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Perspective

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Parkinson disease is a fatty acidopathy

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Abstract

On the basis of extensive mechanistic research over three decades, Parkinson disease (PD) and related synucleinopathies have been proposed to be combined proteinopathies and lipidopathies. Evidence strongly supports a physiological and pathogenic interplay between the disease-associated protein α-synuclein and lipids, with a demonstrable role for lipids in modulating PD phenotypes in the brain. Here, we refine this hypothesis by proposing PD to be a disease specifically involving metabolic dysregulation of fatty acids, a 'fatty acidopathy'. We review extensive findings from many laboratories supporting the perspective that PD centres on fatty acid dyshomeostasis — alterations in the fatty acid-ome — as the critical feature of lipid aberration in PD and other α-synucleinopathies. This construct places transient α-synuclein binding to fatty acid side chains of cytoplasmic vesicles as a principal contributor to the biology of PD-relevant α-synuclein–membrane interactions. We propose that α-synuclein–fatty acid interactions in the fatty acid-rich brain are interdependent determinants of the gradual progression from neuronal health to PD, with attendant therapeutic implications.

Sections

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Key points

- Parkinson disease (PD) and related α-synucleinopathies have increasingly been considered lipidopathies as well as proteinopathies.
- Extensive evidence reviewed herein supports both physiological and pathogenic interplay between α-synuclein and fatty acids as determinants of progression from neuronal health to PD.
- α-Synuclein homeostasis is affected by membrane fatty acid composition, and dysregulated fatty acid metabolism alters transient α-synuclein membrane binding, including at synaptic vesicles.
- We propose that PD is a fatty acidopathy, with fatty acid side chain dyshomeostasis being a chief contributor to lipid aberrations in synucleinopathies.
- The fatty acid-ome holds promise for identifying and validating PD biomarkers and therapeutic targets.

Introduction

Parkinson disease (PD) and other human synucleinopathies have been proposed to be lipidopathies as well as proteinopathies[1–3]. This assertion is founded on several types of data: first, lipidomic analyses of patients with PD versus control individuals indicating that lipids are altered in the brain, cerebrospinal fluid and plasma of patients with PD; second, genetic risk loci for synucleinopathies in lipid pathways (reviewed elsewhere[1,2,4]); third, identification of abundant lipids and/or membranes in the α-synuclein-rich Lewy bodies that are the hallmark of PD[5–10]; fourth, physiological and pathogenic interactions between α-synuclein and membrane phospholipids that regulate its conformation and assembly state[11–17]; and fifth, evidence that α-synuclein can alter cellular lipid homeostasis[18–23]. Collectively, these multiple lines of evidence strongly support an α-synuclein–lipid interplay physiologically and a major role for lipids in mediating PD phenotypes in the brain.

The evidence of lipid abnormalities in PD and other synucleinopathies continues to grow. We now refine this hypothesis, proposing PD to be a disease more specifically of fatty acid metabolic dysregulation: a 'fatty acidopathy'. This Perspective centres on fatty acid dyshomeostasis, that is, alterations in the fatty acid-ome (the complete collection of fatty acids in the cell or system), as the critical feature of lipid aberration in α-synucleinopathies. Here, we explain the biological and genetic basis for our hypothesis, with an emphasis on the transient binding of α-synuclein to fatty acids of various lipids, thereby focusing on disease-related α-synuclein–membrane interactions at synaptic vesicles and certain other membranous organelles. We position fatty acids as the predominant contributor to the biology of PD-relevant α-synuclein–membrane interactions, postulating that these interactions are interdependent determinants of the movement from neuronal health to PD.

The brain is rich in fatty acids. These fatty acids are incorporated into lipids such as neutral lipids and phospholipids as well as free fatty acids. Throughout this Perspective, we refer to fatty acids specifically as those fatty acids incorporated into lipids; free fatty acids are specifically noted as such. Fatty acids and free fatty acids make a major contribution to the extensive diversity and complexity of lipids in the nervous system[24–26]. Importantly, diverse lipids have roles in development, energy storage, signal transduction, receptor activation, neurotransmission, and membrane structure and integrity. Increasing evidence suggests that several chronic neurological disorders result in considerable part from lipid dysregulation, including Huntington disease[27,28], Alzheimer disease[29–31], epilepsy[32] and PD[4]. CNS lipid metabolism, including the uptake and subcellular distribution of fatty acids, is tightly regulated[33,34]. Membrane phospholipids comprise saturated and unsaturated fatty acid chains of differing chain lengths and degrees of unsaturation, thereby determining membrane fluidity and function. These membrane dynamics regulate protein–protein and protein–lipid interactions (for example, α-synuclein–membrane binding).

Phospholipids: headgroups and fatty acids determine α-synuclein–membrane interactions

Almost 100 residues of the 140-amino acid α-synuclein protein are believed to contribute to its membrane binding[17,35–38]. Several familial PD-causing missense mutations are located within this region, including A30P, E46K, H50Q (although a study suggests that H50Q was identified in population databases without enrichment in PD compared with healthy individuals[39]), G51D and A53T. These substitutions affect α-synuclein–membrane binding, some with opposing effects[40–45] (Fig. 1). α-Synuclein–membrane binding directly affects α-synuclein conformation, including the interconversion of monomeric and multimeric forms of α-synuclein and its occasional higher-order aggregation during ageing and in disease[38,46] (reviewed elsewhere[47–49] and discussed further subsequently) (Fig. 1).

Binding of α-synuclein to the outer surfaces of vesicle membranes and its resulting switch in conformation from 'natively unfolded' to α-helix-rich is partially determined by phospholipid headgroups[50–52] (reviewed elsewhere[53–55]). However, headgroups are not the sole or necessarily primary determinant of membrane binding. α-Synuclein also binds esterified fatty acids and free fatty acids[56–59]. This property seems to be particularly important for α-synuclein–membrane interactions at synapses (discussed in detail subsequently). A study using small, highly curved unilamellar vesicles and ^{19}F-NMR concluded that fatty acids contribute substantially to α-synuclein–membrane binding[60]. Fatty acids can differentially modify α-synuclein aggregation in vitro, including eicosapentaenoic acid (20:5*n*3) and dihomo-gamma-linolenic acid (20:3*n*6) lengthening the lag phase and linoleic acid (18:2*n*6) shortening the lag phase[61]. In addition to altering α-synuclein aggregation, differing fatty acid chain lengths and degrees of saturation can alter the toxicity and secondary structure of α-synuclein, depending on the α-synuclein mutant type (for example, wild-type, A30P or A53T)[62]. However, such studies using pure components in vitro cannot reflect the complex milieu of the cytoplasm.

