK2 mutation) and sPD cases, there are differences in the biochemical properties of aggregated AS in G2019S-linked PD [214]. Parkin enconding ubiquitin carboxy-terminal hydrolase L1 (UCHL1) that ubiquitinates proteins to regulate a variety of cellular processes, linked to chromosome 6q25.2-27, causes autosomal-recessive (ar) juvenile parkinsonism (arJP) [215], most cases showing no LBs [216]. Its mutations account for about 50% of EOPD cases [217] and are the second-most common known cause of PD [218]. They cause loss of E3 Ub ligase activity, resulting in impaired ubiquitination of substrate proteins [219], but how mutant parkin induces pathology in fPD is not exactly known. Late onset PD and healthy controls revealed similar frequencies of genetic variants [220]. Loss-of-function mutations in the nuclear-encoded mitochondrial gene PINK1 (phosphatase and tensin homologue/PTEN-induced kinase 1) (PARK8), are associated with LB pathology [221,222]. DJ-1 (PARK7) or ATP13A2 (PARK9), and PARK2, which encodes E ubiquitin in the UPS [223] disrupting this ligase activity and mitochondrial function [224-226], lead to arPD, but also to sPD [198]. The characteristics and molecular biology of PARK1-18 and of other genes associated with PD have recently been summarized [196,204].

DJ-1 was identified as a causative gene in arEOPD in a Dutch and an Italian family [227]. DJ-1 is a multifunctional redox-sensitive protein serving as a molecular chaperone [228], a transport regulator [229,230], and protecting cells against OS [231,232], thus leading to suppression of apoptosis [233]. DJ-1 downregulation enhances cell death by OS, ER stress, and proteasome inhibition [234], while the localization of DJ-1 to mitochondria is associated with protective actions against some mitochondrial poisons [235]. Exogenously applied DJ-1 was shown to localize to mitochondria, the cytosol, nucleus, and microsomes [227,231,232], while endogenous DJ-1, locating to presynaptic terminals of striatal axons and dendrites [236], revealed interaction with membranes of cultured cells [237]. Furthermore, DJ-1 partly colocalizes with the synaptic marker Rab3A at synaptic terminals, which suggests interaction with membrane trafficking [238]. These and other findings confirm an association between DJ-1 and synaptic vesicles, contributing to the pathogenesis of PARK7-linked PD (Figure 4).

Two of the PARK genes, Parkin and PINK 1, play a pivotal role in the removal of damaged mitochondrial organelles via mitophagy [239-241]. Parkin mediating different chains of ubiquitination [242,243] results in loss of ubiquitination causing accumulation of misfolded proteins [244], and plays a role in maintaining mitochondrial homeostasis [245]. It improves mitochondrial dysfunction, alters

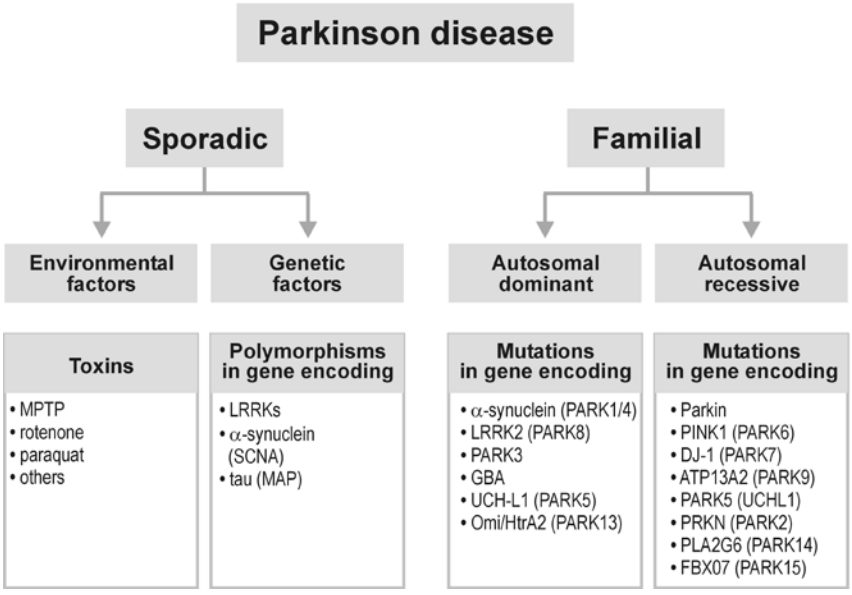

Figure 3. Etiology of PD. Sporadic PD is a complex multifactorial disorder with variable contribution of environmental factors and genetic susceptibility. Mutations of various genes are associated with autosomal-dominant or autosomal-recessive parkinsonism. PARK 16-18: inheritance unknown.

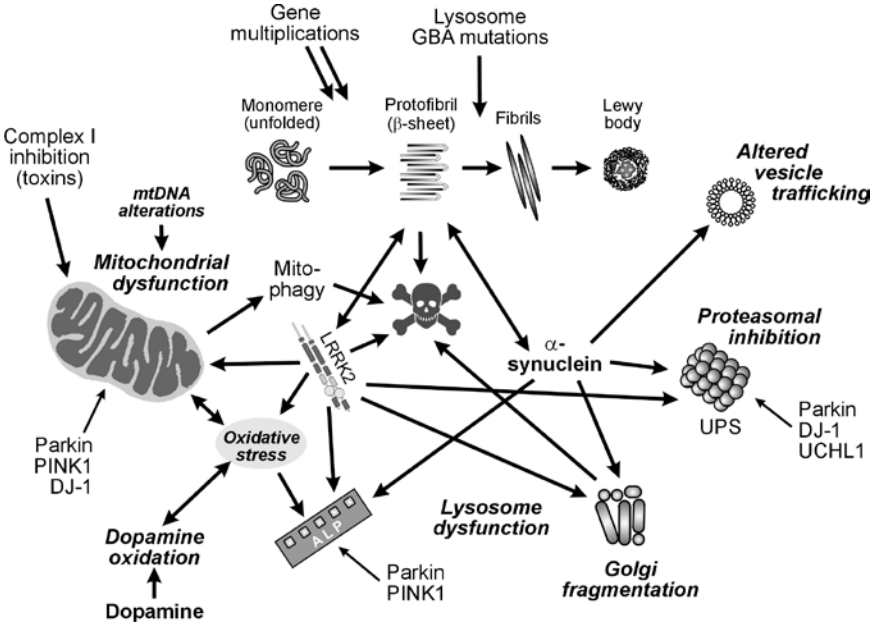

Figure 4. Common pathways underlying PD pathogenesis. Schematic impairment by α-synuclein and gene mutations enhancing α-synuclein misfolding, fibril formation an Golgi fractionation; impairing proteasome and mitochondrial functions, altering vesicle traffic and translation (modified after [31,193,196]).

the intrinsic threshold for cytochrome c release, regulates their remodelling, promotes their autophagy and DNA repair [224,240,246-248]. PINK1, that resides at the OMM [186,249] and is also present in the cytosol [250], modulates mitochondrial morphogenesis, distribution, and dynamics and attenuates ROS production in SN DAergic cells [251-254] (Figure 4). However, the mechanism by which PINK1 or parkin confers neuroprotection is not clear [255]. Both causes of arPD induce mitophagy or defective oxidative phosphorylation [256,257], and GTPase dynamic-related protein (Drp1) is one of the targets of Parkin [258], while PINK1 is involved in mitochondrial trafficking by forming a multiprotein complex with the GTPase Miro and the adaptive protein milton [259]. Parkin, as an Ub ligase, picks up the Miro protein from the mitochondrial membrane that is going to be degraded by the proteasome, which explains the arrested mitochondrial mobility observed in PINK1 cells, and could avoid fusion with other mitochondria or release of reactive oxygen species. Thus, these two PD-related mutations are associated with alterations of mitochondrial mobility [260]. A functional interplay of PINK1 and parkin suggests that both act in a common pathway with parkin acting downstream of and modulated by PINK1 [260-263], causing similar mitochondrial defects with decrease in ATP production and bioenergetic deficiency [256,264-268]. Depletion of PINK1 affects mitochondrial metabolism, calcium homeostasis and energy metabolism [269]. The fascinating interplay of Parkin, PINK1, Drp1 and mitochondrial dysfunction has been discussed recently [34,270].

LRRK2, which has kinase activity, and AS have a synergistic activity on cytoskeletal elements – phosphorylation by LRRK2 or β-tubulin [271], binding of AS to β-tubulin, and its co-localisation with microtubules – suggesting a common microtubule-polymerizing action [45,272]. Although regulation of mitochondrial function by the PINK1/parkin pathway [273] and the role of LRRK2 mutations associated with PD in mitochondrial dysfunction are not definitely understood, association of a small fraction of LRRK2 with mitochondria suggests its role in mediating mitochondrial functions [226,274] and LRRK2 protein expression correlates highly with its mRNA expression [275]. These findings suggest that LRRK2-induced neurodegeneration in PD brain may, at least in part, be mediated by enhanced tubulin phosphorylation, in the presence of microtubule-associated proteins [271]. Furthermore, LRRK2 interacts with several presynaptic proteins [276], and its depletion affects the mobility and transportation of vesicles, vesicle dynamics in the synaptic bouton, and their redistribution in pre-synaptic pools. PD-linked LRRK2 is expressed in circulating and tissue immune cells, which may also be relevant to the susceptibility of developing PD or its progression [201]. Widespread expression of LRRK2 in human brain, particularly in brainstem, suggests its association with early-stage AS pathology in PD [277]. The exact biological function of LRRK2 remains largely unclear and how its mutations lead to neurodegeneration is not known, but protein modifications from altered phosphorylation could lead to misfolding and aggregation of the target protein [278]. Therefore, increasing evidence indicates that protein products of genes mutated in PD have a role in regulating protein stability, such as AS (proteasome) Parkin (F3 ligase), DJ1 (redox sensor) and PINK1 (protein stabilizing), implicating protein quality control and the UPR as key functions in fPD and sPD [27,279]. Several responsible genes for fPD have been found to interact with various cellular systems for homeostasis, such as mitochondrial maintenance (PINK1, DJ-1), synaptic homeostasis (AS), ALP (AS, parkin, PINK1), axonal transport (LRRK2), and UPS (AS, parkin, DJ-1, UCHL1). Suppression of UCHL1 activity has recently been shown to have differential effects on AS in neurons [279a].

Three single point mutations in AS were found to be associated with EOPD: Ala53Thr (A53T), identified in a large Italian family (Contursi) [280] and in Greek kindreds [281-284], showing both AS and tau pathology [285], The A53T mutation was also found in diffuse DLB (DDLB) [286,287], while the relevance of DJ-1 mutation for DLB is not known. Ala30Pro (A30P), in a German kindred [288], shows similarities to PD but more severe pathology [289], and E46K or Glu46Lys reported in a Spanish family with autosomal-dominant parkinsonism, dementia, and visual hallucinations with widespread LB pathology, referred to as DLB [290]. These mutations have different effects on the amyloidogenicity and vesicle-binding activity of AS. Both A53T and E46K mutations cause increased phospholipid binding, increased aggregation from the partially folded intermediate and not the monomeric state [109]. They further cause assembly into filaments [291], or pore-like activity of AS [292], whereas mutant (A53T) AS results in greater neuronal permeability, providing a molecular explanation for the process of AS oligomerization in the membrane, and supports the role of formation of pore-like structures in the pathogenesis of neurodegeneration in PD [293]. A53T and E46K mutations, located in rigid β-strands of the WT fibrils, are associated with structural perturbations of AS [78]. A53T and A30P mutants share similar membrane interactions, but show different lipid binding involved in disruption of membrane sequence maintenance [294] and increased propensity to self-aggregate to form oligomeric species and LB-like fibrils *in vitro* compared with WT AS [77]. The effect of these mutations on the fragmentation, conformation, and association of AS in the presence of the 20S proteasome suggest that 20S mediated truncation of AS may play a role in both familial (f) and sporadic (s) PD [295]. Tg A53T mice develop a movement disorder with AS inclusions and loss of DAergic terminals, due to mitochondrial (mt) DNA damage [296] and mitochondrial autophagy [297], whereas double tg mice, also expressing BS, presented a milder phenoype [298]. The subcellular distribution of AS mutations, A30P and A53T, is influenced by its phosphorylation at Ser-129 [299], and acclerates neurodegeneration in a rat model of PD [300]. PARK4, another dominantly inherited form of fPD, is caused by duplication or triplication of parkin in the UPS [223], resulting in the production of large amounts of WT AS.

