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Review

The Bidirectional Interplay of α-Synuclein with Lipids in the Central Nervous System and Its Implications for the Pathogenesis of Parkinson's Disease

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Abstract: The alteration and aggregation of alpha-synuclein (α-syn) play a crucial role in neurodegenerative diseases collectively termed as synucleinopathies, including Parkinson's disease (PD). The bidirectional interaction of α-syn with lipids and biomembranes impacts not only α-syn aggregation but also lipid homeostasis. Indeed, lipid composition and metabolism are severely perturbed in PD. One explanation for lipid-associated alterations may involve structural changes in α-syn, caused, for example, by missense mutations in the lipid-binding region of α-syn as well as post-translational modifications such as phosphorylation, acetylation, nitration, ubiquitination, truncation, glycosylation, and glycation. Notably, different strategies targeting the α-syn-lipid interaction have been identified and are able to reduce α-syn pathology. These approaches include the modulation of post-translational modifications aiming to reduce the aggregation of α-syn and modify its binding properties to lipid membranes. Furthermore, targeting enzymes involved in various steps of lipid metabolism and exploring the neuroprotective potential of lipids themselves have emerged as novel therapeutic approaches. Taken together, this review focuses on the bidirectional crosstalk of α-syn and lipids and how alterations of this interaction affect PD and thereby open a window for therapeutic interventions.

Keywords: α-synuclein; lipids; Parkinson's disease; post-translational modification

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1. Introduction

Alpha-synuclein (α-syn) is a small 14-kDa protein first discovered by Maroteaux and colleagues in 1988 [1]. In the central nervous system (CNS), α-syn is expressed abundantly in neurons [2], while it is also present in the peripheral nervous system (PNS), gut, muscle, liver, heart, lungs, kidney, and blood cells [3,4]. Since α-syn is enriched in presynaptic terminals and associated with synaptic vesicles, a large number of studies indicates the important role of α-syn in neurotransmission and synaptic plasticity [5–7]. In addition, α-syn plays a role in transcriptional regulation of dopamine synthesis [8]. Diverse physiological forms of α-syn have been reported: the protein may exist as unstructured monomer [9,10], α-helical monomer or multimer [11,12] that interacts with biological membranes [13]. Pathological alterations in the α-syn structure are predominantly linked to its abnormal aggregation from monomers to oligomeric or fibrillar species [11,14] showing varying degrees of assembly, solubility, and pathogenicity [15]. Neurotoxic effects of aggregated α-syn are multifaceted. For example, addition of α-syn oligomers to primary neurons in culture induces reactive oxygen species, increases cytosolic calcium, disrupts membranes, and thus leads to cell death [15,16]. Furthermore, exposure of neurons to fibrillar forms of α-syn induces prion-like propagation of α-syn aggregation, resulting in the formation of inclusions that are morphologically and biochemically similar to those detected in diseased brains [17,18]. Diseases associated with α-syn aggregation are collectively

termed synucleinopathies, consisting of Parkinson's disease (PD), multiple system atrophy (MSA), and Lewy body disease [19].

PD is the most prevalent neurodegenerative movement disorder and is clinically characterized by motor deficits such as bradykinesia, rigidity, and resting tremor [20,21]. The neuropathological hallmarks of PD are the formation of Lewy bodies or Lewy neurites containing aggregated α-syn accompanied with a substantial loss of dopaminergic neurons in the substantia nigra [22,23]. The involvement of α-syn in dopaminergic neuronal cell death was suggested after the identification of the first missense mutations (A30P, E46K, and A53T) in the α-syn encoding gene, *SNCA*, linked to monogenic PD phenotypes [22,24,25]. The primary structure of α-syn is composed of three well-described domains that determine its biological functions: the N-terminal amphipathic region [26,27], responsible for lipid binding [27]; the central hydrophobic non-amyloid-β component (NAC) region [28], important for aggregation of the protein [29,30] as well as axonal transport [31]; and the acidic C-terminal domain [32], decisive for protein interactions [33] and oligomerization of the protein [34] (Figure 1). Interestingly, all missense mutations linked so far to familial forms of PD (e.g., A30P, E46K, H50Q, G51D, A53E, and A53T) reside in the lipid-interacting N-terminal domain of α-syn [22,24,25,35] (Figure 1). Thus, these mutations may represent a functional "hot spot" resulting in a detrimental impact on the lipid-binding properties of α-syn and its physiological function. Moreover, α-syn conformation and aggregation propensity may be consequently changed after exposure to distinct lipid classes [36].

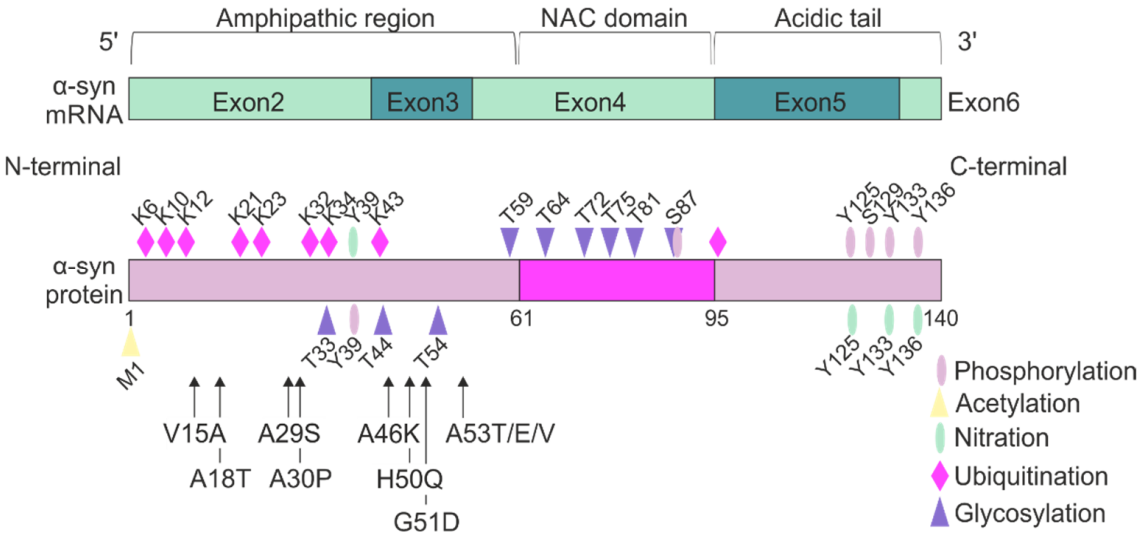

Figure 1. Structure of alpha-synuclein (α-syn). α-syn is encoded by the *SNCA* gene. This gene is transcribed into mRNA consisting of five exons. Following translation, the protein consists of distinct domains: the amphipathic region at the N-terminus, the non-amyloid-β component (NAC) domain, and the C-terminal acidic tail. Moreover, α-syn undergoes a variety of post-translational modifications (PTMs), including phosphorylation, acetylation, nitration, ubiquitination, truncation, glycosylation, and glycation. Monogenic PD-associated point mutations are indicated with arrows and are exclusively present in the N-terminal amphipathic region.

Lipids play an essential role in the CNS. Besides ensuring compartmentalization of cells and organelles through the formation of lipid-rich membranes, lipids act as bioactive signaling molecules [37]. Furthermore, they participate in mitochondrial metabolism [37]. In the CNS, lipids are predominantly metabolized in neurons and astrocytes [37]. However, lipids are one of the main components of myelin sheaths generated by oligodendrocytes and thus present a major player in lipid metabolism as well [38]. Furthermore, there is a physiological interaction of α-syn with different lipid classes, especially biomembranes, [27,39,40] and lipids are dysregulated in PD [41]. Since current therapeutic approaches for PD predominantly restore dopaminergic tone to control motor symptoms, though without

altering disease progression, interfering with the interaction between α-syn and lipids offers potential avenues for therapeutic strategies in PD [42].