Headgroups contribute, including on the basis of their charge, given that α-synuclein preferentially binds headgroups of negative over neutral charge[17,60,63–65]. However, interaction strength varies even for phospholipid headgroups of the same charge, reinforcing the idea outlined earlier that fatty acids contribute substantially to interactions. Membrane dynamics are determined by unsaturated versus saturated fatty acid nature and are a determining factor for α-synuclein binding[60]. α-Synuclein has a greater binding preference for polyunsaturated fatty acids (PUFAs, such as docosahexaenoic acid (DHA) (22:6*n*3) and arachidonic acid (20:4*n*6))[52,57,66]. This binding preference probably stems from the increased chain lengths and double bonds associated with PUFAs altering membrane dynamics more extensively than monounsaturated fatty acids (MUFAs)[67]. Fatty acid chain length and saturation

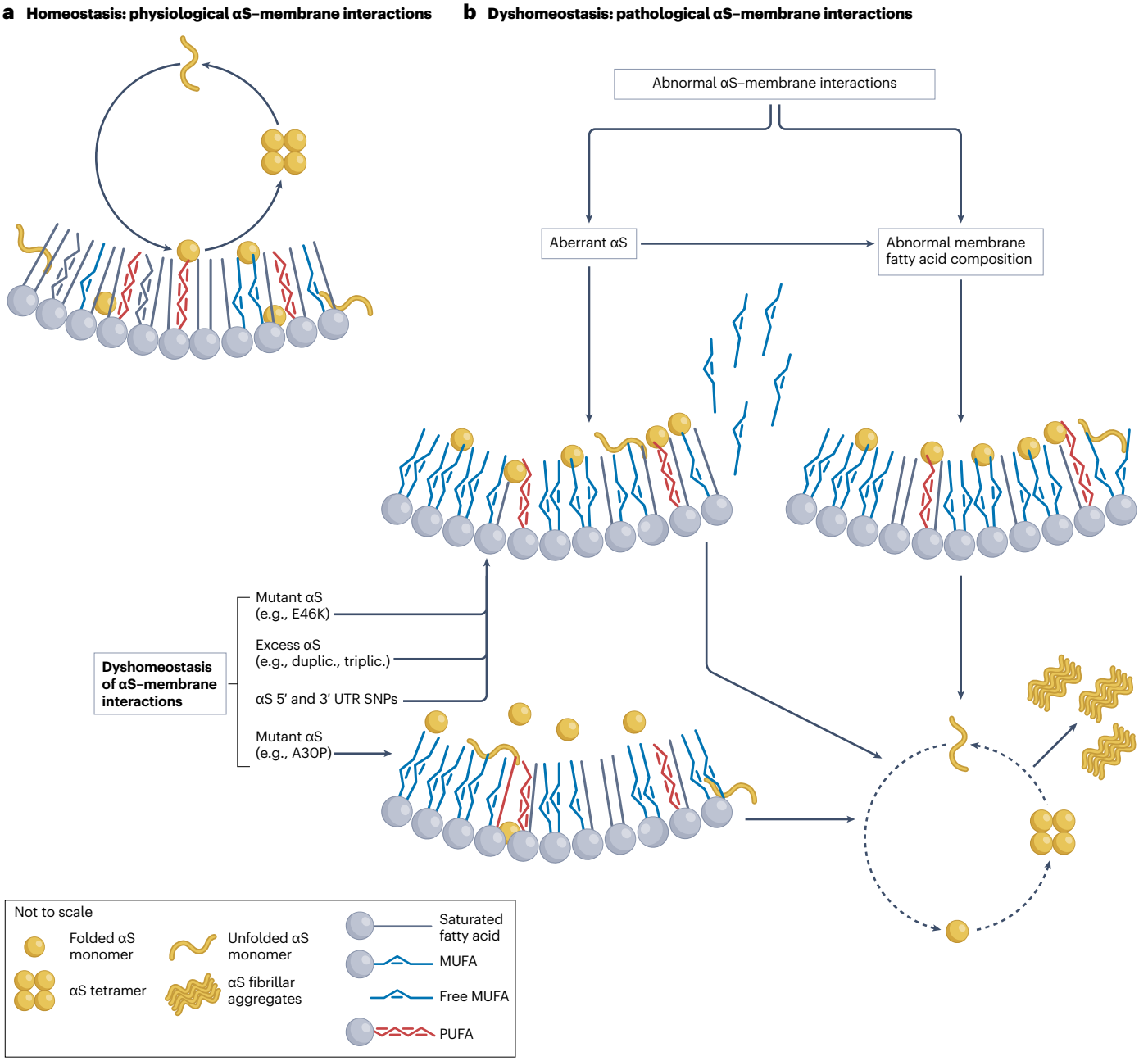

Fig. 1 | α-Synuclein–membrane interactions. a, Under conditions without PD or synucleinopathy, unfolded α-synuclein monomers transiently bind to and dwell on membranes, acquiring α-helical structure and forming native α-synuclein helical tetramers. **b**, With PD or synucleinopathy, abnormal α-synuclein (left; for example, harbouring familial PD α-synuclein mutations) and/or abnormal membrane fatty acid composition (right; sometimes resulting from effects of α-synuclein overexpression) can result in altered α-synuclein–membrane dwell time, with excessive or deficient transient binding. This dysregulation of assembly and disassembly might be a foundation for α-synuclein fibrillar aggregates. αS, α-synuclein; duplic., duplication; MUFA, monounsaturated fatty acid; PD, Parkinson disease; PUFA, polyunsaturated fatty acid; triplic., triplication; UTR, untranslated region.

affect membrane α-synuclein dwell time, α-synuclein accumulation at membranes and ultimately α-synuclein aggregate formation[54,55].

Longer and more unsaturated fatty acids (such as PUFAs) can promote α-synuclein aggregate formation and cytotoxicity, whereas saturated fatty acids decrease α-synuclein aggregation[56,58,68–70]. Interestingly, the PUFA DHA (22:6*n*3) interacts with α-synuclein to alter the interaction environment by concomitantly increasing DHA-containing phospholipids and depleting non-DHA containing phospholipids. As a PUFA, DHA forms more lipid packing defects in membranes than do MUFAs and saturated fatty acids[71] and has been

shown to increase α-synuclein-mediated vesicle clustering[72]. Fatty acid composition influences the physiological and chemical properties of membranes, such as permeability, fusions and fluidity, in turn affecting protein–lipid and protein–protein interactions[73,74]. Notably, a contributor to α-synuclein neuropathology in the mutant glucocerebrosidase form of PD is an accumulation of longer chain (≥C22) fatty acids[75].

