frontiers | Frontiers in Molecular Biosciences

TYPE Review
PUBLISHED 12 August 2024
DOI 10.3389/fmolb.2024.1455817

OPEN ACCESS

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RECEIVED 27 June 2024
ACCEPTED 26 July 2024
PUBLISHED 12 August 2024

CITATION
Schepers J, Löser T and Behl C (2024) Lipids and α-Synuclein: adding further variables to the equation.
Front. Mol. Biosci. 11:1455817.
doi: 10.3389/fmolb.2024.1455817

Lipids and α-Synuclein: adding further variables to the equation

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Aggregation of alpha-Synuclein (αSyn) has been connected to several neurodegenerative diseases, such as Parkinson's disease (PD), dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA), that are collected under the umbrella term *synucleinopathies*. The membrane binding abilities of αSyn to negatively charged phospholipids have been well described and are connected to putative physiological functions of αSyn. Consequently, αSyn-related neurodegeneration has been increasingly connected to changes in lipid metabolism and membrane lipid composition. Indeed, αSyn aggregation has been shown to be triggered by the presence of membranes *in vitro*, and some genetic risk factors for PD and DLB are associated with genes coding for proteins directly involved in lipid metabolism. At the same time, αSyn aggregation itself can cause alterations of cellular lipid composition and brain samples of patients also show altered lipid compositions. Thus, it is likely that there is a reciprocal influence between cellular lipid composition and αSyn aggregation, which can be further affected by environmental or genetic factors and ageing. Little is known about lipid changes during physiological ageing and regional differences of the lipid composition of the aged brain. In this review, we aim to summarise our current understanding of lipid changes in connection to αSyn and discuss open questions that need to be answered to further our knowledge of αSyn related neurodegeneration.