Thus, this review focuses on two key aspects related to the reciprocal interplay between α-syn and lipids: (1) changes in lipid composition or metabolism that may impact the biochemical dynamic of α-syn aggregation and (2) alterations in the α-syn structure due to mutations or post-translational modifications (PTMs) that could influence its interaction with lipids. The final goal of this review is to elucidate this bidirectional crosstalk and how this may drive the pathological events in PD, thus offering novel targets for therapeutic interventions.

2. Lipids and Lipid Metabolism

The four major classes of biomolecules in a mammalian cell are carbohydrates, proteins, nucleic acids, and lipids [43]. The latter are an essential component of the brain. Indeed, the brain has the second highest lipid content after adipose tissue in the human body, accounting 50% of the brain's dry weight [44]. In contrast to adipose tissue, where fatty acids (FAs) are predominantly stored as triglycerides (TAG) for energy storage, the brain primarily utilizes lipids as structural components for membranes [44]. Regular biomembranes typically have a lipid:protein ratio of about 50%:50%. However, in the case of myelination in oligodendrocytes, lipids play a particularly crucial role, as myelin is characterized by an exceptionally high proportion of lipids, with a lipid:protein ratio of 70–85%:15–30% [45]. In general, lipids fulfill a broad range of roles throughout the body such as energy supply, membrane components, and precursors of vitamins and hormones. Moreover, they contribute to blood coagulation and to immune responses [46]. Lipids are taken up by nutrition or are synthesized de novo. Multiple different neural cells are able to produce its own lipids. In this review, we focus on the four major types of lipids: sterols, (including cholesterol), FAs, sphingolipids, and glycerophospholipids (Figure 2). Other lipid classes such as saccharolipids, polyketides, and prenol lipids have been reviewed elsewhere [47].

2.1. Lipid Metabolism in the Brain

All lipids except sterols, such as cholesterol, are generated from FAs [48]. While FAs pass across the blood–brain barrier [49], the entry of cholesterol into the brain is largely restricted [50]. Thus, there is a crucial need for cholesterol synthesis within the CNS [51]. In general, cholesterol can be synthesized de novo by all cells in the brain [52]. However, the neural cell type primarily responsible for cholesterol synthesis shifts from development to adulthood (Figure 3). During embryogenesis, neurons are the primary producers of cholesterol. However, during postnatal myelination, the production site shifts to oligodendrocytes, and later in adulthood, it primarily transitions to astrocytes [51,52]. Astrocytes are considered the major neural cells taking over lipid production in the brain not only of cholesterol, but also of diacylglycerol (DAG) and triacylglycerol (TAG) [53]. Thus, in the adult brain, neurons and oligodendrocytes mainly take up lipids derived from astrocytes to support synaptic function [54] and myelination [53,55]. A simplified overview of lipid metabolism in the brain is depicted in Figure 3.

2.1.1. Cholesterol

The de novo cholesterol synthesis pathway is based on the acetyl-CoA pool that is converted to cholesterol in a multistep mechanism primarily in the endoplasmatic reticulum (ER) (Figure 2). The transport of cholesterol from astrocytes to neurons and oligodendrocytes is facilitated by apolipoprotein E (ApoE), also produced by astrocytes themselves [56]. Bound to ApoE, cholesterol is exported by ATP-binding cassette (ABCA1) transporters [57]. The cholesterol-ApoE complex is consequently endocytosed by low-density lipoprotein receptors (LDLR) expressed by neurons [58,59] and oligodendrocytes [60] (Figure 3). Within oligodendrocytes, cholesterol associates with the proteolipid protein (PLP) and is integrated into the myelin sheath during myelination [61,62].

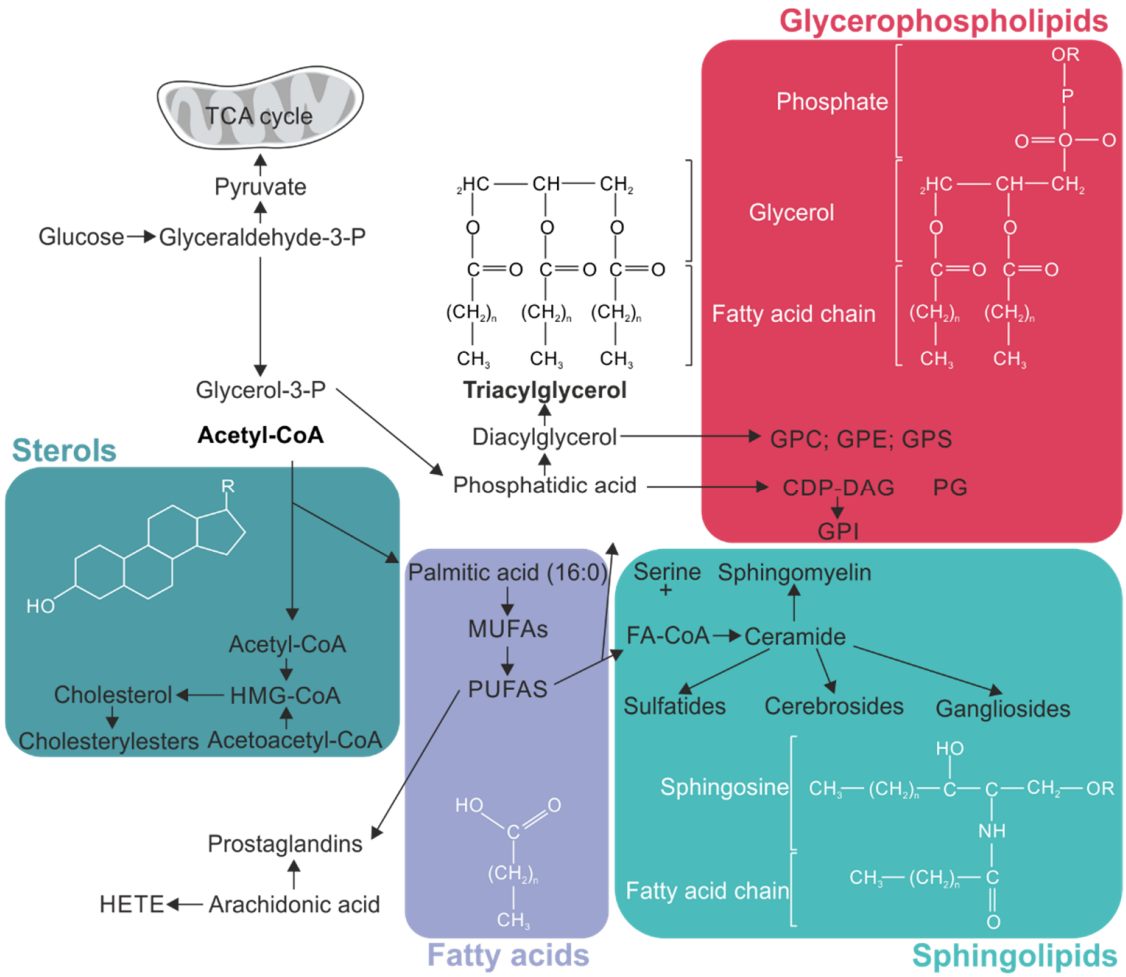

Figure 2. Overview of different lipid classes and their synthesis pathways. The major classes of lipids (sterols, fatty acids (FAs), sphingolipids, and glycerophospholipids) important for this review are depicted with their chemical structure and the key steps of their synthesis pathway. Eicosanoids, such as arachidonic acid, are classified as a type of FAs. CDP = cytidine diphosphate; CoA = Coenzyme A; GPC = glycerophosphocholine; GPE = glycerophosphoethanolamine; GPS = glycerophosphoserine; HETE = hydroxyeicosatetraenoic acids; HMG = β-hydroxy-β-methylglutaryl; MUFAs = monounsaturated fatty acids; P = phosphate; PUFAs = polyunsaturated fatty acids; TCA = tricarboxylic acid.