There is further complexity and specificity to fatty acid composition in determining α-synuclein–membrane binding. Fatty acid chain combinations are important, with some individual fatty acid side chains of phosphatidylserine not supporting α-synuclein binding, whereas a combination of PUFA (20:4 or 22:6) with MUFA (18:1) side chains facilitate α-synuclein interaction[52]. This observation might result from α-synuclein recognizing a complex and physiologically relevant fatty acid composition. In considering the role of headgroup versus fatty acids in α-synuclein–membrane binding, a phosphatidylserine headgroup can be swapped for a phosphatidylcholine headgroup, with phosphatidylcholine 20:4 and phosphatidylserine 18:1 facilitating α-synuclein binding[52]. This complexity suggests that fatty acids are a leading factor in mediating α-synuclein–membrane interactions, probably by determining membrane phase transitions[52]. Ultimately, fatty acid composition helps to determine the dynamics of membranes with which α-synuclein interacts in the cytoplasm. Thus, fatty acid side chain identity seems to be a critical factor in both α-synuclein physiology and synucleinopathy.

α-Synuclein affects the membrane fatty acid-ome

The combined effect of α-synuclein expression level and its regulation of free fatty acid uptake for incorporation into membranes helps to regulate membrane phospholipid composition, contributing to α-synuclein membrane dwell time and thereby influencing α-synuclein folding and conformation (discussed subsequently).

Expression of α-synuclein

α-Synuclein is the primary proteinaceous component of Lewy bodies[5,6,10,76,77] and affects cytoplasmic fatty acid composition. *SNCA* which encodes α-synuclein, is a genetic risk locus for PD and dementia with Lewy bodies (DLB)[42,78–86] Expression of human wild-type or familial PD mutant α-synuclein increases the levels of MUFAs in human neurons, yeast, primary rat cortical neurons and mouse models of PD[18,87–89]. Patient-derived induced pluripotent stem cell (iPSC)-derived neurons expressing familial PD mutations, including α-synuclein locus triplication and A53T α-synuclein, also have increased levels of MUFAs[90,91].

In turn, conditioning cells in MUFAs (particularly oleic acid (18:1)) has the following effects: 1, exacerbates α-synuclein cytotoxicity; 2, decreases the physiological α-synuclein tetramer:monomer ratio in human neurons; 3, increases α-synuclein inclusion formation in neuroblastoma cells expressing an 'amplified' E46K familial PD mutation ('3K' α-synuclein); 4, increases caspase 3/7 activity (indicating increased apoptosis); and 5, increases levels of pSer129 phosphorylated α-synuclein[18,92,93].

The increase in MUFAs caused by α-synuclein expression is specific in that chain-length-matched saturated fatty acids (that is, stearic acid (18:0) and palmitic acid (16:0)) are not increased in these cellular models and do not induce PD-relevant neuronal phenotypes[18,92]. Increased stearoyl coenzyme A (CoA) desaturase activity is hypothesized to be the mechanism through which aberrant MUFA increase occurs. Fatty acid synthase (FASN) might also contribute to increased levels of cellular MUFAs by producing increased levels of saturated fatty acids that are then desaturated by stearoyl CoA desaturase (SCD) (discussed subsequently).

Analyses of mice with genetic deletion of α-synuclein did not identify a change in total phospholipid mass or in the amounts of major phospholipid headgroups, but it did reveal changes in fatty acid composition, namely, increased levels of MUFAs and decreased levels of PUFAs (with the exception of increased 18:2*n*6)[23]. Genetic deletion of *Snca* resulted in a 16% decrease in PUFA:MUFA ratio[23]. Partial similarities in fatty acid phenotypes for knockout and overexpression of α-synuclein might be analogous to the finding that divergent membrane binding of both E46K α-synuclein and G51D α-synuclein can be ameliorated by correcting fatty acid saturation using an SCD inhibitor[94]. Thus, α-synuclein expression, overexpression and deletion data all clearly support the proposition that α-synuclein expression alters cellular fatty acid composition. This regulation at the level of expression of the protein is just one way in which α-synuclein determines membrane fatty acid composition.

Uptake and incorporation

α-Synuclein further regulates membrane fatty acid composition through a role in fatty acid cellular uptake and incorporation[19,20,22,95,96]. For example, mice lacking α-synuclein have reduced uptake and incorporation rates of palmitic acid (16:0) and arachidonic acid (20:4) into brain phospholipids[19,22]. Phospholipids in astrocytes derived from α-synuclein-ablated mice have decreased esterification of palmitic and arachidonic acid, and trafficking of these fatty acids is decreased in specific phospholipid classes, such as phosphatidylinositol[95]. Importantly, specificity in α-synuclein-driven deficiency of fatty acid uptake and incorporation is observed. For example, deletion of α-synuclein did not affect DHA (22:6(*n*−3)) uptake but did increase incorporation of DHA–CoA into specific phospholipids, thereby affecting lipid turnover[20].

Fatty acid binding proteins and α-synuclein

Fatty acid binding proteins (FABPs) are a functional class of certain relatively short polypeptides that have been associated with synucleinopathies through direct and indirect connections with α-synuclein (reviewed elsewhere[97]). Serum levels of FABPs are higher in patients with PD dementia (PDD) or DLB than in control individuals or in patients with Alzheimer disease[98]. FABPs have been investigated as biomarkers for PD, PDD and DLB[97,99–101]. High FABP3 levels in cerebrospinal fluid were reported to be a prognostic biomarker for developing PD; moreover, levels of FABP3 protein are increased in the substantia nigra of post-mortem brains from individuals with PD[98,102,103]. Increased levels of cellular FABPs might be a direct or indirect response to α-synuclein dyshomeostasis and dysregulated fatty acid balance in PD. α-Synuclein associates with FABPs such as FABP3 and FABP7, and FABPs can alter α-synuclein aggregation and toxicity[104–109]. FABP3 is present in neurons and colocalizes in α-synuclein aggregates in the brains of individuals with PD; notably, FABP3 does not colocalize with phospho-tau or amyloid β-protein in the brains of individuals with Alzheimer disease[107]. FABP3 deletion prevents MPTP (*N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) from inducing α-synuclein aggregation in dopaminergic neurons[105]. Furthermore, an FABP3 ligand (MF1(4-(2-(1-(2-chlorophenyl)-5-phenyl-1H-pyrazol-3-yl)phenoxy)butanoic acid)) reduces α-synuclein aggregation and loss of dopaminergic neurons in MPTP-treated mice[110].