Intriguingly, duplication and triplication of the locus as well als point mutations cause fEOPD with severe dementia (see [31]). Short chromosomal duplications or trisomies containing the SNCA gene, plus short flanking regions on chromosome 4, were discovered in patients with PD or DLB [44,301,302], indicating that 50% of the expression of AS is sufficient to cause disease. Therefore, subtle

alterations in expression levels are sufficient to cause a wide spectrum of disease, and as AS dosage increases, the likelihood of more widespread pathology augments. Increased accumulation of AS is also seen in LRRK2 and glucocerebrosidase (GBA) mutations, the two most common genetic causes of both fPD and sPD [303-306], whereas knockout of LRRK2 was protective [307]. Genome wide association studies (GWAS) have shown that SNCA is also linked to sPD [308-310], and indicate a possible link to MSA [4], but suggest population-specific heterogeneity of these diseases [309]. A meta-analysis revealed 10 gene sets with previously unknown association with PD that pinpoint defects in mitochondrial electron transport, glucose utilization and sensing, that occur early in disease pathogenesis, while genes controlling bioenergetics are underexpressed [311]. A GWAS study identified candidate gene regions for PD in an Ashkenazi Jewish population that are implicated in neuronal signalling and the DA pathway [312]. A recent meta-analysis of the PD GWAS consortium identified a novel PD susceptibility locus, RIT2, replicated several previously identified loci, and identified more than one risk allele within SNCA and GBA [313].

The single-prolin AS mutant A56P and the triple-prolin mutant A30P/A56P/A76P (TP) showed reduced propensity to form proteinase K (PK)-resistant aggregates, confirming the characterization of the mutants as prefibrillar AS variants [314]. However, only the AS species with increased aggregating propensities, human WT and A30P, triggered degeneration of nigral DAergic neurons, suggesting that fibril formation of AS promotes the progressive neuronal degeneration [314]. Expansion of Rep1, a polymorphic mixed-dinucleotide repeat in the SNAC promoter region that increases expression in both animal models [315] and humans [316], is associated with elevated risk of sPD [317,318], while short Rep1 genotype is associated with reduced PD risk [319-324], but the effect of SNCA variants on the predisposition of PD is independent of Rep1 [325]. Variants of all 3 members of the Syn family, particularly SA and SG, affect the risk of developing DLBD [326], and detection of a gene for familial DLB in 2q35.q36 emphasized its genetic heterogeneity [327,328].

Genetic research into MSA has so far been lagging behind that of related neurodegenerative diseases, such as PD, but recent studies suggest that genetic factors have a role in this disease [329]. To date the majority of genetic studies in MSA have screened candidate genes for coding mutations, including SNCA, MAPT, and other PD genes, but more recently, some association studies screening for common genetic variants in MSA have been reported, and a GWAS is currently in progress (see [330].

4. α-Synuclein and neurodegeneration

The current theory of the origin of PD places it in a large category of neurodegenerative disorders caused by protein misfolding, summarized as "protein misfolding diseases" or "proteinopathies" [10,39,331]. Proteins implicated in neurodegeneration can be neither refolded by chaperones to their normal configuration nor degraded by proteasomes, leading to their abnormal turnover, elevated concentration, aggregation, and accumulation of insoluble protein deposits [141,142]. Protein folding and refolding are both mediated by a network of molecules, called chaperones and co-chaperones that are also associated with the UPS and ALP pathways that remove irreversibly misfolded proteins [101,102]. The degradation of proteins and other cellular components by the ALP and UPS plays a vital role in maintaining the structural and functional integrity of neurons, while inhibition of the ALP leads to aberrant autophagy and ultimately cell death [101,332]. Molecular chaperones have a central role in maintaining protein homeostasis in order to prevent or modulate neurodegeneration, and by diminishing AS neurotoxicity play a neuroprotective role [333]. Inhibition of CMA leads to increased aggregation of high-molecular-weight and detergent-insoluble AS species in neuronal cells [140], while enhanced CMA-dependent degradation of AS occurs under conditons of stress induced by an excess of AS [334]. Expression of substances regulating CMA, might be reduced in PD brains [147], supporting the notion that dysfunctional CMA, together with functional impairment of the proteasome [335,336], is implicated in PD pathogenesis.

A factor that could drive the aggregation and neurotoxic effect of AS is the total concentration of the protein as suggested by human genetic multiplication studies [32]. High concentrations of normal AS may cause cytotoxity, which suggests a shift in equilibrium between normal and misfolded conformations and increased rate of oligomerization of the misfolded protein. Extracellular AS can be detected in human and mouse brain [337]. Whether total AS concentrations are increased in PD brains is unclear and contradictory data have been reported. Although membrane-associated AS is increased in the SN [338], normal levels in the cytosolic fraction and no correlations between AS and nigral LB intensity have been found [339]. No widespread extranigral AS accumulation in PD, as suggested by most immunohistochemical reports [340-342], has been confirmed by sophisticated neurochemical methods demonstrating only mildly increased high-molecular-weight AS in putamen [339,343]. This suggests that AS pathology revealed by immunohistochemistry might not be caused by AS accumulation but rather by conformational changes. Different mono- and polyclonal antibodies that bind specifically to AS have been described [344-353]. Recently, a monoclonal anti-AS antibody (5GA) was described that distinguishes pathological from non-diseased AS, probably due to a better accessibility during the conformational changes of the protein [354].

Expression of pAS in the brain is very low under normal conditions and is undetectable by immunohistochemical methods, but is increased in PD, DLB and AD with LB pathology [355]. It is the most prominent species of AS isolated from postmortem brains with LB disease [118]. PD shows a significant increase in soluble and lipid-associated pAS over the disease course, with progressive decrease of soluble nonphosphorylated AS, becoming increasingly phosphorylated [22]. These findings are in contrast to the robust increase of AS levels in vulnerable regions in MSA, where the protein accumulates predominantly within glial cells [356]. Increases in pAS have been suggested to promote neurotoxicity, oligomer

formation, formation of LB pathology, and reduce the ability to regulate TH [273,357-361]. Studies about concentrations of SNCA messenger (m)RNA in PD brains have been inconclusive, but increased expression of AS mRNA [315,316,362] suggests that it is a triggering factor for PD pathogenesis. Collectively, genetic and pathological observations indicate that PD can be associated with factors that could account for an increased production or impaired clearance of misfolded proteins; a vicious circle could develop whereby an increase in unwanted proteins could overwhelm and impair the UPS/lysosomal clearance systems, which could lead to further protein accumulation, and to proteolytic stress, with formation of toxic oligomers, interference with critical cell processes, and cell death [27] (Figure 4).

The compelling reports on the pathophysiology of AS *in vivo* raised several speculations as to how aberrant activity of this protein might lead to neurodegeneration in PD and other synucleinopathies. A key question, in light of the suggested function for LB formation, namely to provide a cellular protective response against misfolded or abnormal proteins, is whether an aberrant chaperone activity of AS could interfere with synaptic integrity. Moreover, it is not certain that the AS aggregation is the primary cause or an epiphenomenon in the pathogenic process of AS-related diseases.

Proteomic studies of cellular and animal models have not only confirmed that mitochondrial dysfunctions, abnormal protein aggregation, OS, and impaired bioenergetics are the main contributors to PD [8,34,363-371]. However, better characterization of the features that make selective neuronal populations vulnerable in PD [364,371-373], the role of inflammation, and other factors in neurodegeneration [374-376], are clearly needed.

4.1. Neurotoxicity of α-synclein and the oligomer hypothesis

The relation of AS behavior to toxicity is complicated by several conditions: the expression levels of AS are critical for toxicity, and phosphomimic S129D/E AS variants may have different biophysical properties compared to the phosphorylated WT protein [377]. These facts raise some caveats about comparison of properties of AS and its concentration-dependent behaviors, e.g. aggregation and toxicity [134].

Mutant AS protein tends to acquire abnormal configuration easier than its WT counterpart. AS, especially in PD-associated mutants, forms pore-like annular and tubular protofibrils [378], while BS inhibits formation of AS protofibrils [379]. The tendency of A30P to accumulate as oligomers instead of mature fibrils suggested that AS may have a similar toxic mechanism as intermediates of other proteins, such as β-amyloid (Aβ), tau protein, prions and polyglutamine peptides [380-386] (Figure 5). The "toxic oligomer hypothesis" [387-389] gained support by a study in model systems of PD with increased neurotoxicity by over-expression of AS variants that exhibited increased propensity to form oligomeric, prefibrillar structures and decreased propensities to form fibrillar aggregates [390].

While the normal physiological role of AS appears to be dependent on its interaction with membrane lipids, the pathogenic AS mutants are particularly prone to formation of such oligomers and AS mutations cause increased levels of protofibrils possibly being the more toxic form of the protein [77]. A toxic conformation of AS as the consequence of abnormal membrane interaction, alteration in vesicle traffic, involvement of mitochondria, or lysosomal membranes could promote neurodegeneration [391]. This may be a result of the toxic action of substances produced during early phases, i.e. soluble oligomers and protofibrillar derivatives of misfolded proteins [392-394]. Accumulation of misfolded AS in the ER is the main event leading to the induction of the ER stress-related unfolded protein response (UPR) that is activated in nigral DAergic neurons in PD and in experimental models of PD [395,396], induced by oligomeric species of AS, and is important for the manifestations of α-synucleinopathies *in vivo* [397]. In PD, the cause is a high level of misfolded AS molecules, which subsequently leads to formation of neurotoxic intermediates, i.e. oligomers and probably small soluble complexes of AS with other proteins [398] (Figure 6). Involvement of ER stress with activation of the UPR has also been observed in early stages of MSA, thus playing a pivotal role in the pathology of this synucleinopathy [399]. Which particular species of AS are toxic has been debated. Some evidence favored fully fibrillar or the intermediate soluble oligomeric species [77,400], but cytotoxicity can occur without aggregated AS [401]. Recent studies indicate that early oligomeric forms and not the final