2.1.2. Fatty Acids

FAs are essential for various components of cell membranes and myelin, as well as for providing energy. Although FAs are able to cross the blood–brain barrier and pass through cellular membranes, neurons, oligodendrocytes, and astrocytes are able to synthesize the majority of required saturated and monounsaturated fatty acids (MUFAs) by themselves (reviewed by [63]). However, the brain and other organs severely lack the ability to produce polyunsaturated fatty acids (PUFAs) [64]. Thus, PUFAs need to be taken up by the diet [65]. FA synthesis takes place in the cytoplasm and the ER [66]. Besides serving as basis for the synthesis of complex lipids, FAs are stored as energy-rich TAGs in lipid droplets. Astrocytes are the most prominent cell type responsible for producing lipid droplets in the adult brain. However, neurons and oligodendrocytes also generate lipid droplets (as reviewed in [67]). Lipid droplets serve two important purposes: first, they help sequester free cytosolic FAs which, in the absence of lipid droplets, can be toxic to cellular structures like mitochondria by disrupting their membranes (reviewed by [68]); second, lipid droplets facilitate the transport of FAs into mitochondria, providing an essential energy supply during starvation and enabling β-oxidation [69,70]. In the brain, β-oxidation, the process

of degrading FAs, is primarily observed in astrocytes, and it is also present in neurons and oligodendrocytes [71].

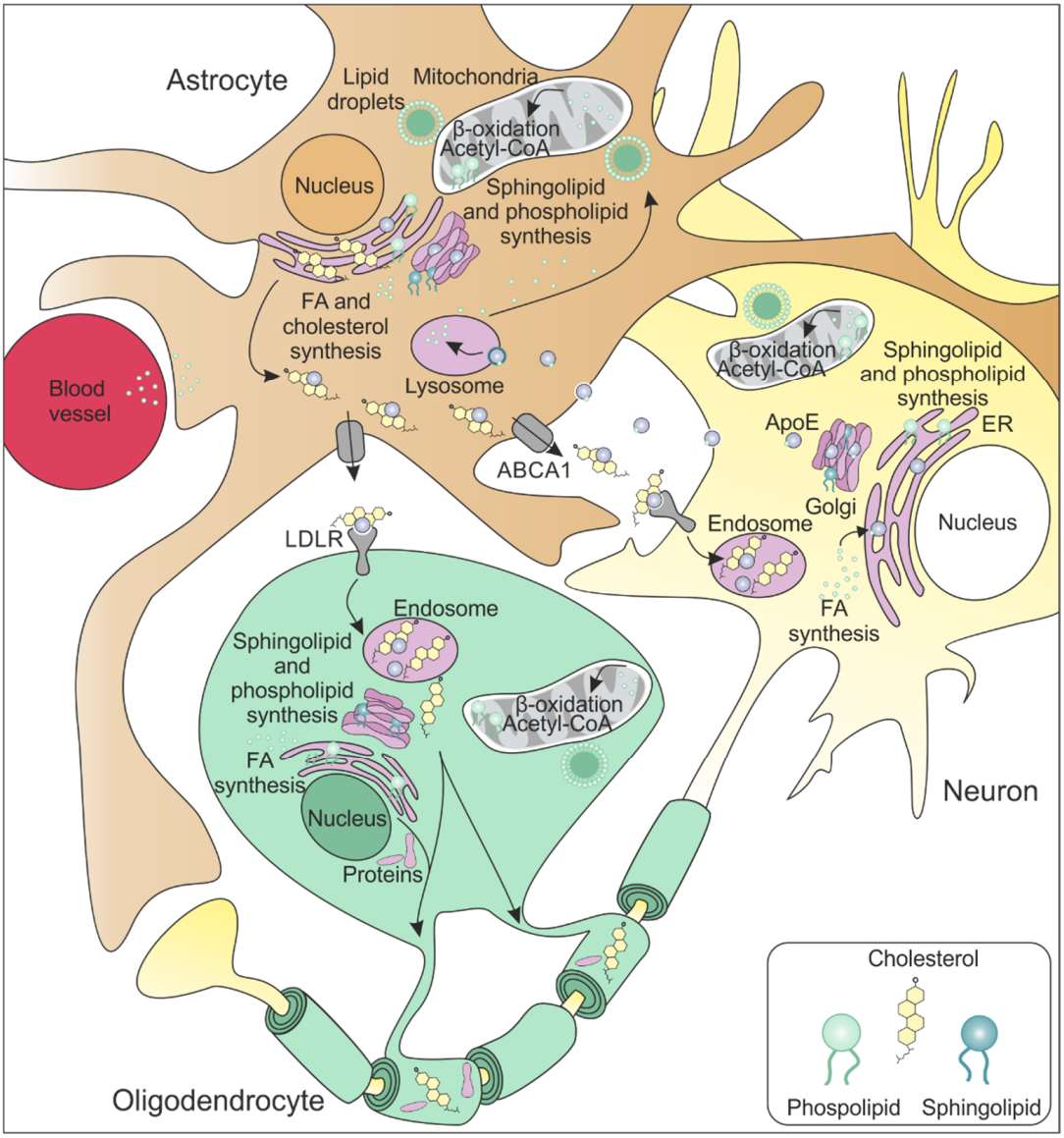

Figure 3. Lipid metabolism in the adult brain. All lipids are produced based on two main components: cholesterol and FAs. Cholesterol is synthesized primarily at the ER of astrocytes and is further transported to neurons and oligodendrocytes via ApoE and ABCA1 transporters. FAs, however, are produced by neurons, astrocytes, and oligodendrocytes. Additionally, FAs also bind to ApoE for their transport. FAs are used as a fuel source in β-oxidation predominantly by astrocytes, but also by neurons and oligodendrocytes. Alternatively, all neural cell types contain lipid droplets for storage. Finally, all cells are able to produce phospholipids and sphingolipids within the ER. ABCA1 = ATP-binding cassette transporter A1; ApoE = apolipoprotein E; ER = endoplasmatic reticulum; LDLR = low-density lipoprotein receptor.

2.1.3. Sphingolipids

Sphingolipids, including glycolipids such as gangliosides, cerebrosides, and sulfatides, require FAs for their production, particularly ceramide, which is subsequently incorporated into various complex sphingolipids, predominantly in the Golgi (reviewed by [72]).

2.1.4. Phospholipids

Phospholipids, the main component of biological membranes, are produced by all the major neural cells in the brain using FAs as biochemical building blocks. The synthesis of all classes of phospholipids takes place in the ER and is initiated by two common precursors: phosphatidic acid (PA) and DAG (reviewed by [73]).