It has been hypothesized that α-synuclein could itself be a FABP that transports fatty acids between the aqueous cytosol and phospholipid membranes (premised on similarities in structural and biochemical properties)[57]. The lipid-binding nature of α-synuclein, coupled with

its α-helical structure upon lipid interaction and its amino acid length (140 residues), support the hypothesis that α-synuclein is a FABP[57]. Furthermore, 7 of 11 amino acids in the lipid-interacting repeat domain are shared between α-synuclein and apolipoproteins. The C terminus of α-synuclein interacts with membranes through interaction with these motifs. Other studies suggest that α-synuclein might not be a classical FABP, as its binding properties do not sufficiently resemble those of FABPs[58]. Differing spectra of α-synuclein to that of FABPs in high-resolution NMR spectroscopy indicate that the high-affinity binding of fatty acids to α-synuclein is different from that of FABPs, suggesting that α-synuclein is unlikely to be an intracellular transporter of free fatty acids[58]. Rather, α-synuclein seems to principally elicit its action with fatty acids through its membrane interactions.

α-synuclein–membrane interactions

Effects on α-synuclein conformation

α-Synuclein folding (and thereby its misfolding in PD) seems to be principally determined by α-synuclein–membrane interactions (Fig. 1). Misfolding of α-synuclein might promote its aggregation and, ultimately, formation of Lewy bodies. α-Synuclein was originally described as being a natively unfolded monomer and later shown to acquire α-helical structure upon membrane binding[17]. Endogenous α-synuclein examined using non-denaturing conditions from erythrocytes (which have α-synuclein levels rivalling those of neurons), neural cells and brain tissue was unexpectedly discovered to also exist as an α-helical tetramer, and this form is far less prone to aggregation in vitro[111]. Natively unfolded cytosolic monomers are hypothesized to transiently bind to highly curved lipid vesicle membranes in the cytoplasm to become α-helical, as originally shown by mixing unfolded α-synuclein monomers with small unilamellar vesicles in vitro[15,112]. Four of these α-helical α-synuclein monomers can apparently assemble transiently into an energetically favoured α-helical tetramer, although the biophysical mechanism underlying this assembly is unknown[113–117].

Natural disassembly or experimental depolymerization of physiological tetramers in cells leads to accumulation of unfolded monomers; this cycling of the tetramer:monomer (T:M) equilibrium occurs physiologically in cells. Destabilization of tetramers with age or in PD and DLB is hypothesized to enable more monomers to accumulate, misfold and assemble into β-sheet-rich aggregates[111,113–116]. Substantial experimental evidence indicates a causal relationship between α-synuclein T:M disequilibrium and PD-like phenotypes, as all familial PD-causing missense mutations tested to date consistently reduce the α-synuclein T:M ratio and increase levels of aggregation-prone monomers in cultured cells and in transgenic mouse brain tissue[70,91,113,115,118–123]. As an unexpected finding and new concept, the physiological α-synuclein T:M hypothesis has incurred healthy debate, with some laboratories continuing to focus solely on unfolded monomeric α-synuclein[116,124]. Similarly, the chronically elevated α-synuclein levels seen in patients with familial PD α-synuclein triplication might saturate unknown tetramer-stabilizing cytoplasmic factors (possibly fatty acids or membrane vesicles) to allow accumulation of excess unfolded monomers prone to Lewy-type aggregation[111,115]. In short, α-synuclein–membrane interactions – regulated in part by membrane fatty acid composition – are involved in α-synuclein T:M equilibrium and thus might contribute to the aggregation of excess monomers into α-synuclein fibrils, which accumulate in disease[63,68,125,126] (reviewed elsewhere[127]).

On the basis of the many studies cited earlier, we postulate that re-establishing normal membrane fatty acid composition could help to restore native α-synuclein helical conformation and membrane dwell time and thus α-synuclein assembly into metastable tetramers. Similar to all proteins, α-synuclein's structure and conformation help to determine its function, and altered conformation and assembly might ultimately lead to synucleinopathy.

Impact of membrane curvature

α-Synuclein has particular affinity for small, highly curved membranes[15,17,68,112,128–132] such as those of synaptic vesicles. Increased membrane curvature favours increased α-synuclein association[15,64,112,133]. α-Synuclein senses curvature[129,133–135] and can also modify membrane curvature[12,15,135–141]. Lipid headgroup size contributes to membrane curvature[142,143], but curvature is also dictated by membrane fatty acid composition. Membrane curvature involves packing defects[15,128,137], significantly dictated by fatty acids, which α-synuclein can modify directly[20,144] or indirectly by affecting fatty acid uptake (covered earlier)[19]. Increased levels of unsaturated lipids result in packing defects[145]. Reducing levels of unsaturated fatty acids (such as MUFAs), for example, by reducing SCD, reduces the degree of transient α-synuclein–membrane association[18,92]. α-Synuclein membrane dwell time is an important determinant of α-synuclein conformation. A longer membrane dwell time and/or increased α-synuclein–membrane interaction (for example, α-synuclein triplication resulting in more total α-synuclein and hence more α-synuclein at membranes, or E46K α-synuclein mutant having longer dwell time owing to increased positive charge) or a shorter membrane dwell time and/or less membrane interaction (for example, A30P and G51D mutant α-synuclein, both of which have lower affinity for membrane binding owing to increased negative charge) have both been shown to have adverse consequences[12,40,41,44,131,146–152] (Fig. 1).

Interactions at synaptic vesicles

α-Synuclein contributes to regulating vesicle recycling[153,154] (Fig. 2). Hence, the α-synuclein–membrane interaction is particularly relevant to physiology and disease at synaptic vesicle membranes[155]. α-Synuclein is enriched at presynaptic terminals[35,37,132,153,156], colocalizes with and binds synaptic vesicles[118,157] and participates in SNARE (soluble NSF attachment protein receptors) assembly[16,70,158–169]. α-Synuclein might control SNAREs without directly interacting with them, instead interacting with a SNARE 'regulator', arachidonic acid (20:4), which modulates the structure and function of both α-synuclein and SNARE proteins (and ultimately SNARE complex formation)[155,170]. This process contributes to α-synuclein–synaptic vesicle interactions and trafficking. Docking of α-synuclein to synaptic vesicles is influenced by vesicle membrane composition[51]. α-Synuclein–membrane binding influences synaptic vesicle size, location, structure, recycling and neurotransmitter release[159,166,171–178] (Fig. 2).