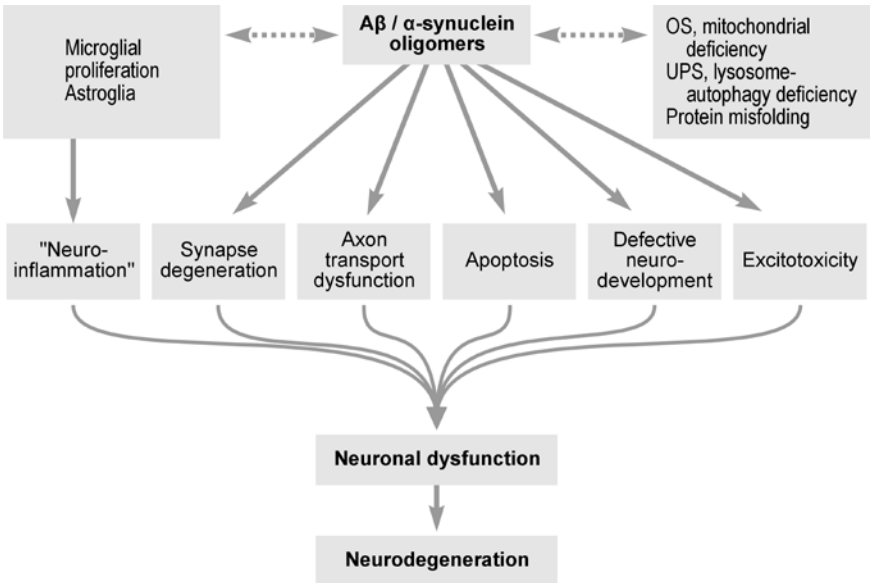

Figure 5. Cascade of neurotoxic effects of protein oligomeres leading to neuronal dysfunction/neurodegeneration; illustrated by the suggested relationship between Aβ and α-synuclein oligomers.

protein aggregates are responsible for its toxicity [387,402]. WT BS has been suggested to protect against AS toxicity based on *in vitro* (inhibition and fibril formation) [110] and *in vivo* (reduced aggregation and LB formation) evidence [403]. Small intermediates/soluble oligomers in the aggregation process might lead to synaptic dysfunction, and neuronal death, whereas large, insoluble deposits might function as reservoir of the bioactive oligomers [404]. The polymerization of AS from unstructured monomer to mature amyloid fibrils rich in β-sheets is a multistep process that proceeds through the formation of altered-sized oligomers and polymeres [67]. Pre-fibrillar AS variants with impaired β-structure increase neurotoxicity in PD models [390]. In PD brain, tissue transglutaminase (tTG) induced crosslinks have been identified in AS monomers, oligomers, and aggregates, suggesting an interaction between AS and tTG [405], while Hsp 70 modulates extracellular AS oligomers and rescues trans-synaptic toxicity [406]. Ferric iron may catalyse the formation of AS oligomers [407-409], and exposure of AS to oxidative agents also induces formation of high-order oligomers [410]. Missense mutations of SNCA, e.g. A30P, increase oligomerization of AS, but not fibril formation [77,411].

Spheroidal oligomers contain a significant amount of α-helical structure, which decreases in protofilaments, while β-sheet structure content of AS increases from spheroid oligomers, through protofibrils, to fibrils [412]. Methods to detect morphologically distinct oligomeric forms of AS have been described [413]. Elevated levels of soluble AS oligomers were found in post-mortem extracts of PD [414] and DLB brains [415,416]. Loss of DAergic nigral cells in animals with AS variants that form oligomers (E57K, E35K) showed that these are toxic *in vivo* and might disrupt membranes [417]. DA and its metabolites inhibit the conversion of protofibrils to fibrils and may promote protofibril accumulation [418]. Intervention in the early part of the aggregation pathway by prevention of oligomer formation or increased clearance may be neuroprotective [419,420].

Oligomeric species can be isolated from cells [139,421,422], from human [423] and mouse brain [424], particulary found in membrane-enriched fractions [128,414]. While small-sized oligomers are not resistent to K protease (KP) digestion [425], the generation of both soluble oligomers and aggregates consisting at least partly of fibrillar AS resistent to PK digestion [381,426] is required for the induction of degeneration of nigral neurons. Fibrillar and profibrillar AS variants also cause divergent axonal lesions, exemplifying that they induce neurotoxicity by various means [314].

The pathogenic AS mutants, DA AS modifications, and the association of AS with polyunsaturated lipids favor the formation of protofibrils by inhibiting the manufacture of larger, less reactive aggregates [72,414], which may produce the LBs [427]. If DA synaptic vesicles in SN neurons are damaged by pathological interaction with AS, a vicious circle of dysregulated cytosolic DA and further damage to targeting DA neurons could ensue [162]. The UPS renders mutated or damaged proteins less toxic than their soluble forms [428], which suggests that the ubiquitinated proteins in LBs may be a manifestation of a cytoprotective response designed to eliminated damaged cellular components and to delay the onset of neuronal degeneration [10,429-432].

Although direct *in vivo* data supporting the "toxic oligomeric AS hypothesis" are still limited and most of the evidence is circumstantial, studies in cultured cells support this notion [112,189,401,433-438], but others demonstrated a lack of association between intracellular oligomers and toxicity [439-444]. Nevertheless, several different mechanisms, including proteasomal inhibition, effects on signal transduction pathways, mitochondrial alterations, increased levels of free radicals, membrane clustering of DA transporter resulting in increased DA uptake, and others, have been reported as mechanisms associated with excess of WT or mutant AS [189,436,445-450] (Figure 4). The reasons for the discrepancies about the toxic effects of AS are not clear, but may be influenced by a variety of factors [69,450].

4.2. Mitochondrial involvement in PD

Mitochondrial alterations are an important part of the multifactorial pathogenic process of PD [34,255,365,451-462]. Beyond ATP generation, mitochondria are involved in a number of critical pathways, including regulation of the electron transport chain, calcium homeostasis [463-466], mitochondrial morphology, dynamics, microtubule-dependent cellular traffic, ALP [467], programmed cell death [468], or apoptosis [469]. Mitochondrial dysfunction triggers increased free tubulin, which destabilizes the microtubule network and promotes AS oligomerization [424]. Misfolded AS accumulates within both the inner (IMM) [338] and the outer mitochondrial membrane (OMM), and can induce dysfunction and fragmentation of mitochondria [470], causing energy depletion [471,472], which is relevant given the importance of mitochondria in maintaining neuronal viability [473,474]. Overexpression of AS impairs mitochondrial complex I function, decreasing respiration and increasing free radical production [82,338,472,475,476] or complex IV activity [296]. Complex-I is inhibited in DA-neurons by systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [477], probably linked to mtDNA defects [478]. but its activity is not impaired in other neurodegenerative diseases [479]. AS apparently can interact with complex-I, resulting in its reduced mitochondrial activity, increased free radical production, and mitophagy [475]. Impaired complex-I mitochondrial biogenesis has been found in PD frontal cortex [480]. AS may bind to mitochondrial membranes leading to mitochondrial fragmentation followed by loss of mitochondrial transmembrane potential and neuronal death [225,472]. This, however, would not account for the direct effects of AS on complex-I [338]. Mitochondrial metabolic control of microtubules dynamic impairs the autophagic pathway in PD [481].

Structural changes of mitochondria occurring with even low overexpression of AS or other misfolded proteins, and in the virtual absence of structural defects in other intracellular organelles, indicate that mitochondrial dysfunction, and direct effects on the OMM are caused by the exposure to these toxic factors [470,472]. A specific interaction of AS and COX, the key enzyme of the mitochondrial respiratory chain, suggests that AS aggregation

contributes to mitochondrial dysfunction [296,365]. Which AS species cause these effects are not clear. Its inhibitory effect on membrane fusion may represent an intrinsic property of the monomeric protein. By contrast, an *in vitro* assay suggests that small oligomers are the cause [472]. A change in synaptic physiology, brought on by AS and other pathologic proteins, evokes homeostatic shifts in the ratio of mobile to stationary mitochondria, coordination of this relation being critical to ensure optimal neuronal function [482].

The effects of AS on mitochondria could be related to those on other intracellular constituents such as interactions with (pre) synaptic vesicles, the lysosomal membrane or the ER-Golgi apparatus [1]. They further may lead to release of oxidative species , which may in turn lead to secondary induction of AS, oligomerization, and aggregation and, therefore, create a vicious cycle [483].

Reduction of cerebral mitochondrial metabolism was seen in early PD, but whether mitochondrial dysfunction is a primary or secondary event, or part of a multifactorial process remains to be elucidated [452]. Much evidence suggests involvement of AS and mitochondrial dysfunction, in particular oxidative damage to both nuclear (n) DNA and mitochondrial (mt) DNA, protein misfolding, abnormal autophagy, and respiratory chain deficits in the pathogenesis of PD [226,254,484] (Figure 6), but to what extent dysregulated mitochondria dysfunction and turnover contribute to the pathogenesis of sPD remains to be elucidated [485]. A close relationship between mitochondrial function and autophagy/mitophagy which is crucial for degradation of surplus or injured mitochondria is beneficial to orchestrate numerous metabolic pathways in the cell. Defects in one of these elements could simultaneously impair the other, resulting in risk increments for various human diseases [486].

4.3. Lysosomal dysfunction and autophagy; role of glucocerebrosidase

Overexpression of AS impairs macroautophagy, a main route for clearance of aggregate-prone intracytoplasmic proteins, whereas AS depletion enhances this pathway [146]. Increases in macroautophagy lead to decreases in AS load and improvements of neuronal function [136,487], while its inhibition protects against toxic effects of AS. This indicates that macroautophagy can be harmful rather than protective [488,489]. Aberrant AS can bind to the membranes of lysosomes, inhibiting CMA [138,187,490], lysosomal function [445,446], and the proteasome [137,335,336,436,445-447,491]. Degradation of AS becomes diminished, and further lysosomal damage occurs, but whether accumulation of AS precedes the impairment of autophagic pathways or *vice versa* is unclear [1]. For a critical evaluation of the role of ALP and UPS in PD see [147,428,492,493].

Mutations of the GBA (glucocerebrosidase) located on chromosome 1q21 [494] (which encodes cerebrosidases) suggest a link between PD and other synucleinopathies, including DLB with Gaucher disease [306,495-501] through a toxic loss of functions and overexpression of such mutants promoting AS accumulation, whereas inhibition of glucocerebrosides had no effect on AS levels [502]. There are also genetic and pathological links between PD and the lysosomal disorder Sanfilippo syndrome [503]. GBA mutations – more than 28 of which are presently recognized [504] - are the most frequent genetic risk factor for PD [505,506], particularly in fPD [507], and glucocerebrosidase is present in AS inclusions in LB disorders [494]. Downregulation of its activity led to decreased lysosomal protein degradation, subsequent AS accumulation and dependent neurotoxic effects in human neurons and models, while accumulation of glucosylceramide in Gaucher disease owing to GBA dysfunction stabilized oligomeric intermediates of AS, further increasing its pathogenic effects. GBA alterations might secondarily overwhelm the ability of UPS to remove accumulated AS, promoting aggregation and neurotoxicity [508]. Overexpression of AS inhibits the intracellular trafficing and normal lysosomal activity of WT GBA, which leads to decline in its activity, forming a pathogenic positive feedback loop [497]. Recent genetic studies suggest that mutations in the GBA gene not only increase the risk of both PD and DLB but also influence the course of PD with respect to the appearance of dementia [509]. Whether mutant GBA leads to an increased risk of PD and DLB through gain or loss of functions, or both, is not clear, but recent demonstration of the relevanve of lysosomal proteolytic dysfunction in PD [140,492,497,501] could provide insight into the link between altered macroautophagy, GBA, and synucleinopathies.