3. α-syn and Lipids

α-syn was originally discovered in the nucleus and the presynaptic terminals [1], where it is involved in neurotransmission and synaptic plasticity [74]. Immediately after the discovery of α-syn within Lewy bodies [75], the lipid-binding properties of α-syn were described in numerous studies where α-syn was found to associate with synaptic membranes [76]. It displays a preference for binding to negatively charged head groups of anionic lipids. This interaction is mediated by the amphipathic N-terminal region of α-syn, which is rich in lysine residues [77]. Additionally, α-syn exhibits a specific affinity to the phospholipids phosphatidylethanolamine (PE), PA, phosphatidylinositol (PI), and ganglioside due to their acidic head groups, rather than to phosphatidylserine (PS) or phosphatidylglycerol (PG) [78–81]. Moreover, α-syn contains a cholesterol-binding site (residues 67–78) [82] as well as one for glycosphingolipids (residues 34–45) [83]. It also interacts with membranes, including myelin, with a preferential interaction with membranes containing unsaturated FAs [84]. Further, α-syn preferably binds to lipid raft domains of membranes [85]. Intracellularly, α-syn also associates with mitochondrial membranes [86], although the physiological role of this interaction is still unclear.

After α-syn is bound to a membrane, it forms an α-helical structure. Membrane binding of monomeric α-syn is mediated by two steps: (1) anchoring to the membrane with the N-terminal residues 3–25, and (2) a coil-to-helix transition of residues 26–97 that are responsible for the lipid binding and act as membrane sensors [87–89]. Physiologically, binding of α-syn to membranes and the consecutive formation of an α-helical structure are important for soluble N-ethylmaleimide-sensitive-factor attachment receptor (SNARE)-complex assembly [14,90].

The interaction of α-syn monomers with membranes was investigated extensively; however, binding of α-syn multimers to membranes remains elusive. While monomer binding to the membrane leads to the formation of an α-helical structure, multimers do not change their secondary structure upon membrane binding [16,91]. Moreover, different α-syn multimers species with distinct structures and membrane interaction properties exist [16,92]. Nevertheless, similar to monomeric α-syn, multimers prefer binding to lipids having acidic, negatively charged head groups [78,93] and lipid raft domains of membranes [78].

There are different mechanisms underlying the interaction of α-syn and lipids in PD, which will be further elaborated in this review: (1) multiple alterations in lipid classes and metabolism have been observed in PD patients and PD models affecting the aggregation propensity of α-syn; (2) missense mutations of α-syn identified so far in familial monogenic PD are localized at the *N*-terminus, where lipid binding takes place, and indeed change its lipid-binding properties; and (3) PTMs of α-syn change its binding properties toward different forms of lipids.

3.1. Alterations of Lipids and Their Metabolism in PD

PD is frequently characterized as a proteinopathy; however, emerging evidence suggests that it might be described as a lipidopathy, or most likely as a combination of both (reviewed by Fanning and colleagues [94]). An analysis of three genome-wide association studies (GWAS) revealed four main biological processes relevant for PD—oxidative stress response, endosomal-lysosomal functioning, ER stress response, and immune response activation [95]. Interestingly, lipids and lipoproteins are key to all four processes [95]. Furthermore, α-syn is involved in several lipid metabolic pathways, including FA [96–98], TAG [99], and cholesterol metabolism [100]. Indeed, alterations in lipid metabolism have

been found throughout different metabolic pathways, including FA [101,102], cholesterol [103,104], sphingolipid [105,106], and glycerophospholipid metabolism [102].

3.1.1. FA Metabolism

Recently, it was demonstrated that α-syn overexpression in yeast-, rodent-, and induced pluripotent stem cell (iPSC)-derived neurons increased the formation of MUFAs, specifically oleic acid, which subsequently enhanced α-syn toxicity by altering the equilibrium of the membrane bound to soluble α-syn [107]. Coincidentally, neuronal and plasma levels of PUFAS are increased in PD patients [108,109]. Along this line, α-syn oligomerization is regulated by PUFA levels [110]. Especially docosahexaenoic acid (DHA) and α-linolenic acid (ALA) are able to bind α-syn and elevate its aggregation at low ratios, while reducing the aggregation at high ratios.

3.1.2. Cholesterol Metabolism

Several oxysterols are increased in PD brains [111], and, importantly, cholesterol accumulates in lysosomes of glucocerebrosidase (*GBA*)-PD patients [112]. *GBA* mutations are associated with monogenic PD. Moreover, an increased brain cholesterol level was detected in methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice, which is a neurotoxin-induced PD model, exacerbating dopaminergic loss in the striatum and substantia nigra. Furthermore, a high-cholesterol diet alleviated motor functions in the animals [113]. Similarly, high cholesterol levels in SH-SY5Y-differentiated neurons led to decreased dopaminergic neuronal survival [114]. Thus, selectively targeting cholesterol synthesis in the CNS might be a promising therapeutic approach.

3.1.3. Sphingolipid Metabolism

Notably, several enzymes involved in sphingolipid metabolism are associated with PD. Emerging evidence implies that distinct variants within the genes for *GBA* [115] and serine palmitoyltransferase (*SPTLC1*) [116] are important risk factors for developing PD. Moreover, sphingolipids can associate with cholesterol to form lipid rafts involved in signal transduction and membrane trafficking [117], while sphingolipid metabolites such as ceramides and sphingosine-1-phosphate play important roles in cell proliferation, differentiation and apoptosis [118,119]. Thus, pharmaceutical intervention in the sphingolipid metabolic pathway might be useful for intervening in pathological processes in PD.

3.1.4. Glycerophospholipid Metabolism

Farmer and colleagues observed that 17 glycerophosphocholine and lysophosphatidylcholine species were significantly reduced in the substantia nigra of 6-hydroxydopamine (6-OHDA)-lesioned PD mice using high-performance liquid chromatography coupled with mass spectrometry [120]. Specifically, the lysophosphatidylcholine species (16:0/0:0) and (18:1/0:0) were increased in this mouse model, which were also found to be increased in human fibroblasts deficient in *PARKIN*, being a risk factor for monogenic PD [121]. Both lysophosphatidylcholine species contribute to inflammatory signaling in the pathogenesis of PD [122]. Moreover, the *PARKIN*-mutant fibroblasts exhibit higher levels of glycerophosphoserine, glycerophosphoinositol, and gangliosides GM2 and GM3 [121]. Elevated levels of glycerophosphoinositol and glycerophosphoserine may cause defects in mitochondrial turnover [121]. Additionally, PE was found to be reduced in the substantia nigra and midbrain of PD patients [123,124]. In yeast cells, PE deficiency has been linked to the disturbance of α-syn homeostasis, highlighting a potential functional role in the pathology of PD [125]. To produce glycerophospholipids, DAGs are needed. Moreover, DAG is able to act as second messenger in nuclear lipid signaling. Using liquid chromatography–mass spectrometry, Wood and colleagues identified increased levels of DAGs, with both monounsaturated and polyunsaturated hydrocarbon chains, in the frontal cortex of PD patients correlating with the severity of neuropathology [126]. Moreover, they observed a significant decrease in the levels of PA 16:0 in PD patients [126].

3.2. Effects of Missense Mutations on the Binding Capacity of α-syn to Lipids

While membrane binding of α-syn may be important for its physiological function, abnormal alterations of α-syn such as overexpression, aggregation, or mutation may have pathological effects upon membrane binding. For example, association of abnormal α-syn with mitochondrial membranes has detrimental effects [127,128]. In dopaminergic and primary neurons overexpressing α-syn, mitochondrial impairment associated with an increase in oxidative stress and reduced cell viability was observed [128,129]. Typically, α-syn binds to membranes with its first 25 amino acid residues at the N-terminus when the lipid-to-protein ratio is high. However, a reduction in the lipid-to-protein ratio causes α-syn to interact with the membrane by binding with the first 97 amino acid residues [130]. Thus, the N-terminal domain of the α-syn gene, where missense mutations identified so far in familial PD have been found, is of special interest.