It is well established in vitro that synaptic vesicles with lipid packing defects attract α-synuclein[14,128,130,133]. The combination of phospholipid membrane negative charge with the highly curved nature of synaptic vesicles is ideal for α-synuclein binding. α-Synuclein also regulates the clustering of synaptic vesicles[164,179,180], probably through its membrane interactions. α-Synuclein has great affinity for negatively charged lipid headgroups[17,112]. In this context, synaptic vesicles are enriched in phosphatidylserine headgroups[65,181,182], of which a large percentage contains a PUFA chain[66]. However, as discussed, headgroups might not be as critical to α-synuclein binding to the external surface as fatty acid side chains. Interestingly, fatty acids (for example, DHA) are enriched at synaptic termini[183–190]. Establishing the fatty acid

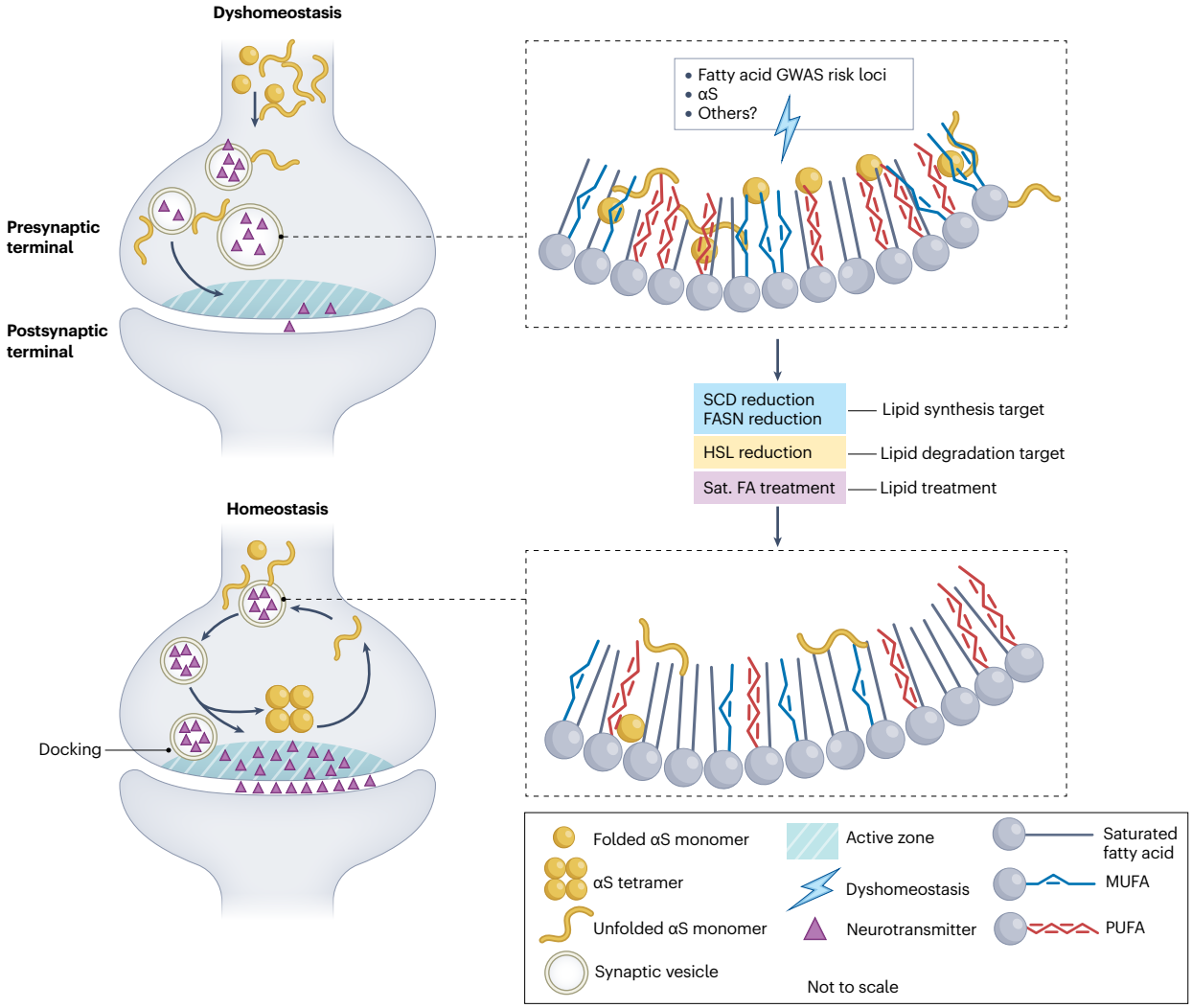

Fig. 2 | α-Synuclein–membrane binding influences neurotransmitter release. Restoring synaptic vesicle membrane dynamics by re-establishing membrane fatty acid composition is a rational therapeutic approach to correcting α-synuclein–membrane interactions and restoring synaptic vesicle phenotypes such as docking, priming, fusion and neurotransmitter release. Under disease conditions (top), α-synuclein dyshomeostasis and/or fatty acid imbalance can modify membrane fatty acid composition and therefore membrane fluidity and curvature dynamics. Membranes with aberrant fatty acid composition (for example, with increased MUFAs) can alter α-synuclein–membrane interactions at synaptic vesicles. Such interactions at synaptic vesicles ultimately determine neurotransmitter release. Aberrant synaptic vesicles (elongated, irregular diameter) result in dysfunctional docking (in the active zone), priming, fusion and neurotransmitter release. Correcting membrane fatty composition corrects membrane dynamics and α-synuclein–membrane interactions (bottom). Aberrant membrane fatty acid composition could be corrected by targeting fatty acid synthesis (FASN or SCD inhibition) to reduce levels of abnormal MUFAs. Targeting HSL (HSL reduction) reduces free fatty acid generation through lipid droplet degradation. This maintains MUFAs in the lipid droplet, diglyceride (DG) and triglyceride (TG) forms resulting in fewer MUFAs in phospholipid membranes. Balancing elevated levels of unsaturated fatty acids via diets enriched in saturated fatty acids might also correct membrane dynamics. αS, α-synuclein; FA, fatty acid; FASN, fatty acid synthase; GWAS, genome-wide association study; HSL, hormone-sensitive lipase; MUFA, monounsaturated fatty acid; PD, Parkinson disease; PUFA, polyunsaturated fatty acid; Sat., saturated; SCD, stearoyl coenzyme A desaturase.

composition of synaptic membranes for PD and non-PD vesicles will be important for mechanistic understanding of disease and for investigating α-synuclein–membrane interactions specifically at synaptic vesicles.