4.4. Oxidation and nitrative injuries

In PD, many biochemical changes indicating compromised antioxidant systems are suggested to underlie cellular vulnerability to progressive OS, which generates excessive reactive oxygen species (ROS) or free radicals in SN with subsequent cell damage [510-512]. Overexpression of human WT or mutant AS elevates the aggregation of intracellular ROS [513,514], and increases cytotoxicity of DA oxidative products [435]. Truncation of AS and OS have been linked to increased AS aggregation [401,515-518] that can enhance sensitivity to oxidative and nitrative stressors, although it can also be protective in some situations [519,520]. Nitration of AS, signifying the presence of reactive nitrogene species, is a major signature of PD and other synucleinopathies [521].

Increase of iron in the SN with a shift of Fe (II): Fe(III) of 2:1 compared to 1:2 in controls can promote DA synthesis with accompanying increased generation of reactive metabolites [522-524]. AS increases cellular ferrireductase activity and iron/Fe(II) levels in DAergic cells leading to their selective loss in PD [525]. This suggests that iron and AS act in concert for disease propagation. Protein misfolding in sPD has been associated with ROS formed as products of O_2 reduction by combination of DA and Fe [526]. Both glutathione and glutathione peroxidase activity are decreased in SN and incidental LB disease (iLBD/preclinical PD), preceding both complex I and DA loss [527]. Peroxynitrite, formed by reduced superoxide dismutase (SOD), induces aggregation of AS *in situ*, and nitrated AS is found in the core of LBs [512]. Cross-linking of AS by AGEs may reflect early disease-specific changes, accelerating inclusion body formation [528]. Formation of AS protofibrils is stimulated by translational

modifications that occur under conditions of OS, while its aggreation is inhibited by antióxidants and proteins with chaperone activity [529]. These findings in human PD and models indicate a multicomponent process in its pathogenesis, and cell death pathways are caused by many interacting factors [530,531] (see Figures 4 and 6).

4.5. α-Synuclein and neuroinflammation

AS can trigger inflammation and activation of microglia [532,533], which, by releasing toxic factors or by phagocytosing cells, and degrading AS more avidly than neurons or astrocytes [534], may form a selfperpetuating cycle for neurodegeneration [535-537]. Overexpression of mutant AS modulates microglia cells releasing pro-inflammatory cytokines, nitric oxide, complements, elevated levels of arachidonic acid metabolizing enzymes, reactive species. and OS, excessive levels of ROS triggering more inflammation [538,539]. This supports the notion that WT and A30T AS have an important role in the initiation and maintenance of inflammation in PD, through activation of a pro-inflammatory response in microglia [540,541]; this differs depending on the type of AS (WT/A53T) and/or whether AS expression results in cell death or not. Upregulation of inflammatory mediators and microglia-mediated neuroinflammation has been hypothesized to play an important role in the pathogenesis of PD [374,542-544]. This inflammatory response may occur after neuronal death, but it is also possible that AS is released via exocytosis [534] or even that cleaved portions are presented via antigene presentation, which could lead to a vicious cycle of inflammatory response, release of (modified) AS, and further inflammation.

In PD, SN cell degeneration is associated with astroglial reaction and HMC class II positive microglia that may be both inducing factors or sequelae of neuronal death [545-547], while oligodendroglia does not seem to play a role in promoting inflammation, although they may be damaged by it [533]. Although a specific receptor for AS binding to microglia is still unknown, these cells can take up extracellular AS [540,548,549], which in turn triggers the release of immune modulatory mediators.

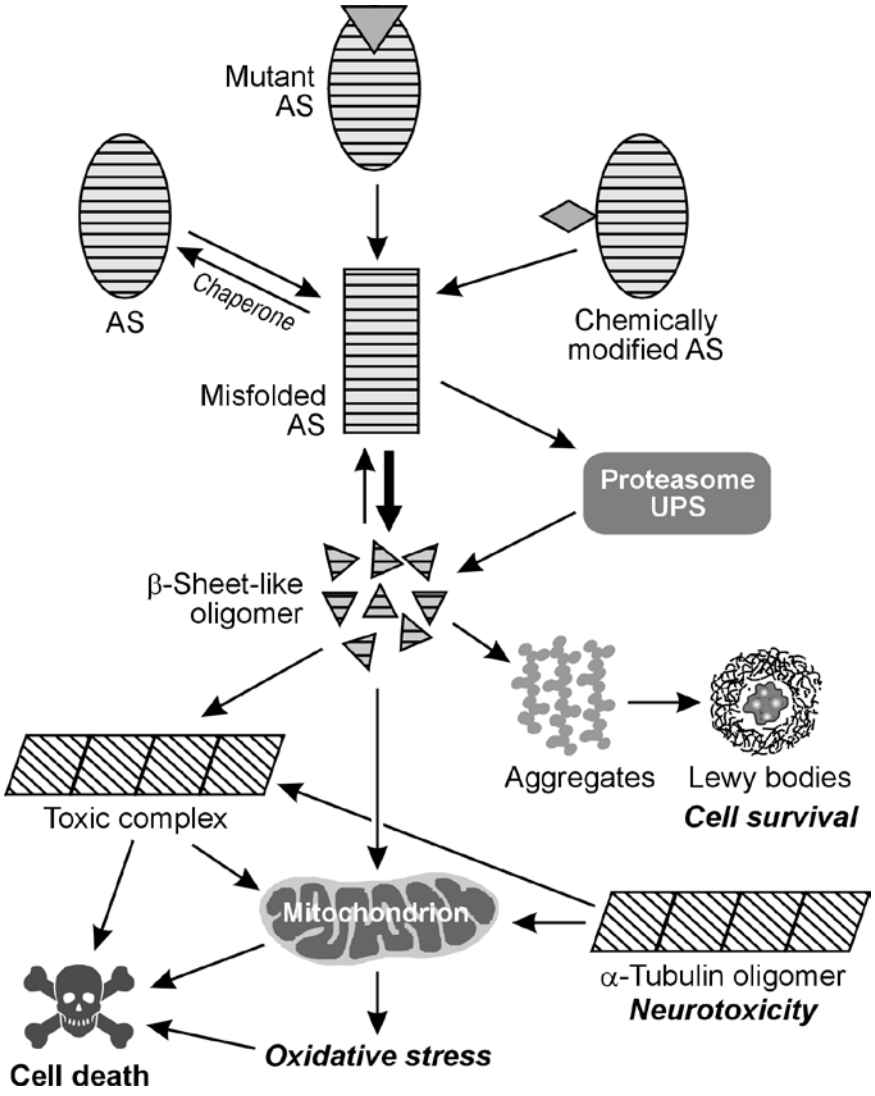

Figure 6. Role of α-synuclein (AS) in neurodegeneration in PD. Neurotoxic oligomers of α-synuclein are the key factors of neurodegeneration. One potential mechanism leading to neuronal death is invasion of α-tubulin oligomers which affects the dynamics of microtubules (modified after [398]).

Parkin deficiency increases vulnerability to inflammation-related nigral degeneration [550], while human neuromelanin induces inflammation and degeneration in the rat SN [551]. Microglial activation and corresponding DAergic terminal loss in early PD support the notion that neuroinflammatory responses by intrinsic microglia contribute to the progressive degeneration in PD [552]. Part of the specific vulnerability of the SN could be a consequence of h-TNFα hypomethylation [553], overexpression of which induces apoptosis. On the other hand, microglia may be affected by the disease process and may therefore not be able of exerting neuroprotective function, such as glutathion peroxidase expression [554]. A critical review about how neuroinflammation may contribute the prion-like behavior of AS and progression of neurodegeneration in PD was given recently [555].

5. α-Synuclein and protein interactions

Despite clinical, genetic, and neuropathological differences, there is considerable overlap

between synucleinopathies and other protein-misfolding diseases. Inclusions characteristic of these disorders suggest interactions of pathological proteins engaging common downstream pathways [8,10,13,368-370,432,556]. The co-occurrence of both AS and tau or other proteins in various neurodegenerative disorders [557-559] highlights the interface between these misfolded proteins, which may be co-aggregated in the same brain or even in the same region or in the same cell in human brain [560-562] and tg mice [563]. Interaction with tubulin suggests that AS could be a microtubule-associated protein similar to tau [272,564]. Recent studies revealed physiological correlations between tau and AS and a stimulatory effect of accumulated AS (promoted by OS) on tau phosphorylation by glycogen-synthase kinase-3β (GSK-3β) [565-567], while Hsp70 may suppress AS-mediated tau phosphorylation in early stages of disease [568]. PD-associated risk factors, e.g. environmental toxins and AS mutation, may promote tau phosphorylation, causing microtubule instability, which leads to neuronal loss in PD brain [569]. Independent and joint effects of the SNCA and MAPT (tau) genes in PD have been described [570,571], and the MAPT H1 haplotype has been reported to be a risk factor for PD [572], while it reduces the severity of AD pathology [573]. Polymorphisms between SNCA and MAPT interact to influence the rate of progression of PD, which is more prominent in the early stages of the disease [574]. Recent GWAS show that polymorphism in the MAPT and SNCA genes confers a 25.6% increased risk factor for PD [308,571,575].

Whereas AS can spontaneously polymerize into amyloidogenic fibrils *in vitro*, tau polymerization requires an inducing agent, e.g. AS seeds [121].

Cellular, various tg and other experimental PD models provided new insight in the hyperphosphorylation of tau [566,569,576-580]. They suggest that oxidatively modified AS is degraded by the proteasome and plays a pro-aggretatory role for tau [581], and that AS is an *in vivo* regulator for tau phosphorylation at Ser 262 leading to deposition of both proteins [582]. Oxidatively modified AS degraded by the proteasome further promotes the recruitment of tau to protein inclusions in oligodendroglial cells in synucleinopathies [581]. E46K modification of AS may induce tau inclusions both direct and indirect mechanisms being involved in the formation of protein inclusions [583]. On the other hand, tau enhances AS aggregation and toxicity and disrupts AS inclusion formation in cellular models [584]. Recent postmortem studies showed increased accumulation of p-tau in the striata of PD patients and in the A53T mutant mouse model [343,577], related to increased activity of GSK-3β [566,579]. This is stimulated by AS that associates with the actin cytoskeleton [585] and by GSK-3β [568]. DA D1 receptor activation induces tau phosphorylation via cyclin-dependent kinase 5 (cdk5) and GSK-3β signalling pathways [586].

Tau in MPTP models and human postmortem striata is hyperphosphorylated at the same sites (Ser 202,262, and 396/404) as in AD [343]. However, tauopathy in PD striata is restricted to DAergic neurons, whereas degeneration of the frontal cortex, associated with increased AS deposits, because of reduced proteasomal activity is not associated with tauopathy [343]. In the AS overexpressing mouse model of PD, tauopathy, along with microtubule destabilization, exists primarily in the brainstem and striatum, the two brain regions expressing high levels of AS and undergoing the most severe degeneration in human PD. Thus, tauopathy in PD may have a restricted pattern of distribution [578], which differs from its generalized affection in AD.