Missense mutations within the N-terminal region of the *SNCA* gene have detrimental effects on the binding capacity of α-syn to lipids. Here, we present a summary of the impact of point mutations in the *SNCA* gene (V15A, A18T, A29S, A30P, E46K, H50Q, G51D, A53E, A53T, A53V) associated with monogenic PD, focusing on their effects on α-syn aggregation and, in particular, their interaction with lipids (Table 1). The effect of the mutations on the aggregation of α-syn is reviewed more comprehensively elsewhere [131].

Table 1. Summary of PD-related point mutations of α-syn and their effects on its binding capacity to membranes.

Mutation	Effects on Lipid Membranes	Ref.
V15A	• decreased affinity to phospholipids accompanied by an increased aggregation and seeding activity	[132]
A18T	• less toxic than wildtype α-syn • altered triglycerides reduce α-syn toxicity	[133]
A29S	• less toxic than wildtype α-syn • altered triglycerides decrease α-syn toxicity • enhanced acetylation or SUMOylation are protective against α-syn toxicity	[133]
A30P	• reduced binding to membranes • formation of metal ion-induced pathologic oligomers was increased • fibril formation is slower in A30P mutants compared to wildtype • interaction of α-syn with lipid rafts is hindered	[85,134–136]
E46K	• increased lipid interactions and disrupted membrane selectivity • increased N-to-C interactions and coil compactness in the structure of lipid-unbound α-syn • conformation of α-syn is altered upon interaction with a curved lipid bilayer	[137,138]
H50Q	• enhances α-syn aggregation and toxicity without affecting the binding capacity to lipid membranes	[139]
G51D	• decreased binding to lipid membrane • fibril formation was accelerated	[136]
A53E	• α-syn exhibits a low lipid binding capacity compared to wildtype	[140]

Table 1. *Cont.*

Mutation	Effects on Lipid Membranes	Ref.
A53T	• does not change the binding capacity of α-syn to membranes • formation of metal ion-induced pathologic oligomers and fibril formation are increased • α-syn monomers cause membrane thinning and facilitate the interaction with artificial lipid rafts • iron-mediated oligomers do not impair the membrane, but facilitate the interaction with artificial lipid rafts • no effect on the interaction of α-syn with lipid rafts	[85,136,141,142]
A53V	• low binding affinity to membranes compared to wildtype • less toxic than wildtype α-syn • altered triglycerides reduce α-syn toxicity • enhanced acetylation or SUMOylation are protective against α-syn toxicity	[133,140]

A recently discovered V15A mutation led to alterations in the binding capacity of α-syn to lipids in vitro [132]. V15A-mutated α-syn showed a decreased affinity to phospholipids accompanied by an increased aggregation property and seeding activity compared to wildtype α-syn [132].

A18T and A29S are less toxic than wildtype α-syn in yeast [133]. Moreover, yeast strains with altered triglycerides reduce α-syn toxicity in both variants [133].

A reduced binding to membrane lipids was observed in the A30P variant in vitro [134] and in vivo [135]. Fibril formation was slower compared to wildtype α-syn in the A30P variant [136]. Interestingly, lipid raft association is required for the synaptic localization of α-syn, and the interaction of α-syn with lipid rafts is hindered by the A30P mutation [85].

It is additionally noteworthy that alterations at the N-terminal glutamate residues appear to exert a significant influence on the interaction between α-syn and lipids. Several studies have demonstrated that three glutamate-to-lysine mutations, namely, the pathogenic mutation E46K and two additional artificial mutations, E35K and E61K, in different combinations ("1K": E46K; "2K": E35K, E46K; and "3K": E35K, E46K, E61K) enhance lipid interactions and disrupt membrane selectivity [137,138]. In these studies, the lipid-binding and lipid-remodeling abilities of "3K" were characterized. Nuber and colleagues first observed that E46K mutants increase N-to-C interactions and coil compactness in the structure of the lipid-unbound protein. Moreover, the conformation of α-syn was also affected upon interaction with a curved lipid bilayer in the E46K-like mutants. Interestingly, glutamate-to-lysine mutations mildly increased the affinity for curved membranes and caused a progressive loss of curvature selectivity [137].

The H50Q mutation enhances α-syn aggregation and toxicity without affecting the binding capacity to membranes in vitro [139,143].

In the G51D variant, a reduced binding to membrane lipids was detected in vitro [134] and in vivo [135]. Furthermore, the formation of metal ion-induced pathologic oligomers was increased, and fibril formation was accelerated in this variant [136].

While fibril formation was increased in the A53T variant [136], the binding capacity of α-syn to membranes was not changed [141]. Perissinotto and colleagues analyzed the interaction of A53T α-syn specifically with artificial lipid bilayers mimicking lipid rafts [142]. They demonstrated that distinct monomeric and multimeric α-syn species interact differently with the artificial lipid rafts. The α-syn monomers caused membrane thinning, while iron-mediated oligomers did not impair the membrane. In both aggregation states, the A53T variant facilitated the interaction with membrane lipids [142].

Furthermore, recent studies have shed light on a potential impact of α-syn mutation on retromer-mediated endosomal trafficking. The proposition arises from the identification of mutations in the retromer gene VPS35, known to cause late-onset PD [144]. Retromer is a multi-subunit protein complex coating the cytosolic site of early endosomes, and it plays a pivotal role in endosomal trafficking and sorting [145]. Notably, a recent yeast model study provided mechanistic insights by revealing that the A53T α-syn mutation specifically reduces retromer-mediated trafficking of the conserved membrane-bound proprotein convertase Kex 2 [146]. This disruption might be caused by alterations in the binding ability of the A53T α-syn to the anionic phospholipid phosphatidylinositol 3′-phosphate (PI3P) in the endosomal membrane [146].

Surface plasmon resonance spectroscopy suggests that the A53V and A53E variants exhibit a low binding affinity to membranes compared to wildtype [140]. This low membrane binding capacity may be due to the nonpolar nature of valine which does not interact with the negatively charged membrane surface [140].

3.3. Binding Capacity of Posttranslational Modified α-syn to Lipids

Numerous studies have demonstrated that the interaction between α-syn and membranes is modified by PTMs. Despite its small size, α-syn undergoes a variety of PTMs including phosphorylation, acetylation, nitration, ubiquitination, truncation, glycosylation, and glycation (reviewed by [147]) (Figure 1). PTMs regulate the physiological function of α-syn but may also be linked to the pathogenic potential of the protein. Specifically, PTMs significantly influence the structure and aggregation propensity of α-syn as well as its interactions with lipids. The effects of PTMs on protein aggregation and toxicity have been extensively reviewed elsewhere [148–151]. Here, we in particular address the impact of PTMs on α-syn-lipid interactions. An overview of the detailed effects of PTMs on α-syn-lipid interactions is depicted in Table 2.

Table 2. Summary of PD-related point mutations of α-syn and their effects on its binding to membranes.