Human genetics connects PD to the fatty acid-ome

Beyond the familial PD α-synuclein missense mutations outlined earlier, several fatty acid-specific risk loci identified in genome-wide association studies (GWASs) alter membrane composition, modulating α-synuclein interactions with fatty acid tails. Systematic GWAS data analysis has identified lipids as common among several PD pathogenic processes[4,82,86]. Several genes in lipid metabolism pathways have been identified as PD risk loci[81,191] (Table 1). Additionally, the kinase gene *LRRK2*, a PD risk locus, is now being considered for its association with lipid pathways. Aberrant pSer129 α-synuclein and α-synuclein T:M ratio of both G2019S and R1441C *LRRK2* mutations in patient

Table 1 | Parkinson disease genome-wide association study risk loci

Gene	Lipid or fatty acid association	Refs.
SNCA	Binds fatty acids and lipids, modulates lipid metabolism	80,81,83,85,191–196
GBA	Glycosphingolipid metabolism	254–258
LIMP2	Lipid modulator via GBA	81,82,193
DGKQ	Diacylglycerol kinase	191,259,260
SREBF1	Sterol synthesis regulator	193
VPS13C	Lipid transporter	82,86,192
CRLS1	Cardiolipin synthase	82
SYNJ1	Phosphoinositide phosphatase	261
FASN	Fatty acid synthase	198
ELOVL7	Fatty acid elongase	86,199
PLA2G6	Phospholipase	202–207

RAB29, *RAB39B*, *VPS35* and *SYT11* are Parkinson disease genome-wide association study risk loci with indirect connections to lipid biology that may affect it, including through lipid droplets.

iPSC-derived neurons was corrected by SCD inhibition[119] (although this does not on its own prove that LRRK2-related PD acts principally via lipid pathways).

Importantly, *SNCA* itself is a PD risk locus[80,81,83,85,191–196], and, as outlined earlier, binds specific fatty acids and modulates fatty acid metabolism and uptake. Several PD risk loci specifically determine fatty acid composition (Table 1). Interestingly, these cover the full suite of synthesis, type determination, localization and membrane composition. The first of these is fatty acid synthase (*FASN*), responsible for de novo fatty acid biosynthesis from acetyl-CoA and malonyl-CoA with NADPH[197]. Indeed, the lipid-related risk locus *SREBF1* (Table 1) can regulate expression of *FASN*[198]. Following fatty acid synthesis, the next determinant of membrane composition is species type. Initially, synthesized fatty acids are elongated to differing chain lengths by elongases. The fatty acid elongase gene *ELOVL7* is a PD risk locus[86,199]; transcriptional analysis has revealed that regional levels of *ELOVL7* mRNA correlate with Braak PD stage[200]. ELOVL7 is particularly active in elongating fatty acids of C18 chain length[201], thereby determining membrane fatty acid composition.

Desaturation is another fatty acid modification mechanism. To the best of our knowledge, a desaturase has not yet been identified as a PD risk locus. However, the risk locus *SREBF1* (noted above) is a transcriptional activator of SCD[18,87,88,92]. Another determinant of membrane fatty acid composition is governed by lipases that act on membrane phospholipids, hydrolysing acyl and phosphate esters. The phospholipase gene *PLA2G6* is a known PD risk factor, with loss of function leading to early-onset PD[202–207]. Although not formally observed as risk loci, the roles of other phospholipases in PD continues to be debated[208–212]. Taken together, these genes contribute to our understanding of fatty acid dysregulation in PD and strongly support identification of related therapeutic pathways for PD.

A biomarker outlook

Studies investigating alterations in the fatty acid-ome in samples from patients with PD, including post-mortem brain tissue and biofluids, support changes to the fatty acid-ome in PD[213–222], with some such changes correlating with PD progression[219]. A key goal of discerning the contribution of fatty acids to PD pathobiology is to identify fatty acid biomarkers for synucleinopathies. The highly complex dynamics of the lipidome are such that a rigorously validated lipid or fatty acid biomarker has so far been elusive. Most studies have focused on lipid class, species and ratios of certain lipid classes. Studies are now beginning to address lipid subspecies, for example, analysis at the level of specific fatty acid alterations. The key to a PD biomarker might lie not only in the lipid headgroups but also in the fatty acid composition of human biofluids. To date, most studies have not comprehensively examined alterations in the fatty acid-ome at the resolution required to detect a specific fatty acid biomarker in biofluids. However, those that have attempted this task are beginning to identify differences in fatty acids and fatty acid metabolites between biofluids from patients with PD and individuals as controls (Table 2).

Targeted fatty acid biomarker studies premised on a candidate therapeutic target, SCD, have begun[223]. As this research advances, it will be critical to observe longitudinal changes correlating with PD progression and to establish to what degree changes in biofluids reflect changes in the brain. A potentially major complication of fatty acid biomarkers in biofluids such as plasma is the effect of diet. To what degree fatty acid changes in the brain arise from fluctuations in daily diet is yet to be determined.

Table 2 | Emerging fatty acid differences in Parkinson disease versus control biofluids

Fatty acid or fatty acid metabolite	PD alteration	Biofluid	Analysis	Ref.
Arachidonic acid	Increased	Plasma	UPLC-MS	215
13-Hydroxy-octadecatrienoic acid	Increased			
Docosahexaenoic acid	Decreased			
12-Hydroxy-eicosatetraenoic acid	Decreased			
Dihydroxy-eicosatrienoic acid	Decreased			
Hydroperoxy-octadecadienoic acid	Decreased			
Decanoic acid	Increased	CSF	FT-ICR-MS	216
Valeric acid	Increased			
Arachidonic acid	Increased			
Dihomo-y-linoleic acid	Increased			
Palmitic acid	Decreased	Plasma	GC-TOFMS	217
Linoleic acid	Decreased			
Oleic acid	Decreased			
Stearic acid	Decreased			
Palmitoleic acid	Decreased			
Valeric acid	Decreased	Plasma	PLC-Q-TOF-MS	218
2-Octanoic acid	Increased			
Docosene	Decreased			
α-Linoleic acid metabolism pathway	Increased	Plasma	GC-TOFMS	213
Arachidonic acid	Decreased	Plasma	UPLC-MS/MS	220
Eicosapentaenoic acid[a]	Increased			

Studies compared PD with control samples. FT-ICR-MS, Fourier transform ion cyclotron resonance mass spectrometry; GC-TOFMS, gas chromatography time-of-flight mass spectrometry; PD, Parkinson disease; PLC-Q-TOF-MS, liquid chromatography quadrupole time-of-flight mass spectrometry; UPLC-MS, ultra-performance liquid chromatography mass spectrometry.
[a]Derivatives of these fatty acids are also modified in PD ompared with control samples.