There is a strong interaction between AS, tau and β-amyloid (Aβ), particularly in their oligomeric forms, which might synergistically promote their mutual aggreation *et vice versa* [68,165,582,587]. Cross-seeding beween dissimilar proteins that share β-sheet structures has been described, for example for tau and AS [588]. *In vivo* interactions between AS and tau are supported by genetic studies that link MAPT gene, which encodes tau, with increased risk for sPD [309,589,590], and in fPD, fibrillation of AS and tau is caused by the A53T mutation [588]. Tau phosphorylation was found in synapse-enriched fractions of frontal cortex in PD and AD [355] and in brainstem of AS mice [591] and EO familial DLB shows extensive tau pathology [592]. Other links between AS and tau are suggested by the co-localization of both proteins in neurofibrillary tangles (NFT) and LBs, especially in neuronal populations vulnerable for both aggregates [560,593-596], and in GCIs and NCIs in MSA [597,598]. DLB-3xtg-AD mice exhibing accelerated formation of AS and LB-like inclusions in the cortex and enhanced increase of p-tau deposits in hippocampus and neocortex provide further evidence that tau and AS interact *in vivo* to promote accumulations for each other and accelerate cognitive dysfunction, although accumulation of AS alone can disrupt cognition [599].

Other studies have suggested that Aβ is more likely to promote the desposition of AS than tau [600], and Aβ is known to initiate hyperphosphorylation of tau [601]. Cortical AS load is associated with Aβ plaque burden in a subset of PD patients [602]. Aβ peptides enhance AS accumulation and neuronal deficit in a tg mouse model [603], and AS-induced synapse damage is enhanced by Aβ-42 [604], while LB formation may be triggered, at least in part, by AD pathology [562].

PD and AD could be linked by progressive accumulation of p-tau, GSK-3β, and AS [10,343,432,577], while activation of caspase and caspase-cleft Δ-tau may represent a common way of intracellular accumulation of both AS and tau, promoted by Aβ deposition, and unifying the pathology of AD and LB disease [605]. This suggests a complex continuum characterized by variable amounts of pathogenic proteins [606,607] generated by the same stimulus probable depending on genetic backgrounds and environmental factors. Despite documented co-localisation of AS and tau in LBs [593], and Aβ and tau in synaptosomes [607], the basic mechanisms (regional differences in proteasomal and GSK-3β activities, OS in the presence of AS deposits etc) of the synergistic effects of AS, p-tau, Aβ, and other proteins, suggesting a dualism or triad of amyloidogenic neurodegeneration remain to be elucidated (f. rev. see [9,370]).

6. a-Syunclein spread and disease propagation

Mounting evidence implicates that templated corruption of disease-specific proteins and their promotion may be a mechanism of disease propagation in neurodegenerative disorders by transneuronal spread through neural networks [608]. The concept that AS lesions ramify within the CNS by a seeding-like process is supported by the observation that fetal DA transplants in the striatum in a subset of PD patients surviving more than 5 years may develop AS-positive LBs [609-611]. These data imply for a host-to-graft propagation, and a neuron-to-neuron (interneuron) transmission or transsynaptic spread of AS appears important for the propagation of the disease. Similar accumulation of AS occurs in stem cells transplanted to tg mice [612]. Development of LBs in transplanted DAergic neurons has been suggested to develop similar to that in the host SN [613], but it could not be determined whether the LB-like inclusions were formed by the spread of AS fibrils, or due to some other toxic effect of the neighbouring diseased neurons [60]. Since the transplants were derived from multiple, genetically unrelated sponsors, it seems likely that the inclusions were a consequence of factors inherent in the PD brain.

The effects of LBs in the grafted neurons are unclear, as their presence does not necessarily mean functional impairment. Oligomers of AS can recruite and aggregate AS endogenously expressed by cortical neurons, and this effect increases with time and with concentration of applied oligomers [614]. Secreted AS can recruit endogenous AS in the recipient cells, act as a permissive template and promote misfolding of small aggregates [615]. Some of the uptake of AS from the extracellular space appears to occur via endocytosis, although additional mechanisms might also contribute [26,548]. It is probable to trigger the formation of LB-like aggregates in cultured cells, when arteficial methods, bypassing physiological uptake mechanisms, are used [609,612]. This is supported by the observation that neural grafts placed into tg mice expressing human AS take up the human protein and form AS-positive aggregates [26,616,617]. AS fibrillation starts *in vitro* with soluble oligomers forming a nucleus, but once the nucleus forms, aggregates form rapidly [618]. Therefore, permissive templating may be efficient and less dependent on the concentration of the protein than of the initial misfolding, which would explain the variable age of onset of the disease.

Preformed fibrils generated from full-lenght and truncated recombinant AS were shown to enter primary hippocampal neurons, probably by endocytosis [26,548], and promote recruitment of soluble endogenous AS into insoluble LBs and LNs, perhaps via a controlled type of diffusion or specialised binding [137,548]. Endogenous AS was sufficient to form these aggregates, and overexpression of WT or mutant AS was not required. Aggregates of the disease isoform build up, and propagate between cells leading to disease progression.

Secreted forms of AS might be biologically important because of the potential for causing paracrine effects on neighboring cells; they lessen the viability of recipient neuronal cells in culture models, in a concentration-dependent fashion [137], and this effect is largely mediated by oligomeric species [614]. Extracellular AS could also trigger a neuroinflammatory response through microglial activation binding to integrin α-M receptors [619,620]. By contrast, astrocytes internalise AS via endocytosis in an attempt to clear potentially toxic conformations of the protein [548,621]. Excessive uptake of AS could also lead to inflammatory response and might account for astroglial pathology [1,19]. Likewise, aberrant tau has been proposed to be secreted from cells via exosomal release early in the AD disease process [622], and trans-synaptic spread of tau pathology is seen in vivo [626].

Prions are composed solely of PrP^{Sc}, which is an aberrantly folded form of the naturally occurring cellular protein PrP^{C}. Prion toxicity is suggested by neither PrPc nor PrPSc but via a toxic intermediate, generation of which requires local availibility of PrPC. If a similar mechanism might work in synucleopathies, the implications of increasing SNCA expression becomes clear: time to onset of diseases is shorter [31]. The fundamental event in the biology of prion diseases is a conformational transition in PrP^{C} to the disease-causing isoform PrP^{Sc} [623]. PrP^{C}, which has an α-helix-rich conformation, is refolded into PrP^{Sc}, with a high β-sheet content. Its accumulation can trigger further misfolding of PrP^{Sc} through a "prion conformer", ultimately leading to its polymerization into amyloid that coalesc into toxic oligomers causing neurodegeneration. These events could be mirrored by the behavior of AS, which exists in an α-rich conformation when associated with membranes, but under pathological conditions form a β-rich protein that is prone to assemble into fibrils, and is associated with neuropatholoy [387,624].

In vivo approaches in cell culture could not discriminate between a "prion-like" corruptive templating mechanism – host-derived- translocated AS inducing its misfolding generated in the graft, *versus* simple translocation of the aggregated protein from the host to the graft, as in cell culture all mechanisms needed for prion-like behavior of misfolded AS appear possible [26,616,617]. Recent studies showed that prion infection promotes accumulation of AS in aged human AS tg mice [625]. This might suggest that AS pathology could be induced in cells and spread by a "prion-like" mechanism transmitting the conformationally altered AS [24,25,28]. There is also direct evidence that, as in prion diseases, aggregated AS proteins can be transmitted from affected nerve cells to healthy, unaffected DA neurons, thereby potentially triggering the neurodegenerative process [27]. Although the mechanism of spread remains uncertain, there is evidence that prions can be conveyed between neurons by transsynaptic transport. Thus, the propagation of AS lesions by cell-to-cell passage appears to be similar as that in other neurodegenerative disorders (see [9,626]). Early sites of Lewy pathology in PD are the olfactory bulb and enteric plexuses, lending support to the "dual hit" hypothesis suggesting that pathogenic AS may reach the brain via a consecutive network of projection neurons [627,628].

7. Neuropathology of synucleinopathies

7.1. Parkinson's disease

In sPD, the essential neuropathology is considerable neuronal loss not only in the

DAergic SN but in many other parts of the CNS, peripheral and autonomic nervous system and other visceral organs, associated with AS-positive Lewy pathology throughout these systems (for rev. see [8,9,37,38,368-370,629,630]. The recently improved but still provisional criteria for PD require these two key features – neuronal loss in the SN compacta and Lewy pathology [372]. Standardized methods for the assessment of these changes by use of a semiquantiatitive grading system and immunohistological methods for the detection of Lewy pathology have been proposed [37,38,372,630]. Recent studies have confirmed the multiorgan distribution AS and Lewy pathologies, with negative involvement of the muscular-skeletal system and sciatic nerve [7,9,631,632]. The LC and cholinergic pedunculopontine/laterodorsal tegmental nucleus (PPN/LDT) are vulnerable to AS pathology in LB disease associated with significant neuronal loss [28,633].

7.1.1. Formation and development of AS/Lewy pathology

Biochemical increase of AS phosphorylated at Ser 19 precedes histopathology of LB diseases [634] and AS aggregation precedes the formation of LBs and dystrophic neurites (LN) [123,635], but does not necessarily correlate with LB pathology [19,429-431,636]. The formation of axonal AS deposits and "pale bodies" [637] preceds the development of LBs in affected neurons. Loosely packed AS filaments as earliest or premature "pale neurites" are initiated at axon collaterals and extend centripetally into proximal segments [638]. The early intraaxonal aggregation of AS could damage the parental neurons by interfering with axonal transport [639,640], but the presence or absence of abnormal immunostaining for AS cannot be interpreted as evidence that the cell suffers or is free of dysfunction.related to abnormal protein deposition [9,641]. Reduced TH immunoreactivity in neurons may represent a cytoprotective mechanism [642], but it can also be preserved in neurons with early AS accumulation [641].

LBs occur in 2 types. *Classic LBs* are spherical cytoplasmic intraneuronal inclusions, 8-30μm in diameter with a hyaline eosinophilic core, concentric lamellar bands, and a narrow pale-stained halo. They may occur as single or multiple inclusions (Figure 7A,B). Ultrastructurally, they are non-membrane-bound, granulofilamentous structures composed of radially arranged, 7-20nm intermediate filaments associated with electron-dense granule material and vesicular structures, with the core showing densely packed filaments and dense granular material and the periphery having radially arranged 10 nm filaments [643] (Figure 7C). *Cortical LBs* – eosinophilic, rounded, angular, or reniform structures without halo – are poorly organized with a felt-like arrangement composed of 7-27 nm wide filaments, mostly devoid of a central core [644].

Antibodies that preferentially recognize N-terminal epitopes (Syn 505, 506, and 514) detect AS, consistent with the conformational changes associated with its polymerization into amyloid fibrils [352]. AS adopts an altered 3-dimensional structure and undergoes N-terminal ubiquitination but the mechanisms of its aggregation that may serve as a nidus for LB formation *in vivo* have no yet been elucidated. Both classic and cortical LBs share immunochemical and biochemical characteristics, the major components being AS, Ub, phosphorylated neurofilamens and many other substances (Table 2). Recent studies revealed cell-specific sequestration of choline acetyltransferase (CAT) and TH within LBs, suggesting that LBs may disrupt cholinergic and catecholaminergic neurotransmitter production by sequestration of the rate-limiting enzymes for their synthesis [648]. Recent demonstration of the autophagy adapter protein NBR1, which interacts with Ub via the Ub-associated (UBA) domain for degradation of ubiquitinated substrates in a way similar to p62 [649], suggests that NBR1 is involved in the formation of cytoplasmic inclusions in α-synucleinopathies [650]. AS can be recovered from purified LBs from PD and DLB brain [651], and recumbinant AS tends to form LB-like fibrillar structures *in vitro* [652].

Co-localization of AS, synphilin and parkin within LBs suggests that parkin plays a role in post-translational modification of AS, which results in changes in protein size, structure-enhancing fibrillation and formation of LBs [11]. Proteomic analysis of cortical LBs revealed 296 proteins related to multiple or unknown functions. In brainstem LBs, 90 proteins were identified [595], whereas another study identified 1263 proteins in SN [653]. A recent proteomic analysis of *post mortem* locus

Table 2. Major biochemical components of Lewy bodies (modified from [8]).