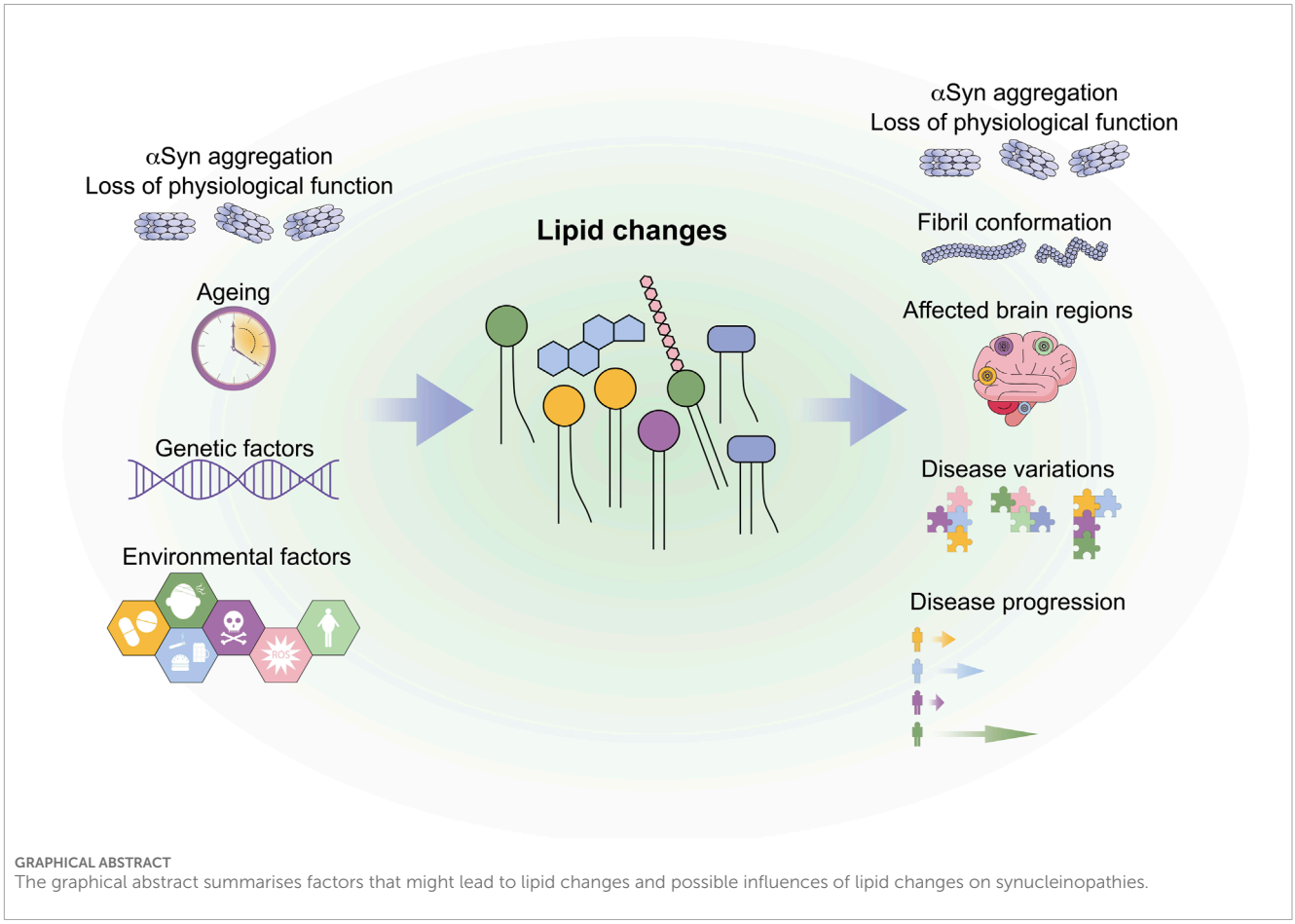
KEYWORDS

alpha-Synuclein, Parkinson's disease, DLB, MSA, membrane lipids, lipid metabolism

1 Introduction

With approximately 50% of the dry weight of the human brain being lipids, it has one of the highest lipid contents in the human body (Hamilton et al., 2007; Bruce et al., 2017). Strikingly, lipid changes in Alzheimer's disease (AD) have already been described by Alois Alzheimer upon discovery (Alzheimer et al., 1995) but have not been consequently investigated at that time, perhaps partly due to the lack of adequate methodology. Nowadays, changes in lipid metabolism of the brain are implicated in several neurodegenerative diseases such as, among others, AD, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (Wei et al., 2023). For example, it was shown that the lipid metabolism in AD brain tissue is changed, including changes in the fatty acid composition (Nasaruddin et al., 2016; Yin, 2023), accumulation of cholesterol (Xiong et al., 2008; Ahmed et al., 2024), and the presence of the lipoprotein APOE4 isoform as risk factor for AD (Zhu et al., 2015; Lefterov et al., 2019; Miranda et al., 2022; Pires and Rego, 2023; Lozupone and Panza, 2024).

In this review, we focus on α-Synuclein (αSyn) and its growing connection to lipids, not only in the context of its putative physiological functions but also during neurodegenerative



GRAPHICAL ABSTRACT
The graphical abstract summarises factors that might lead to lipid changes and possible influences of lipid changes on synucleinopathies.

processes. Aggregation of αSyn in different neuronal tissues is associated with different neurodegenerative diseases that are collected under the term synucleinopathies. These include, among others, PD, dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA) (Calabresi et al., 2023). To understand disease formation and progression, a lot of successful research has already been conducted, connecting αSyn-aggregation and neurodegeneration to mitochondrial dysfunction and oxidative stress, lysosomal dysfunction, inflammatory processes, and a perturbed Ca^{2+} homeostasis and excitotoxicity (Rocha et al., 2018; Wang et al., 2020; Sahoo et al., 2022; Lyra et al., 2023; Forloni, 2023; Rcom-H'cheo-Gauthier et al., 2016). However, more recently, the link between PD pathogenesis and lipids has gained more and more attention (reviewed in (Alecu and Bennett, 2019; Fanning et al., 2020; Battis et al., 2023; Flores-Leon and Outeiro, 2023)). For example, it was shown that Lewy Bodies (LBs) contain an abundancy of different membranes (Shahmoradian et al., 2019).