Therapeutic opportunities

SCD inhibition

Although α-synuclein–fatty acid interactions are recognized as physiologically and pathogenically important, the rational pharmacological modification of fatty acid homeostasis for therapy is still in its infancy (Fig. 2). Premised on the afore-cited evidence for an α-synuclein-induced excess of MUFAs, SCD1, the rate-limiting enzyme for MUFA synthesis, has emerged as a candidate target that has entered clinical trials for PD. Genetic reduction or pharmacological inhibition of SCD can alleviate PD-associated phenotypes in preclinical models, including α-synuclein-dependent neurotoxicity and α-synuclein 3K (E46K-amplified) inclusion formation. SCD reduction decreased levels of pSer129 α-synuclein in several PD models, including patient-derived α-synuclein triplication neurons, *LRRK2* mutant (G2019S or R1441C) iPSC-derived neurons and neurospheres from patient-derived α-synuclein A53T neurons[18,87,90–94,119,224]. Correcting MUFA dysregulation by reducing SCD restored the physiological α-synuclein T:M ratio in E46K and 3K α-synuclein-expressing human cells and in LRRK2 G2019S and R1441C patient neurons[18,92,119]. Moreover, the increased unfolded protein response that occurs in α-synuclein triplication neurons was corrected by reducing SCD[91,225].

Re-establishing MUFA equilibrium in phospholipid membranes also restored α-synuclein–membrane distribution to the physiological state[18]. Reducing the homologous desaturases in *Caenorhabditis elegans* expressing wild-type or A53T α-synuclein or exposed to rotenone (a mitochondrial complex I inhibitor that damages neurons) relieved PD-associated phenotypes and prevented neuronal degeneration[18,226]. Reducing SCD genetically or pharmacologically (using either Pfizer's '5b' inhibitor or YTX-7739, which has entered clinical trials[227]) ameliorated PD-type neuropathology and dopamine-responsive motor deficits (for example, pole climbing) in the 3K α-synuclein mouse model[87,88,118]. In agreement with results in cellular α-synuclein models, in vivo SCD reduction decreased pSer129 α-synuclein deposits in both wild-type and 3K α-synuclein mouse brains, reduced proteinase K-resistant α-synuclein aggregates and increased both soluble (cytosolic) α-synuclein levels and the α-synuclein T:M ratio[87,88]. These benefits were associated with reduced gait asymmetry, prevention of progressive motor deficits, reduced resting tremor and enhanced motor skill learning[87,88].

HSL reduction

Beyond SCD inhibition, approaches for correcting aberrant membrane MUFA composition involve distinct candidate targets (Fig. 2). An increase in PD-associated MUFA synthesis can result in elevated levels of diglycerides, triglycerides and lipid droplets that store excess fatty acids[18]. Neutral lipid lipases (for example, hormone-sensitive lipase (HSL, encoded by *LIPE*)) generate free fatty acids from these lipid droplets that can be incorporated into phospholipid membranes, adversely affecting α-synuclein–membrane homeostasis. Accordingly, HSL reduction decreased several PD-like phenotypes in α-synuclein cellular models, including patient-derived α-synuclein triplication neurons[91]. Specifically, HSL inhibition reduced 3K α-synuclein inclusion formation, lowered pSer129 α-synuclein levels in E46K-expressing neuroblastoma cells and α-synuclein triplication neurons, fixed the abnormal unfolded protein response and improved α-synuclein T:M equilibrium. The rescue of these PD-like phenotypes correlated with re-establishing MUFA homeostasis in phospholipid membranes and restoring physiological α-synuclein–membrane interactions[91]. Reduced HSL expression in the 3K PD model reversed neuropathology and motor deficits principally in male mice, which are more symptom-prone than female mice, as in human PD[228]. In contrast to SCD inhibition, HSL inhibition does not alter the rate of MUFA synthesis; rather, it maintains MUFAs within neutral storage lipids that would otherwise be degraded to release MUFAs. These MUFAs are then not available for incorporation into phospholipid membranes.

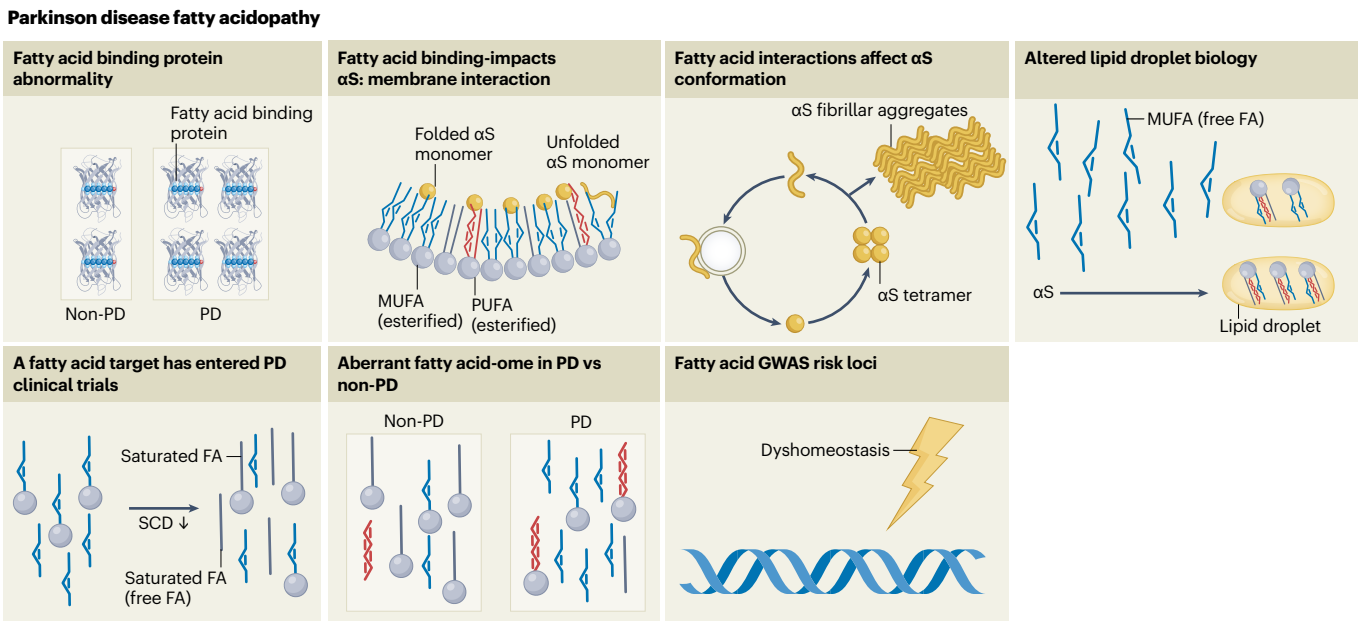

Fig. 3 | Parkinson disease is a fatty acidopathy. Various lines of evidence suggest that Parkinson disease and other synucleinopathies might be considered fatty acidopathies. αS, α-synuclein; FA, fatty acid; GWAS, genome-wide association study; MUFA, monounsaturated fatty acid; PD, Parkinson disease; PUFA, polyunsaturated fatty acid; SCD, stearoyl coenzyme A desaturase.