α-Synuclein (major component)
α-B-crystallin
Ubiquitin
Phosphorylated neurofilament proteins
Synaptophysin
Chromogranin A
Synphylin
Synphylin-1
γ-Tubulin
P25α (tubulin-binding protein)
Parkin
Pael-R (parkin-associated endothelin receptor-like receptors)
Calbindin
Torsin A
Gelsolin-related amyloid
Amyloid β-peptide (Aβ)
Amyloid precursor protein (APP)
Actin-like protein
Ubiquitin-pathway associated enzymes
α-B-crystallin
α-Microglobulin
Cu/Zn superoxide dismutase
Tau proteins (phosphorylated at Ser129)
MAP-1B / MAP1-LC3 [645]
MAP-2
MAP-5
MAP-9
Lipids
Calmodulin
Septin 4 (substrate for Parkin)
Tubulin
Tyrosine hydroxylase
14-3-3 protein
Redox-active iron
Cytochrome c
Advanced glycation end products (AGE)
Dorfin, an E3 ubiquitin kinase p62 protein
Cyclin B
Redox-active iron
Vesicular monoamine transporter 2 (VMAT2)
LC3, GABARAP and GATE-16 (autophagosomal proteins) [646]
Histone deacetylase 6 (aggresome-related protein) [647]

ceruleus tissue in 6 autopsy-confirmed PD cases detected 2495 proteins, of which 87 were differentially expressed in locus ceruleus. The majority was involved in mitochondrial dysfunction, OS, protein misfolding, cytoskeleton dysregulation and inflammation, but some additional proteins involved in calcium homeostasis and microtubular transport were detected [654].

The formation of LBs runs through several phases. Classic LBs show initial intraneuronal appearance of dust-like AS particles related to neuromelanin or lipofuscin, homogenous deposition of AS and Ub in the center, stepwise condensation to ubiquitinated filamentous inclusion, and final degradation to extraneuronal LBs after disappearance of the involved neuron [123]. Cortical LBs show diffuse AS and Ub labeling, while subcortical LBs have a distinct, central Ub domain with AS appearing in the periphery and ubiquitination being the later event. Their development shows initial accumulation of AS in the neuronal cytoplasm, stepwise accumulation of dense filaments (Lewy neurites – Figure 7D), spreading to dendrites, deformation of LBs, and final degradation by astroglial processes [640]. LBs are accompanied by dystrophic neurites, which according to recent 3-dimensional studies may evolve into LBs, with Ub at the core and neurofilaments at the outermost layer [655].

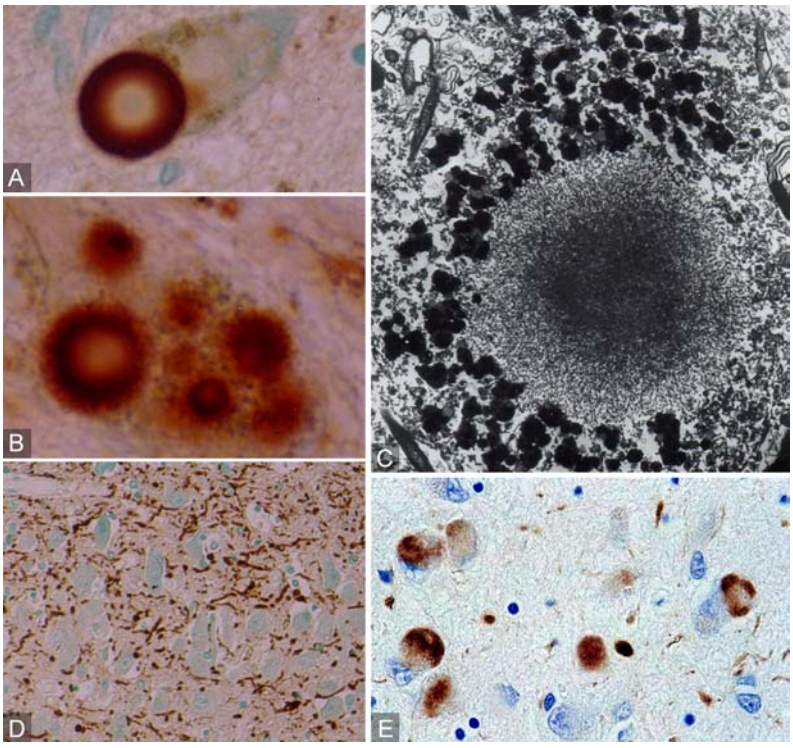

Figure 7. (A) Lewy body in substantia nigra whose peripheral rim is stained with anti-AS x 300; (B) Multiple Lewy bodies in nigral neuron; anti-AS x 1200; (C) Electron microscopy of nigral Lewy body showing a central electron dense filamentous core with a loosely fibrillary rim (x 2500); (D) Dystrophic Lewy neurites in the hippocampal C2/3 region, anti-AS x 150; (E) Multiple cortical Lewy bodies in frontal cortex in DLB; double label immunohistochemistry (brown: AS, red: tau), x 200. AS = α-synuclein.

7.1.2. Relationship between α-synuclein and Lewy pathology

Based on semiquantitative assessment of LB inclusions in a large autopsy series of PD, a staging of the spread of Lewy pathology was proposed to designate a predictable sequence of lesions in the nervous system beginning in the lower brainstem and anterior olfactory nucleus with caudo-rostral progression to the neocortex [340,656-658]. The validity of this 6-staging scheme, which corresponds roughly to the classification of LB disorders into 3 phenotypes – brainstem predominant limbic/transitional, and diffuse neocortical [659] - has been a matter of vigorous debate [7,430,636,660-663], since between 6.3 and 47% of all cases of autopsy-proven PD and 18% of iLBD did not follow a caudo-rostral spread of LB pathology [340,429,663-665]. Longitudinal clinico-pathologic studies showed that 17-31% of PD patients have a fast disease progression [666,667].

A recently proposed unifying system for LB diseases correlates AS pathology with nigrostriatal degeneration, cognitive impairment, and motor dysfunctions [660]. Whereas the old classification left 45-50% of individuals unclassified [668,669], all were now classified into 1 of 4 stages (Figure 8). This is supported by an increase of pAS restricted to the olfactory bulb and brainstem in early stages of LB pathology [634]. Progression through these stages was accompanied by stepwise deterioration of striatal TH concentration, SN cell loss, and clinical scores. Significant correlations between these measures and AS pathology documented improvement of the previous staging.

The duration and severity of motor dysfunction in PD, the corresponding decrease of DA transporter (DAT), and vesicular monoamine transporter 2 (VMT2) immunoreactivity in the striatum are inversely correlated with the total AS burden and neuronal loss in the SN [670-673], but not with LB counts in the SN, which supports the concept of synaptic dysfunction and/or impairment of axonal transport [641]. Both neuron number and densitie in SNc decrease with time [672]. About 15% of SN neurons contain LBs [674] and may survive for 7.5 years (2% neuronal death per year). AS alterations affect neurotransmitter release [88,159-161,675], possibly through impaired assembly of SNARE complex [675]. This supports a dying back mechanism in diseases with neuronal AS pathology in which dysfunction starts at the synapse and leads to axonal degeneration and AS accumulation in LBs and LNs [631,676,677]. According to this hypothesis, although AS aggregates may be cytotoxic, LBs are markers of an ongoing neuronal damage [678], or they might even

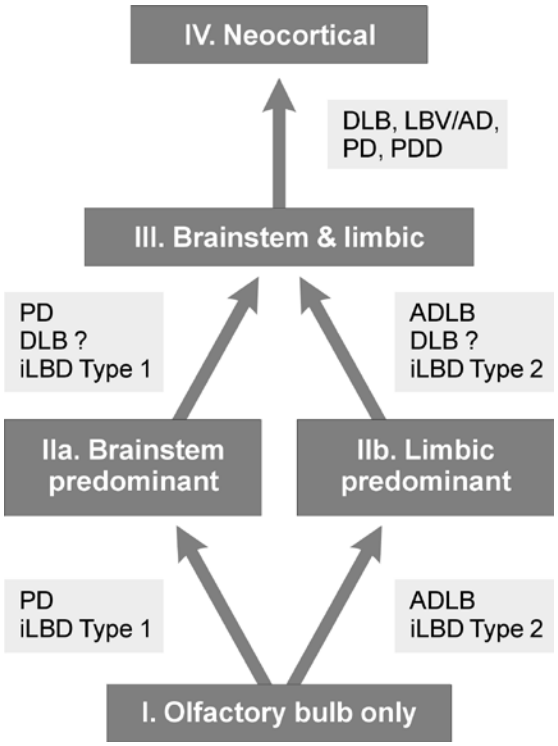

Figure 8. Scheme of the hypothetic progression pathways and stages of Lewy body (LB) disorders. The pathway for Parkinson's disease (PD) is suggested to proceed through stage IIa (brainstem predominant), and that for dementia with LBs (DLB) and Alzheimer's disease (AD) with LBs probably passes through stage IIb. For incidental LB disease (iLBD), both pathways seem possible, whereas only PD/ PD dementia (PDD), DLB, and the LB variant of AD (LBV/AD) progress to the neocortical stage [660].

be harmless end products of sequestration of toxix molecules as a type of cell-protective mechanism [8,10,369,370,432]. However, the ultimate upstream mechanism responsible for the regulation of the machinery that handles toxic waste by segregating it into aggregates (LBs) is still poorly understood.

A BAC mouse model, created with the most frequent disease-causing human mutant (LRRK2 /R1441R), recapitulating cardinal features of human PD, showed no loss of mesencephalic DA neurons, but diminished DA release and axonal pathology of nigrostriatal DA projections [679]. According to recent studies, overexpression of human AS in rat nigral neurons leads to a deficiency in DA release preceding outright neuron loss via decreased presynaptic vesicle density, indicating that lack of DA is due to axonal fiber loss [680].

These data and demonstration of accumulation of small AS aggregates at presynaptic terminals in human LB disease and A53T AS tg mice [681-683] suggest that AS related synaptic dysfunction or axon degeneration, not nerve cell loss, may be the primary determinant of progression of the neurodegeneration [682,683], and loss of neurons is an epiphenomenon after the loss of synapses, defining PD a "synaptopathy". This may allow to single out novel potential therapeutic targets among the AS synaptic partners for new treatment strategies in PD [684].

7.2. Dementia with Lewy bodies and Parkinson disease-dementia

DLB and PDD are considered part of a spectrum associated with α-synucleinopathy. PDD implies PD with subsequently developing dementia; DLB is a pregressive dementia syndrome associated with several core clinical neuropsychiatric features, considered to be the second most common neurodegenerative dementia syndrome in the elderly [685]. An arbitrary cut-off is used: PD develops first followed after more than 1 year by dementia, the suggested diagnosis is PDD; if dementia develops first or within 1 year of PD diagnosis, then DLB is diagnosed. Distinction of the clinical, pathological and biochemical findings in both disorders may be difficult [9,686-689]. There is no "gold standard" for the pathological diagnosis of DLB and PDD. Their hallmark is AS pathology manifested as LBs or a variable mixture of AS and AD pathologies, which may interact synergistically [690-692]. Both cortical and subcortical AS pathologies have been suggested to be the main determinant [693,694], whereas others suggested AD pathology to be more important, particularly when the Aβ load may be similar to that in AD [695]. The severity and extent of AS are variable, and according to revised guidelines are scored semiquantitatively in specific brain areas [593,696-699]. AD pathology is a consistent but not universal finding in both disorders, differentiating two types of DLB: The "common form" is characterized by abundant neocortical senile plaques and NFTs in the limbic cortex; while "pure DLB" shows minimal AD lesions [700]. NFTs, being frequent in both DLB and PDD, are often restricted to limbic regions, whereas excessive tau pathology may be absent [687]. Beween 10 and 50% of PDD cases had enough AD lesions to attain the pathological diagnosis of definite AD using CERAD criteria [92,701-704], but PDD may also develop in the absence of significant AD pathology, related to higher Braak LB stages [702]. Reduced cortical cholinergic innervation in DLB and PDD is similar and lower than in AD [705,706]. Synaptic loss is a consistent feature in DLB and is of equal severity as in AD [707].