PTM	Position	Effects on Membranes	Ref.
Phosphorylation	Y39	• diminished lipid binding of α-syn and increased axonal pathology in transgenic PD mice	[152]
	S87	• conformational change in membrane-bound α-syn • decreased affinity to lipid vesicles • reduced aggregation of α-syn	[153]
	S129	• reduced binding of α-syn monomers and Fe^{3+}-induced oligomers to lipid vesicles • fewer α-helical structures, decreased binding, and disruption of lipid vesicles • no difference in membrane binding to synaptosomes • in the A30P variant, α-syn membrane binding was increased, leading to disruption of membranes • in the A53T variant, binding to membranes was reduced	[154–156]

Table 2. *Cont.*

PTM	Position	Effects on Membranes	Ref.
Acetylation	M1	• increased affinity of α-syn to membrane binding without structural alterations	[157]
Nitration	Y39	• less α-helical structure formation upon lipid vesicle binding • disrupted binding affinity of α-syn to membranes	[158]
	Y125	• less α-helical structure formation upon lipid vesicle binding • disrupted binding affinity of α-syn to membranes	
	Y133, Y136	• disrupted binding affinity of α-syn to lipid vesicles	
Ubiquitination	K6, K23, K43, K96	• no alterations in secondary structure of α-syn upon lipid binding	[159,160]
Truncation	1–100	• less potential inducing curvature upon membrane binding compared to full-length protein	[161]
	1–103	• produces mature fibrils in the presence of phospholipid vesicles	[162]
	1–115	• upon lipid binding, 1–115 truncated α-syn shows higher α-helical levels compared to full-length α-syn facilitating lipid binding	[163]
	1–119	• aggregates faster than full-length α-syn in the presence of phospholipid vesicles	[162]
	1–120	• reduced α-syn fibrillation and increased lipid binding predisposition upon methylphenidate treatment	[164]
	1–121	• similar aggregation to full-length α-syn in the presence of phospholipid vesicles • decreased ability to distort phospholipid membranes • higher toxicity compared to full-length α-syn	[165]

Table 2. *Cont.*

PTM	Position	Effects on Membranes	Ref.
Glycosylation	T72	• reduction in fibril formation, aggregation, and toxicity of monomeric α-syn in vitro, while binding affinity to lipid vesicles was unaltered	[166]
	T75	• reduction in fibril formation, aggregation, and toxicity of monomeric α-syn in vitro, while binding affinity to lipid vesicles was unaltered	
	T81	• reduction in fibril formation, aggregation, and toxicity of monomeric α-syn in vitro, while binding affinity to lipid vesicles was unaltered	
	S87	• reduction in fibril formation, aggregation, and toxicity of monomeric α-syn in vitro, while binding affinity to lipid vesicles was unaltered	
	T72, T75, and T81	• inhibited the α-helical structure of α-syn upon membrane binding	
Glycation	Lysine	• reduced binding affinity towards sodium dodecyl sulfate (SDS) micelles without affecting the α-helical structure of α-syn • disruption of lipid vesicles upon α-syn binding	[167]

3.3.1. Phosphorylation

Phosphorylation is mediated by kinases [168] and reversed by phosphatases, respectively [169]. Phosphorylation is an esterification reaction involving the attachment of a phosphoryl group to the hydroxyl group of the side-chains of specific amino acids such as serine, tyrosine, and threonine [170]. α-syn is most commonly phosphorylated on serine [153,171] and tyrosine residues [172–175]. In particular, phosphorylated α-syn at S87 [153] and S129 [171] is enriched in Lewy bodies [176]. S129 is even enriched by 90% [176]. The current literature presents divergent findings concerning the adverse and beneficial effects of phosphorylation on the interaction of α-syn with lipids. Phosphorylation on S87 and S129 was shown to alter the conformation of membrane-bound α-syn by destabilizing the α-helical conformation, leading to a decreased affinity to lipid vesicles [153–155]. However, conflicting results from Samuel and colleagues demonstrated no difference in membrane binding to synaptosomes upon phosphorylation at S129 [156].

3.3.2. Acetylation

Acetylation of α-syn is mediated by irreversible addition of an acetyl group to the amine group of the N-terminus (methionine) by histone acetyl transferase, resulting in a decreased positive charge [177]. It has been estimated that over 80% of α-syn molecules are acetylated [171]. Interestingly, acetylated α-syn is found to be enriched in Lewy bodies and affected brain regions from PD patients [171,178]. N-terminal acetylation induced α-helical structures of monomeric, soluble α-syn and thereby decreased its aggregation rates [179]. Due to the decreased positive charge upon acetylation, binding to negatively charged phospholipid head groups is influenced in a way that the affinity of α-syn for membrane binding is enhanced [157], while its structural properties were not altered [157]. In addition, N-terminal acetylated α-syn localizes to highly curved, ordered membranes

with a preference for lipid rafts under cell-free conditions [180]. The effect of site-specific acetylation as well as its neurotoxic potential need to be further investigated.

3.3.3. Nitration

Nitration is an irreversible aversive PTM that occurs on tyrosine residues, in particular in the presence of oxidative stress [181]. This PTM has been associated with several neurodegenerative diseases, including PD [181,182]. Nitrated α-syn was not only enriched in Lewy bodies [181,183], but also led to increased oligomerization of α-syn [184] as well as cytotoxicity in cells [185] and in the substantia nigra of rats [186]. Furthermore, α-syn nitration induced a reduced formation of α-helical structures and a decreased binding affinity of α-syn to negatively charged lipid vesicles [158]. Specifically, after nitration at Y39 or Y125, α-helix formation upon α-syn binding to lipid vesicles was diminished, and fibrils showed a distinct morphology compared to wildtype α-syn [158]. Moreover, nitration of Y125, Y133, and Y136 interfered with the binding affinity of α-syn to lipid vesicles [158].

3.3.4. Ubiquitination

Ubiquitination is a reversible PTM important for intracellular protein homeostasis. This type of PTM involves the attachment of ubiquitin, a small regulatory protein consisting of 76 amino acids, to lysine residues of a target protein through an isopeptide bond. This process is essential for targeted degradation and is mediated by three enzymes: the ubiquitin-activating enzyme E1, the ubiquitin-conjugating enzyme E2, and the ubiquitin ligase E3 [187]. α-syn contains nine lysine residues potentially being ubiquitinated (K6, K10, K12, K21, K23, K32, K34, K43, and K96). Ubiquitinated α-syn is present in Lewy bodies [188] and promotes fibril formation to a different degree depending on the position of ubiquitination in α-syn [189]. In detail, ubiquitination at K10 and K23 displayed similar fibril levels with altered kinetics of formation compared to wildtype α-syn, while K6, K12, and K21 slightly reduced fibril formation, and K32, K34, K43, and K96 reduced fibril formation more severely [189]. Moreover, it was demonstrated that ubiquitination at K6, K23, K43, and K96 had no effect on the α-helical secondary structure of α-syn after binding to lipid vesicles [159,160]. Alterations of the lipid-binding properties of α-syn upon ubiquitination are still largely unknown. It was suggested that ubiquitination of lysine residues within the N-terminal KTKEGV repeat motifs may prevent membrane binding of α-syn [190].

3.3.5. Truncation

Truncation of proteins occurs due to a dysfunctional protein homeostasis machinery leading to incomplete metabolization of α-syn by a number of enzymes, such as plasmin [191], neurosin [192], cathepsin D [193], caspase 1 [194], calpain 1 [195], and other proteinases [196]. α-syn is irreversibly truncated at the N- or C-terminus and present in over 15% of α-syn in Lewy bodies [197]. An overview of the possible truncations of α-syn is reviewed by Sorrentino and colleagues [198]. Notably, N-terminally truncated α-syn variants, 5–140, 39–140, 65–140, 66–140, 68–140, and 71–140, and C-terminally truncated α-syn variants, 1–101. 1–103, 1–115, 1–122, 1–124, 1–135, and 1–139 have been detected in different brain regions of PD patients so far [171,197,199]. Since the N-terminal domain of α-syn determines its lipid-binding capacity, truncation within this site may reduce physiological membrane binding. In general, truncation of α-syn is able to induce aggregation and toxicity in vitro [200] and in vivo [201] by increasing the spread of α-syn through synaptically coupled neuroanatomical tracts [202]. The impact of C-terminal truncations of α-syn on the aggregation of the protein was investigated in more detail, since oligomerization and aggregation of α-syn is mediated mainly by the C-terminus [162]. In any case, C-terminal truncation of α-syn reduces its solubility and affects its membrane-binding properties as well leading to site-specific neurotoxic effects [161–165].