We focus on lipid changes and its impact on synucleinopathies, summarising how changes in membrane lipids might contribute to disease progression and whether differences in the membrane composition could contribute to differences in aggregate conformation and localisation. We summarise putative physiological functions of αSyn in connection to membrane lipids as well as lipid-associated processes and discuss lipid changes connected to PD, DLB, and MSA. It is important to keep in mind that, while these three diseases are distinguishable from each other, especially PD and DLB share overlapping disease phenotypes and risk factors (Calabresi et al., 2023). Thus, we compare common factors connecting lipid metabolism that might play a role in all three synucleinopathies but also discuss differences.

As ageing is known to be connected to neurodegenerative synucleinopathies (Poewe et al., 2022; Calabresi et al., 2023), we further discuss current knowledge of changes of the lipid composition of the aged brain. To date, little is known about lipid changes in the brain during physiological ageing even though it might be possible that changes in the regional lipid composition of the brain might explain why different brain regions are affected in different patients. Whether synucleinopathies are induced by age-related lipid changes in the brain remains unclear.

It is known that αSyn forms amyloid fibrils that are rich in β-sheets during pathological processes. During amyloid fibril formation, the structurally disordered αSyn monomers oligomerise to form aggregates that grow into β-sheet rich *protofibrils*. These protofibrils grow to form long amyloid fibrils, that can be detected in LBs (Ghosh et al., 2017; Alam et al., 2019; Mehra et al., 2021). It is known that these amyloid fibrils can adapt different conformations, referred to as *strains* (Bousset et al., 2013). In this review, we address aggregation formation of αSyn in the presence of lipids and discuss how conformational variations of αSyn *strains*, might, to a certain extent, depend on the lipid environment.

To date, there are no disease-modifying treatments available for PD, DLB, and MSA. For PD, the use of L-Dopa to restore

dopaminergic function, developed in the 1960s (Cotzias et al., 1967), is still the most common treatment (Fernagut et al., 2014; Stoker and Barker, 2020). Developing alternative treatments and ways to detect pathological events earlier is urgently needed. Thus, understanding the connection between lipid changes, αSyn aggregation, and disease progression has the potential to open new, possible ways of disease-modification and earlier detection.

2 Alpha-Synuclein

αSyn is a 14 kDa protein of the small synuclein protein family, which was initially described in the Pacific electric ray *Tetronarce californica* in 1988 and is evolutionary highly conserved (Figure 1A) (Maroteaux et al., 1988; Zhu and Fink, 2003). In humans, the *SNCA* gene, which spans five canonical exons and is located on the PARK1/4 locus of chromosome 4, encodes αSyn. The full-length protein consists of 140 amino acids (aa) and can be divided into three domains (Figure 1B) (Emamzadeh, 2016).