Despite many similarities between DLB and PDD, several morphological differences have been demonstrated, in particular higher amyloid plaque load in striatum, usually absent in non-demented PD [37,38,630,708], and more severe AS load in hippocampal CA2/3 areas [429-431]. A recent study showed DLB cases having more severe Aβ load than PDD, but no differences in neuritic Braak and AS scores, while others found higher Aβ scores in cortical and subcortical areas [692]. Other differences between PDD and DLB are more

marked nigral cell loss and postsynaptic DA upregulation [709], and more severe cholinergic deficit in temporal cortex in PDD [710]. Both DLB and PDD are usually associated with mild cerebrovascular lesions, except in cases with severe AD pathology and cerebral amyloid angiopathy [691], and recent studies confirmed an inverse relationship between cerebrovascular lesions and the severity of LB pathology [711]. The role of microglia and inflammatory pathology in DLB and PDD is unresolved [687]. In conclusion, both DB and PDD show heterogenous pathology and neurochemistry, which depend on the different patterns of pathology supporting the hypothesis that these AS-related disorders and AD share a common, underlying molecular pathogenesis.

7.3. Multiple system atrophy

MSA is a usually sporadic, adult-onset, progressive neurodegenerative disease of unknwon etiology, the morphologic hallmark of which is the abnormal AS positive glial cytoplasmic inclusions (GCI) in oligodendrocytes [18] or Papp-Lantos bodies [712], see [13], and rare neuronal cytoplasmic inclusions (NCIs), associated with systemic neuronal loss, gliosis, myelin pallor, and axonal degeneration. The clinical terms MSA-P and MSA-C classify cases according to the predominant motor disorder due to abnormalities in the striatonigral (SND) and olivopontocerebellar systems (OPC) [29,30]. Macroscopic changes are atrophy and discoloration of putamen, depigmentation of SN, and/or atrophy of cerebellum, middle cerebellar peduncle, and pontine basis [330]. Histology shows neuronal loss and gliosis in the striatonigral system, locus ceruleus, and other regions, associated with widespread occurrence of argyrophilic AS-positive GCIs (Figure 9A-C) and, less frequent, NCIs (Figure 9D) in gray and white matter. They are often related to neuronal loss and disease duration [713-716], although GCIs are more widespread [717]. A grading scheme of neuropathology, based on semiquantiative assessment of GCIs and neuronal loss in essential brain areas differentiated the various subtypes of MSA showed considerable variations in the morphological expression, but correlated well with clinical deficiencies and disease duration [718,719].

Ultrastructurally, GCIs are composed of randomly arranged tubules and filaments with 20-40 nm diameter associated with granular material [720]; showing AS in these structures [721]. NCIs show a meshwork of granule-associated filaments 18-28nm in diameter, similar to those of oligodendroglia [722]. Involvement of the autonomous nervous system leads to clinical autonomic disturbance [717,723]. It was discussed whether myelin loss in many networks is a primary event in MSA or due to neuronal depletion [724].

Biochemical studies showed increased insolubility of AS even in brain areas with few GCIs, indicating that AS aggregation precedes the formation of inclusions [21,346]. Immunoblotting of brain extracts showed 19kDa species with higher molecular weight bands, representing aggregated protein [346], and a newly described specific antibody (5GA) detects AS deposits with much higher sensitivity [354]. GCIs contain modified AS nitrated and phosphorylated at Ser 129, which has an enhanced ability to form fibrils, while nitration may indicate a role of oxidative damage [122,521,725]. In addition to AS, GCIs and NCIs contain a large number of proteins, oligodendroglial markers, myelin basic protein (MBP), as well as p25α tubulin-polymerization-promoting protein (TPPP) [726,727]; which promotes AS phosphorylation [728] and shows interaction with MBP (see [13,729]) (Table 3). The generation of tg animal models of MSA coupled with an increasing understanding of the biochemical structure and function of AS has highlighted the key pathological pathways thought to underly the neurodegeneration in MSA. OS and chronic inflammation [733], reduced oligodendroglial trophic support, and neuronal dysfunction associated with AS inclusions (GCIs) are suggested to contribute to neurodegeneration. The effect of AS on micro- and astroglia is currently a topic of intense research in MSA and PD [19]. Increasing evidence suggests that oligodendroglial dysfunction due to AS aggregation resulting in abnormalities of myelination, degeneration of the oligodendroglia-myalin-axon-neuron complex leading to neuronal degeneration may be important in MSA, supporting the

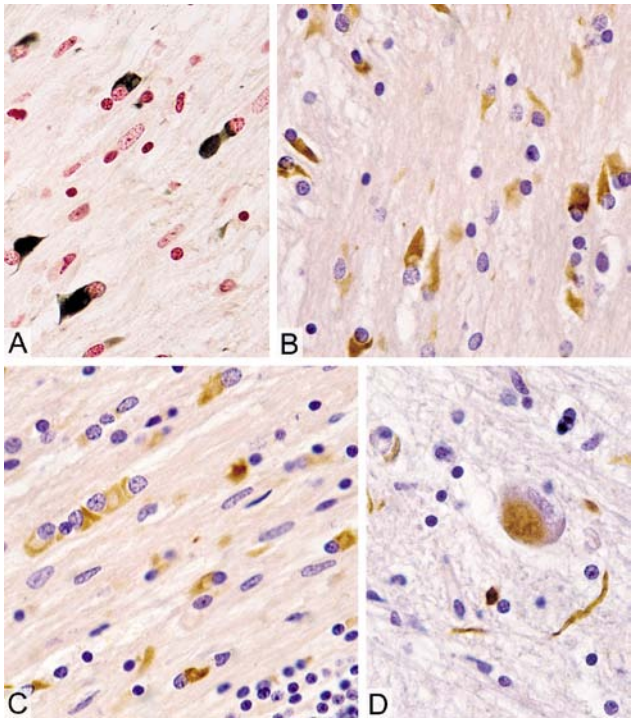

Figure 9. (A-C) Glial cytoplasmic inclusions (GCIs) in MSA: (A) in globus pallidus (Gallyas silver impregnation); (B) in pontine basis (α-synuclein); (C) in frontal white matter, anti-ubiquitin. (D) Neuronal cytoplasmic inclusion and neurites in pontine basis (α-synuclein) (GCIs glial cytoplasmic inclusions). A-D x 4000.

Table 3. List of protein constituents identified in glial cytoplasmic inclusions (GCIs) from human multiple system atrophy brain (modified from [729]).

Constituents positively identified by routine immunohistochemistry
α-Synuclein (MS+) (Syn 202, 205, 215 > SNL-4 > LB509 > Syn 208), (S129-P, S87-P)
α-Tubulin (MS+)
β-Tubulin (MS+)
14-3-3 protein (in subset of GCIs)
Bcl-2 (MS+)
Carbonic anhydrase isoenzyme IIa (MS+)
cdk-5 (cyclin-dependent kinase 5) (MS+)
Midkine[a]
Tau2 (reversible on exposure to detergent)
DARPP32
Dorfin
Heat shock proteins Hsc70 and Hsp70 (MS+)
Isoform of 4-repeat tau protein (hypophosphorylated) (MS+)
DJ-1
LRRK2
Rab5, Rabaptin-5
Parkin
Mitogen-activated protein kinase (MAPK)
NEDD-8 (MS+)
Other microtubule-associated proteins (MAPs): MAP-1A and -1B; MAP-2 isoform 1, and isoform 4 (all MS+)
Phosphoinositide 3-kinase (P13K) (MS+)
p25α/TPPP (MS+) (tubulin polymerization-promoting protein)
Septin-2, -3, -5, -6 and -9
Synphilin-1
Transferrin[a]
HtrA2/Omi
Ubiquitin (MS+) SUMO-1 (small ubiquitin modifier 1)
Leu-7a
p62-co-localization with α-synuclein (inconsistent)
Metallothionein-III (MT-III)
Candidate proteins that have so far eluded detection by routine immunohistochemistry
Actin, γ-1 and γ-2 propeptides (MS+)
Amyloid-b precursor protein (MS+)
β-Synuclein (MS+)
Cytokeratin
Desmin
Glial fibrillary acidic protein (GFAP) (MS+)
Myelin basic protein (MBP)-3, -4, -5 (MS+)
Myelin oligodendrocyte glycoprotein (MOG), α- and β-isoforms (MS+)
Myosin (9 distinct isoforms) (MS+)
Neurofilaments (NF-3, NF-HC, NF-LC) (MS+)
Vimentin

MS+: polypeptides identified by mass spectrometry following affinity purification of glial cytoplasmic inclusion body purification as described in [730-732]
[a]: Known oligodendroglial markers

working model of MSA (Figure 10) as a primary oligodendrogliopathy [729,734].

Recent reviews give insight into current knowledge about neuropathology, pathophysiology, genetics, and animal models of MSA [330,735-737]. The genetical, morphological, and pathogenic relations between PD and MSA are summarized in Figure 11.

8. Animal models of Parkinson's disease

In an attempt to shade light on the neurobiology of PD, numerous experimental models have been developed. They come from essentially 3 sources: pharmacological, e.g. reserpine, toxic e.g. MPTP [738], rotenone and paraquat [739-742], and genetic. Despite the fact that numerous mutations causing hereditary forms of PD have been identified in the last decade, current tg animal models do not adequately reproduce cardinal clinical and neuropathologic features of the human disease [99,743-747]. During the last years a myriad of different models carrying mutations similar to those found in humans, in *Drosophila melanogaster* [748-750], *Caenorhabditis elegans* [492,751] and in mammalians [752] have been developed to study the cellular mechanisms impaired in this disease [746]. Although some genetic models reproduced the key features of PD, most of them induced DA neurodegeneration, but did not succeed in reproducing both the broad pathology and progressive degenerating process in human PD [747,753,754]. To date, viral PD models comprise AS and LRRK2-based overexpression or mimic parkin loss of function by overexpression of parkin substrates [755]. These viral and other recent genetic models models are hoped to provide valuable insights into PD mechanisms in order to contribute to the development of therapeutic targets.