3.3.6. Glycosylation

Glycosylation is a type of reversible enzyme-dependent PTM, in which N-acetylglucosamine (GlcNAc), an amide derivative of glucose, is transferred from uridine diphosphate-GlcNAc (UDP-GlcNAc) to the hydroxyl group of threonine or serine residues of a protein [203]. The addition of GlcNAc is catalyzed by O-GlcNAc-transferase, while its removal is mediated by O-GlcNAcase [203]. So far, nine residues of α-syn (T33, T44, T54, T59, T64, T72, T75, T81, and S87) have been reported as potential sites of glycosylation [204–206]. In general, glycosylation of α-syn at various position reduces aggregation and toxicity of α-syn [207,208], though it does not affect binding of α-syn to phospholipid membranes [166]. Interestingly, triple glycosylation at T72, T75, and T81 inhibited theα-helical structure of α-syn upon membrane binding [166]. Notably, glycosylation has an impact on other PTMs. In particular, glycosylation of α-yn was shown to prevent its phosphorylation at S129, whereas it promotes phosphorylation at S87 [207]. No aversive effects have been reported so far for glycosylation of α-syn.

3.3.7. Glycation

Glycation of α-syn is based upon a non-enzymatic reaction of its lysine residues with reactive carbonyl species as a side product of glycolysis, known as glycation [209]. One of the most prevalent end products of glycation is Nε-(carboxyethyl)lysine (CEL) [210]. It was demonstrated that glycation potentiates α-syn-associated neurodegeneration in PD [211]. Recently, it was observed that CEL formation on α-syn reduces its binding affinity towards sodium dodecyl sulfate (SDS) micelles used as a membrane mimic without affecting the α-helical structure of α-syn [167]. In PD, glycation of α-syn is implicated in protein aggregation and Lewy body formation, while site-specific effects are still poorly understood.

4. Therapeutic Potential

Due to the importance of the interaction of α-syn with lipids, strategies are emerging to modulate this interaction. Several therapeutic approaches have already been investigated and are currently being tested in multiple clinical trials (Table 3). A schematic of the bidirectional interaction of α-syn and lipids and the possible therapeutic interventions is depicted in Figure 4.

Table 3. Summary of current therapeutic approaches investigated experimentally or in clinical trials. https://www.clinicaltrials.gov, accessed on 3 August 2023.

Compound	Target	Effect	Clinical Trial	Clinical Trial PD	Ref.
Lovastatin	HMG-CoA reductase	reduces α-syn accumulation and its phosphorylation in vitro in HEK293 cells, SH-SY5Y cells, and in primary human neurons and in vivo in different transgenic mouse models that neuronally overexpress human α-syn	rheumatoid arthritis, cancer, etc.	Phase II	[212–214]
Simvastatin	HMG-CoA reductase	prevents MPTP-induced striatal dopamine depletion and protein tyrosine nitration in mice, and protects dopaminergic neurons in the substantia nigra, attenuates the expression of proinflammatory molecules, and improves motor deficits in the MPTP model of PD	hyper-lipidemia, diabetes, MS, etc.	Phase II	[212,215,216]

Table 3. *Cont.*

Compound	Target	Effect	Clinical Trial	Clinical Trial PD	Ref.
Myriocin	de novo ceramide synthesis	reduced oxidative stress and inflammation and increased vesicular trafficking in SH-SY5Y cells treated with α-syn fibrils	no	no	[217]
Ellagic acid	α-syn	polyphenolic compound that has an inhibitory effect toward oligomerization and fibrillation of α-syn in vitro, reduces α-syn aggregation, and increases cell survival	prostate cancer phase III	no	[218]
Squalamine	competitive of α-syn	specifically inhibits the initiation of aggregation of α-syn and alleviates its toxicity in neuronal cells and in a *Caenorhabditis elegans* model of PD	macular degeneration phase II and III	no	[219]
Nilotinib	α-syn kinase c-Abl	enhanced clearance of α-syn, reduced neurotoxicity, and improved motor behavior in a mouse model of PD	AD phase 3, leukemia, etc.	no	[220]
MC1568	class IIa histone deacetylases	increased neurite density and cell survival and protected against the neurotoxin-treated SY5Y cells	cancer	no	[221]
VX-765	caspase-1	reduces neurodegeneration, motor symptoms, and neuroinflammation in a mouse model of MSA	no	no	[222]
Arachidonic acid	α-syn	essential FA that induces the formation of ordered, α-helical structured α-syn multimers being resistant to fibrillation	autism, fibrosis, diabetes, etc.	no	[223]
Niacin/Nicotin-amide	Poly (ADP-ribose) polymerase	precursor of NADH and cofactor of mitochondrial enzymes that protects from MPTP-induced neurotoxicity in mice and prevents mitochondrial dysfunction in a cellular model and improves motor behavior in a *Drosophila* model of PD	hyperlipidemia, myopathy, etc.	interventional study	[224–226]
Deferiprone	ferric ions	iron chelator that reduces iron depositions in the substantia nigra accompanied by alleviated motor deficits in a clinical trial in early PD	HIV, ALS, heart disease, etc.	failed	[227]

4.1. Enzymes Involved in Lipid Metabolism

One potential approach is targeting activities of proteins involved in lipid metabolism, including enzymes and lipid transporters. For example, Vincent and colleagues were able to ameliorate α-syn-induced cytotoxicity by inhibiting the highly conserved enzyme stearoyl-CoA desaturase in iPSC-derived neuronal models [228]. This enzyme catalyzes the rate-limiting step in the formation of MUFAs; thus, inhibition of this enzyme reduces the levels of unsaturated membrane lipids [229]. Moreover, inhibition of stearoyl-CoA desaturase was able to reduce the formation of α-syn inclusions in the "3K" variant of the E46K mutation [230]. This result was confirmed by Nuber and colleagues in cultured human neurons, in "3K" neural cultures, and "3K" α-syn mice [42].

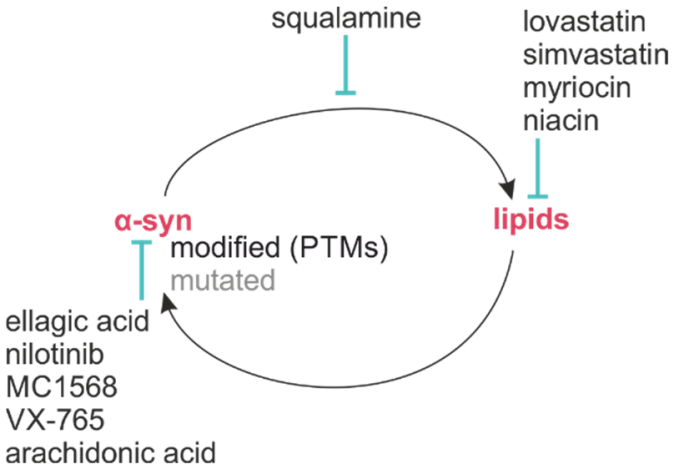

Figure 4. Bidirectional interaction of α-syn and lipids. Modifications of α-syn via mutation or PTMs can alter lipid-binding properties, while changes in lipid composition or metabolism alter pathological properties of α-syn. Moreover, different therapeutics may be used to modulate α-syn and lipids within the CNS, or the interaction between both.