PUFA oxidation products

The biological effects of some PUFAs might be elicited through their oxidation products, for example, oxylipins[55]. Targeting of such signalling molecules and byproducts of fatty acid metabolism might have therapeutic promise. One example under consideration in preclinical studies is reduction of a PUFA peroxidation product, 4-hydroxynonenal (4-HNE), using an inhibitor (CU-13001) of 15-lipoxygenase (15-LO). The complexity and dynamics of PUFA pathways in addition to oxylipins has yet to be elucidated in relation to PD; some PUFAs could be beneficial and others detrimental. ω3 fatty acids have shown some potential as treatments in in vivo models of PD, with a hypothesis that the ω6:ω3 PUFA ratio is important when considering PUFA-directed therapeutics[229–232].

FASN modulators

The fatty acid metabolism GWAS risk locus *FASN* is a potential therapeutic target, with FASN modulators already being tested in cancer biology. Dysregulation of FASN can lead to increased fatty acid synthesis resulting in altered membrane composition and increased levels of free fatty acids. Correcting fatty acid synthesis through FASN reduction could rescue PD phenotypes through α-synuclein-dependent and α-synuclein-independent mechanisms. Partial FASN loss restored flight to PINK1 mutant flies (a model of PD) and corrected their mitochondrial ATP levels. FASN inhibition (cerulenin treatment) protected against ATP (viability) deficits in PD patient fibroblasts in a PINK1-deficient mouse model and in PINK1 patient iPSC-derived dopaminergic neurons[233].

Future fatty-acid-focused therapeutic avenues

Abnormal membranous profiles in Lewy bodies and Lewy neurites are described as originating partly from vesicles. Future liquid chromatography mass spectrometry studies of Lewy bodies focused on the fatty acid species of vesicle membranes will contribute to understanding direct α-synuclein–fatty acid interactions in Lewy bodies. This might support targeting of synaptic vesicles with fatty acid treatment[5]. In this regard, longer fatty acid chains are associated with PD-like phenotypes[75], and shorter fatty acid chains are associated with their reduction[92]. This relationship suggests a therapeutic avenue focused on altering membrane fatty acid chain length, for example, by targeting certain elongases (that is, ELOVL proteins). Altering dietary lipid and fatty acid composition is another avenue for consideration, for example, increasing shorter chain fatty acids in membranes through consumption of short chain fatty acids (such as myristic acid (C14:0)) that cross the blood–brain barrier, and modulating brain–gut axis communications influencing short chain fatty acids, as these are among the most abundant microbial metabolites produced in the gut[234]. Although not an absolute therapeutic requirement, advancing the various candidate targets discussed earlier to achieve relative brain specificity might become a therapeutic priority.

Conclusions

The extensive and rapidly emerging literature reviewed herein suggests that approaching PD as a fatty acidopathy is an important new direction in uncovering pathogenic mechanisms, therapies and biomarkers of PD (Fig. 3 and Box 1). Fatty acids are fundamental mediators of both physiological and pathological α-synuclein–membrane interactions. Focusing on the nuances of the fatty acid-ome will be important in progressing our understanding of PD and other synucleinopathies. The dynamics of fatty acid cellular distribution (for example, in neutral lipid storage droplets versus free versus acylated in phospholipid membranes) seem to be key to α-synuclein–membrane interactions in health and disease. Research focused on fatty acid–α-synuclein interactions in cellular and in vivo systems in the context of the endogenous cellular milieu will contribute to the advancement of this field. Co-culture and in vivo systems will be important analysis models, given the diversity of the fatty acid-ome between brain regions and brain cell types, cell crosstalk and transport of fatty acids between cell types[235–240]. Understanding the impact of the dynamic fatty acid-ome and fatty acid flux in subcellular compartments will also be important for progressing mechanistic understanding of the fatty acid–PD relationship. Furthermore, dissecting the individual and combined effects of α-synuclein and fatty acids on the immune response in PD will be important. Consideration will also need to be given to dietary fatty acid intake and the control of fatty acid blood–brain barrier penetration. To date, findings on associations between different dietary fatty acid consumptions and PD have generated conflicting findings[241–248].

We view the role of fatty acids in determining α-synuclein–synaptic membrane interactions as a key process in health and PD. Aside from this direct interaction, fatty acids have been found to affect neurotransmission, including dopaminergic neurotransmission in the nucleus accumbens in rats with chronic deficiencies in *n*–3 PUFAs[249]. Supplementation with such fatty acids rescued neurotransmission deficits[250]. Indeed, a dynamic relationship exists between fatty acids as precursors to certain neurotransmitters and neurotransmitters stimulating fatty

Box 1 | From research to real-world benefits

An urgent need exists to identify mechanism-based disease-modifying treatments for Parkinson disease (PD) and associated diagnostic and pharmacodynamic biomarkers. An understanding of lipid homeostasis in the brains of individuals with PD and the relationship between the self-aggregating protein α-synuclein and fatty acid metabolism are key emerging topics in the fundamental study of PD. Indeed, the pathognomonic Lewy bodies of PD and dementia with Lewy bodies (DLB) — long thought to be principally composed of fibrils of α-synuclein — have been shown to contain abundant altered membrane fragments and other abnormal lipid material. Here, we review in detail how fatty acid balance helps to regulate α-synuclein conformation and stability, with evidence for the special importance of α-synuclein–membrane interactions via both lipid headgroups and fatty acyl tails. Approaching PD as a fatty acidopathy and a proteinopathy has led to the identification of specific fatty acid-related therapeutic targets, for example, the enzymes stearoyl coenzyme A (CoA) desaturase and hormone-sensitive lipase. An inhibitor of stearoyl CoA desaturase (the rate-limiting enzyme for biosynthesis of monounsaturated fatty acids) has reached clinical trials in patients with PD. We propose that refining the PD lipidopathy paradigm by focusing on fatty acids is a strategy for understanding disease progression in PD and DLB and might lead directly to approaches for validating novel therapeutic compounds and associated biomarkers. As reviewed herein, many laboratories have contributed to our growing understanding of the role of fatty acid homeostasis — both dependent on and independent of α-synuclein — in the pathogenesis of these diseases and are advancing candidate therapeutics as well as pharmacodynamic biomarkers of target engagement that might benefit patients with PD and DLB.

acid levels in the brain: for example, dopamine increases levels of arachidonic acid, and increased levels of arachidonic acid stimulate dopamine release[251–253].

Mechanistically, future analyses of the vesicle membrane components of Lewy bodies to achieve fatty-acid-specific identification will contribute to understanding direct α-synuclein–fatty acid interactions at synaptic vesicles normally and in PD. We propose that the fatty acid-ome holds great promise for the identification of PD biomarkers and therapeutic targets.

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