Although the precise origin of AS in oligodendrocytes in MSA remains unknown, its presence as a key pathological hallmark of the disease in many tg animal models tried to reproduce the human disorder [99,756,757]. These and other models provide evidence of oligodegeneration as a result of human

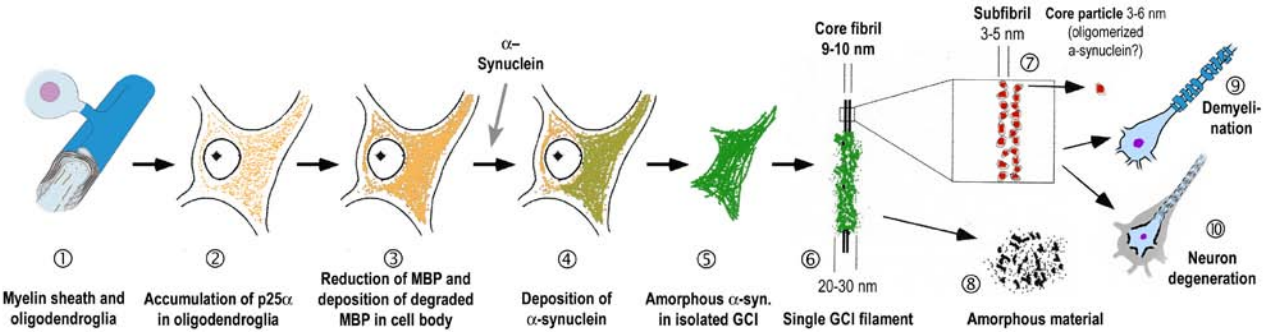

Figure 10. Summary of working model for oligodendroglia dysfunction in multiple system atrophy (MSA). (1) Normal oligodendroglia and myelin sheath; initial altered function of p25α and myelin basic protein (MBP). (2) Accumulation of p25α within oligodendroglia. (3) Reduction of MBP and deposition of degraded MBP in affected cell body. (4) Deposition of amorphous and fibrillary α-synuclein species within oligodendroglia, thereby forming glial cytoplasmic inclusions (GCIs). (5) Amorphous material (α-synuclein) of isolated GCIs. (6, 7) Schematic of core fibril comprising two subfibrils and a strand of interconnected 3 to 6nm fibrils. (8) Amorphous material deposited within neuropil. (9) Resultant glia degeneration and demyelination. (10) Resultant neurodegeneration. After [729].

AS overexpression in oligodendrocytes and a secondary neurodegenerative process, although, due to several deviations from human disease they are less than ideal as a model for MSA [330,758]. However, continued work with several models of MSA [759] and human samples, and lessons from other synucleinopathies, will shed new light on the underlying pathogenic mechanisms and increase the likelihood of developing disease-modifying interventions.

9. α-Synuclein as a biomarker for synucleinopathies

Numerous forms of AS can be released into cerebrospinal fluid (CSF) and other biological fluids of healthy subjects and patients with neurodegenerative disorders [760] and is also abundantly expressed in the hematopoetic system [190]. Full-length AS has been recovered from lumbar CSF in PD and DLB patients [731,761]. As a candidate biomarker of synucleinopathies, namely PD and DLB, AS determination in CSF [762] was hoped to improve the clinical diagnostic accuracy. Although AS is the main constitutent of LBs, the detection of AS in body fluids of patients with synucleinopathies has yielded promising but inconsistent results [763,764,764a]. Similar to divergent results on the plasma levels of AS in PD [765-767], retrospective studies of CSF provided inconclusive and contradictory results [731,760,768-771]. pAS was detected in PD samples, which was not the case for oligoAS or oligo-pAS [772]. Confirming several studies

Parkinson disease		Multiple system atrophy
Presyn. terminals, axons, neurites (LN), neurons (LB), dendrites, astroglia	Location of aggregates	Oligodendroglia (GCI), neurons (NCI), axons, astroglia
AS, ubiquitin, parkin, synphilin-1, neurofilament proteins, actin, dorfin, MAPs, tau, 14-3-3, P25α (others different)	Content	
Multisystemic: central, peripheral and autonomic nervous system mainly substantia nigra, striatum ← soluble AS → mainly substantia nigra, striatum (MSA-P)	Distribution / neurodegeneration	
SN: AS density; neuron loss +	Correlations	AS –, GCI density –, neuron loss +
Synaptopathy - axonopathy → neuron degeneration	Primary lesions	Oligodendropathy → demyelination, axonopathy → neuron loss
LBs, LNs, no GCIs	Association	LBs + GCIs (10-28%)
SNCA mutations in genetic PD	Genetics	SNCA mutation → MSA risk
Molecular/morphologic overlaps suggest a continuum of lesions rather than distinct entities with similar mechanisms of neurodegeneration, but the etiology of both is poorly understood.	*Synopsis*	

Figure 11. Major genetic, morphological and pathogenetic relations between Parkinson disease and multiple system atrophy. AS: α-synuclein; LN: Lewy neurite; LB: Lewy body; GCI: glial cytoplasmic inclusions; NCI: neuronal cytoplasmic inclusion; MSA-P: multiple system atrophy with predominant parkinsonism; SNCA: α-synuclein gene.

showing relatively low CSF AS concentrations in both PD and DLB [731,773-775], more recent ones reported significantly lower AS levels in PD [776,777] as well as in PD, DLB and MSA than in AD [777-779]. While CSF levels of AS oligomers were significantly increased in PD patients against controls [298,416,780], AD and progressive supranuclear palsy (PSP) [781], others were unanble to detect oligomeric AS in CSF [776]. Recent work detected alterations in AS phosphorylation (Ser129) in the CSF of PD patients [782]. However, CSF AS alone did not provide relevant information for PD diagnosis, showing low specificity, but a better performance was obtained with the total tau/AS ratio, giving a sensitivity of 89% and specificity of 61%, contributing to the determination of PD [777]. A recent study reported different levels of CSF biomarkers in different phenotypes of

PD, non-tremor-dominant (NT-PD) patients showing significantly higher levels of CSF tau and index tau/Aβ than early onset and tremor-dominant PD and controls, but no differences between NT-PD and AD [783]. These data were confirmed by personal studies [9], corroborating the opinion that CSF levels of tau may be a biomarker for the presence and severity of neurodegeneration [784,785], while others did not see such biomarker changes [786-788]. Other recent studies showed that CSF AS is currently unsuitable to differentiate between PD and atypical parkinsonism [789]. The source of PD-linked AS in human CSF remains unknown, but recent studies suggest that despite the higher levels in peripheral blood products, neurons in the CNS represent the principal source of AS in human CSF [790]. Postmortem CSF levels of oligomeric AS and pAS significantly raised in MSA compared to other controls and other synucleinopaties, but did not distinguish PD and DLB from PSP or control groups [791]. CSF AS levels did not differ significantly between DLB and/or PD and AD [792], but AS levels were reduced in DLB patients with long disease duration or worse cognitive performance [760,792]. DLB compared with PD, PDD, and AD showed the lowest CSF levels of Aβ42 and, when combined with CSF tau, differentiated DLB from PD and PDD; but not from AD [788], and PiB PET binding showed higher amyloid loaden in DLB and AD than in PD, PDD and controls [793,794]. While earlier studies showed increased CSF total (t)tau in both DLB and AD [795], others found differences for both t-tau and p-tau differentiating DLB from AD [796], and levels of t-tau and p-tau181 were significantly increased in DLB [797]. Recent studies suggested that combinations of CSF measures may be able to differentiate DLB from other dementias: AS reduction in early DLB, a correlation between CSF-AS and Aβ42 measures (characteristic for DLB only), and total (t)-tau and p-tau 181, differentiating AD from DLB [798,799]. Combined analysis of CSF tau, Aβ42 and Aβ42/40 may differentiate between AD, DLB and PDD [800], while the differential association between amyloid precursor proteins sAPPα and sAPPβ with Aβ and tau species between DLB and AD suggests a relationship with their underlying pathologies [801]. Combination of CSF t-and p-tau, Aβ42, and MHGP (3-methoxy-4-hydroxyphenyleneglycol) discriminated between AD and DLB with a sensitivity of 95% and a specificity of 90% [802]. In autopsy-confirmed cases of DLB and AD, p-tau 181 yielded only a sensitivity of 75%, and specificity of 61%, with diagnostic accuracy of 73% [803]. According to recent studies, reduction of dihydroxyphenylacetic acid was seen in both early PD and MSA, separating recent onset PD from controls with 100% sensitivity and 89% specificity, but was of no value in differing PD from MSA [804].

These conflicting data indicating a differential CSF pattern between synucleinopathies (and tauopathies) imply the development of novel techniques to specifically target and visualize AS and other proteins in brain and biological fluids in order to detect the complex interplay between misfolded proteins in the brain during these diseases. For a recent critical review of molecular genetics and biomarkers in LB related disorders (see [805]). The recently described AS antibody 5GA, and a novel one-step time-resolved Förster's response energy transfer (TR-FRET) immunoassay to quantify distinct AS species in CSF [776], may offer new perspectives for the development of *in vivo* diagnostic assays for AS-related diseases in body fluids. In general, longitudinal studies, pathological confirmation of diagnosis, and the combined approach may be the most promising way for the identification of (imaging and protein) biomarkers [806].

10. Conclusions and final remarks

AS is a small, soluble neuronal protein with predominantly presynaptic location in brain as well as in many other organs. Its physiological functions regulating symaptic vesicle traffic, neuronal function, neurotransmitter release, etc, are not fully understood. In its physiological form, AS occurs in both soluble and membrane-bound form. Under pathological conditions, like due to gene mutations and exogenous factors, or both, AS undergoes post-tranlational changes and aggregation leading to formation of deposits of insoluble proteins. Intraneuronal and axonal deposits, LBs and LNs, the histological hallmarks of LB disorders (PD, DLB), and intracytoplamic deposits in oligodendroglia (GCIs) of MSA, are associated with degeneration and loss of specific neuronal populations and networks in these disorders. They are sequelae of complicated molecular changes due to mitochondrial dysfunction, autophagy, oxidative and nitrative changes, disorders of calcium homeostasis, neuroinflammation, and other deleterious factors leading to energy deficit and cell death. Neurotoxicity of AS, like of other pathogenic proteins, is suggested to be caused by soluble oligomers or intermediate proteins and not by insoluble aggregates. Whether LBs and other protein deposits are detrimental or protective is a matter of discussion; they may either be innocent bystanders or represent an end stage of failed cytoprotective elimination of toxic proteins as a defense mechanism against the primary process underlying nerve cell death [807,808]. The recent demonstration of presynaptic deposition of AS in PD and DLB suggests them to represent synaptopathies, while deposition of AS in oligodendroglia in MSA inducing demyelination and neuronal degeneration supports the working hypothesis of a primary oligodendrogliopathy. Interaction of AS with other pathological proteins may explain the frequent overlap between various proteinopathies, e.g. PD and DLB with AD. "Prion-like" interneuronal seeding/spread of pathological proteins is suggested an important mechanism of disease propagation [27]. Since most of the available models do not exactly reproduce the molecular and morphological key features of PD and other synucleinopathies, new viral and/or genetic models may provide deeper insights into neurodegeneration in these disorders. Although increasing evidence suggests that AS is an interesting therapeutic target in PD [809], future clinical trials need more exact analysis of AS and other pathogenic proteins excreted into body fluids by biomarkers that reflect AS misfolding in the brain to enable more accurate diagnosis of these disorders

[810]. Early intervention into the aggregation process by development of ligands that can bind to misfolded proteins (eg, heat shock proteins, clearing toxic oligomers, stimulation of proteolysis, anti-prion drugs) or modification of AS phosphorylation [811], may allow detection of AS pathology even before the onset of clinical symptoms. Such surrogate markers of disease progression would be important tools for clinical trials aiming to achieve disease modification [812]. These developments and the development of new targets or novel candidate drugs that might be neuroprotective for PD and other proteinopathies are major challenges of modern neurosciences.

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