Along this line, inhibition of the key enzymes within the cholesterol biosynthesis pathway induced accumulation of 8, 9-unsaturated sterols driving oligodendrocyte formation and remyelination [231]. For example, Lovastatin reduces cholesterol levels by inhibiting HMG-CoA reductase, which catalyzes the rate-limiting step in the cholesterol synthesis pathway [232]. Thereby, Lovastatin reduces α-syn accumulation and its phosphorylation in vitro in HEK293 cells, SH-SY5Y cells, and in primary human neurons [212,213] and in vivo in different transgenic mouse models that neuronally overexpress human α-syn [214]. Similarly, Simvastatin or other statins can be used as therapeutic approaches [212].

Furthermore, the inhibition of the de novo ceramide synthesis by myriocin, an inhibitor of serine palmitoyltransferase, reduced oxidative stress and inflammation and increased vesicular trafficking in SH-SY5Y cells treated with α-syn fibrils [217].

In summary, these observations suggest that inhibition of important enzymes participating in lipid metabolism may be able to prevent α-syn-mediated toxicity. Based on this evidence, development of inhibitors specifically targeting these enzymes is emerging as potential therapeutic strategy for PD and other synucleinopathies.

4.2. Membrane Binding of α-syn

Another possibility is to modulate binding of altered α-syn to membranes, for example, by using competitive compounds. It has been described that polyphenolic compounds compete effectively with α-syn for membrane binding and are thus considered a strong potential therapeutic candidate for PD and other synucleinopathies [219]. One polyphenolic compound that has an inhibitory effect toward α-syn oligomerization and fibrillation in vitro is ellagic acid [218]. Hence, α-syn aggregation was reduced, and cell survival increased [218]. Another molecule is squalamine [219], an antimicrobial aminosterol originally discovered in 1993 in the dogfish shark, *Squalus acanthias* [233]. Indeed, squalamine carries a net positive charge and shows a high binding affinity for anionic phospholipids [234]. By competing with α-syn for binding to the membranes, squalamine specifically inhibits the initiation of the aggregation process of α-syn [219]. Thus, it alleviates the toxicity of α-syn oligomers in neuronal cells and in a *Caenorhabditis elegans* model of PD [219].

4.3. PTMs

Since PTMs modify the interaction of α-syn with lipids, interfering with PTM pathways is considered as a novel therapeutic target for PD. Modulation of phosphorylation of α-syn is achieved by pharmacological modulation of kinases and phosphatases [235–238].

For example, using nilotinib, a Food and Drug Administration (FDA)-approved cancer treatment, to inhibit the kinase c-Abl leads to reduced phosphorylation, enhanced clearance of α-syn, reduced neurotoxicity, and improved motor behavior in a mouse model of PD [220].

Another possibility is to enhance the phosphatase activity of phosphoprotein phosphatase 2A (PP2A) by increasing methylation of the enzyme to decrease α-syn phosphorylation at S129, leading to decreased α-syn aggregation and toxicity in mice [239].

To target ubiquitination, antibodies inhibiting the ubiquitin E3 ligase were developed, which decreased the expression and aggregation of α-syn and improved cell viability in vitro [240].

Pharmacological inhibition of class IIa histone deacetylases (HDACs), which are important enzymes for the modulation of α-syn by acetylation, using MC1568 increased neurite density and cell survival and protected against the neurotoxin-treated SY5Y cells [221]. However, effects on the binding capacity of α-syn to lipids are not yet known.

Truncations of α-syn may be reduced by immunotherapy or pharmacological inhibition of caspases [222,241]. So far, therapeutic approaches concentrate on C-terminal truncations. One example is VX-765 that inhibits caspase-1, which cleaves α-syn at D121, thereby improving motor symptoms, neurodegeneration, and neuroinflammation in a transgenic mouse model of MSA [222].

Since glycosylation of α-syn reduces α-syn aggregation, pharmacological inhibition of O-GlcNAcase increases the glycosylation levels of α-syn, resulting in a lower aggregation of α-syn [242]. Moreover, glycosylation inhibits calpain-mediated C-terminal α-syn truncations, thus reducing aggregation of α-syn as well. Similarly, glycosylation competes with phosphorylation in targeting hydroxyl groups on serine and threonine residues, thereby protecting α-syn from increased aggregation caused by phosphorylation [207]. Along this line, accumulation of S129 α-syn was reduced in the substantia nigra in an adeno-associated virus-generated A53T mouse model of PD by pharmacological inhibition of O-GlcNAcase [243].

4.4. Neuroprotective Lipids

Given the neuroprotective effects of some lipids, their direct administration is emerging as a promising therapeutic strategy to alleviate α-syn-mediated cytotoxicity. One example is arachidonic acid, an essential FA that induces the formation of ordered, α-helical structured α-syn multimers being resistant to fibrillation [223]. Another target are PUFAs, especially omega-3, an important component of membranes (reviewed by [244]). Among other positive effects on PD, omega-3 PUFAs inhibit neuroinflammation, maintain α-syn degradation, and improve membrane fluidity (reviewed by [244]), thus emerging as a therapeutic strategy. Another potential nutrient is niacin/nicotinamide, a precursor of NADH and cofactor of mitochondrial enzymes [245,246]. Nicotinamide has already been linked to neuroprotection in PD and has shown to protect against MPTP induced neurotoxicity in mice [224,225]. Furthermore, nicotinamide prevented mitochondrial dysfunction in a cellular model and improved motor behavior in a *Drosophila* model of PD [226].

4.5. Environmental Factors

Since a variety of environmental factors affect lipid homeostasis, targeting these factors is a promising approach. Dietary nutrients are the main substrates of the gut microbiota and can have an impact on the composition and metabolic activity of these microbiota (reviewed by [247]). These processes lead to the production of intermediate metabolites affecting host energy homeostasis, glucose, and lipid metabolism [248]. For example, nutrition rich in antioxidants might be neuroprotective in PD [249]. Since increased lipid droplet formation in dopaminergic neurons has been correlated with iron accumulation, pharmacological administration of iron chelators such as deferiprone arises as a therapeutic strategy. Deferiprone reduces iron depositions in the substantia nigra accompanied by

alleviated motor deficits in an initial clinical trial in early PD [227]. However, it could not be confirmed lately.

Overall, lipids and their metabolism in the CNS contribute profoundly to the identification of novel therapeutic interventions for PD.

5. Conclusions

α-syn has been associated with PD and other synucleinopathies for over two decades. However, this discovery has not yet led to the development of effective and causative therapeutic approaches. Thus, this review focuses on an important aspect of α-syn, namely its interaction with lipids in the CNS. On the one hand, alterations of lipids and different metabolic pathways influence the function and the dysfunction of this protein. On the other hand, the interference of α-syn with lipids is changed in PD due to different factors, such as point mutations within the lipid-binding region (Table 1) or PTMs (Table 2). Focusing on PTMs, researchers have identified compounds that modulate PTMs, which reduce the aggregation of α-syn and modify its binding properties to membranes. Moreover, targeting enzymes involved in various stages of lipid metabolism and exploring the neuroprotective potential of certain lipids have emerged as promising therapeutic avenues. Efforts toward a more detailed characterization of α-syn interventions in lipid metabolism and function will lead to a more in-depth assessment of the protein's implications for therapeutic purposes. In conclusion, investigation of the bidirectional interaction of α-syn with lipids is advancing our comprehension of the pathology in PD and other synucleinopathies, suggesting that these disorders are not solely a consequence of protein pathology but also influenced by lipid-related processes. Thus, PD is not simply a synucleinopathy but rather a meta-disease composed of several different aspects.

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