Residues 1–60 form the positively charged N-terminus, which, because of its amphipathic nature, allows interactions with membrane lipids (Bartels et al., 2010; Pirc and Ulrih, 2015). The high amount of lysine residues conducts interactions with anionic lipids, such as phosphatidic acid, phosphatidylinositol, as well as highly negative phosphoinositide phosphates (Middleton and Rhoades, 2010; Jacob et al., 2021a). Upon membrane binding, the coiled N-terminus transforms into a α-helical structure (Figure 1C) (Bussell and Eliezer, 2003; Bodner et al., 2009). Besides an electrostatic interplay, the robustness of this membrane-binding α-helix is strongly dependent on the amount of lipid molecules per protein (Shvadchak et al., 2011; Roeters et al., 2023). The transition from random coil to helix is facilitated by multiple, imperfect repeats of 11 aa, containing a highly conserved KTKEGV motif. Lipid-binding motifs with high similarity were found in apolipoproteins, such as ApoA-I, which also forms α-helices upon membrane binding (Segrest et al., 1990; George et al., 1995). Two of these KTKEGV repeats in αSyn also reach into the second protein domain, the 35 aa long non-amyloid-β component (NAC) (Ueda et al., 1993). In early studies, this domain was found to be prone to aggregation, presumably because of an 11-residue core region, the so-called NACore. Its β-strand structure tends to stack into multiple β-sheets and induces amyloidogenic protein aggregation (Rodriguez et al., 2015; Tuttle et al., 2016; Xu et al., 2016). *In vitro* studies revealed numerous factors that affect the kinetics of αSyn fibril formation. Endogenous factors for αSyn nucleation include protein modifications and truncations, as well as the presence of lipids and membranes (Galvagnion et al., 2015; Ghosh et al., 2017). Environmental factors, such as metals, pesticides, pH, and temperature changes were also found to promote *in vitro* fibrillation (Morris and Finke, 2009; Ghosh et al., 2017). The third protein domain is the anionic C-terminus, which consists of the remaining 46 aa. It is a proline-rich, intrinsically disordered region (random coil) in which around one third of residues are acidic. This comparatively flexible region was found to be a target for multiple post-translational modifications (PTMs), and the central domain for protein-protein interactions (Cole et al., 2002; Oueslati et al., 2010; Manzanza et al., 2021). The majority of investigated PTMs introduced in αSyn were found to inhibit protein function and enhance its susceptibility to pathological aggregation (Zhang et al., 2019). However, recent studies have identified several physiological functions of C-terminal modifications (Figure 1B). For instance, SUMOylation of lysine residues K96 and K102 is required for the nuclear translocation of αSyn (Krumova et al., 2011; Ryu et al., 2019). Additionally, phosphorylation of tyrosine Y125 has been shown to modulate the interaction between αSyn and phospholipase D in human embryonic kidney cells (HEK-293) (Ahn et al., 2002). Recently, it has been shown that phosphorylation at serine S129, which is predominantly related to αSyn pathology, might also regulate αSyn function in healthy cells (Ramalingam et al., 2023).

Exclusively found in vertebrates, αSyn is localised in several different regions of the brain, such as the *substantia nigra*, the cerebral cortex, and hippocampus, among others (Taguchi et al., 2016). Localisation of αSyn in presynaptic terminals as well as its co-localisation with synaptic vesicles (Maroteaux et al., 1988; Bayer et al., 1999; Taguchi et al., 2016) led researchers to believe that αSyn might play an important role in neurotransmission. In the following years, many studies helped elucidate the transport route of αSyn from its synthesis in the cell soma to presynaptic axon terminals and its interactions with different proteins and whole organelles.

3 From synthesis to function – interactions of αSyn across the neuron

Since αSyn lacks a canonical translocon sequence, *de novo* biosynthesis of αSyn is most likely directed into the cytoplasm. In the neuronal soma, αSyn is able to interact with a variety of organelles (reviewed in (Bernal-Conde et al., 2019)). Localisation into the nucleus is facilitated via C-terminal SUMOylation and subsequent translocation by karyopherin α6 (Ryu et al., 2019). Because of its small size (<40 kDa), diffusion through the nuclear pore complex inside the nucleus might also be possible (Timney et al., 2016). αSyn can affect DNA persistence length, i.e., physical stiffness, and accessibility for transcription factors, either by direct electrostatic interactions with the DNA backbone, or indirectly, by retaining epigenetic proteins (e.g., histone-modifying enzymes) from entering the nucleus (Desplats et al., 2011; Jiang et al., 2018; Surguchov, 2023). It was observed that these interactions influence DNA condensation through H3K9 methylation and altered histone acetylation (Kontopoulos et al., 2006; Sugeno et al., 2016).

Outside the nucleus, αSyn is found at the outer mitochondrial membrane as well as in mitochondrial sub-compartments (Cole et al., 2008; Devi et al., 2008; Georgas et al., 2009; Menges et al., 2017). At the outer membrane, αSyn suppresses mitochondrial fusion events, which is suggested to benefit the transport of small mitochondrial fragments across the axon (Nakamura et al., 2011; Saxton and Hollenbeck, 2012; Bernal-Conde et al., 2020). However, another study found that drastically changed fusion-fission rates, induced by αSyn overexpression, impair axonal transport (Pozo Devoto et al., 2017). Once inside the mitochondrion, the largest proportion of αSyn accumulates at the inner mitochondrial membrane (IMM), where it most likely interacts with the highly anionic mitochondrial signature phospholipid cardiolipin (Cole et al., 2008; Dudek, 2017; Ryan et al., 2018). This IMM-localisation was mainly found around the electron

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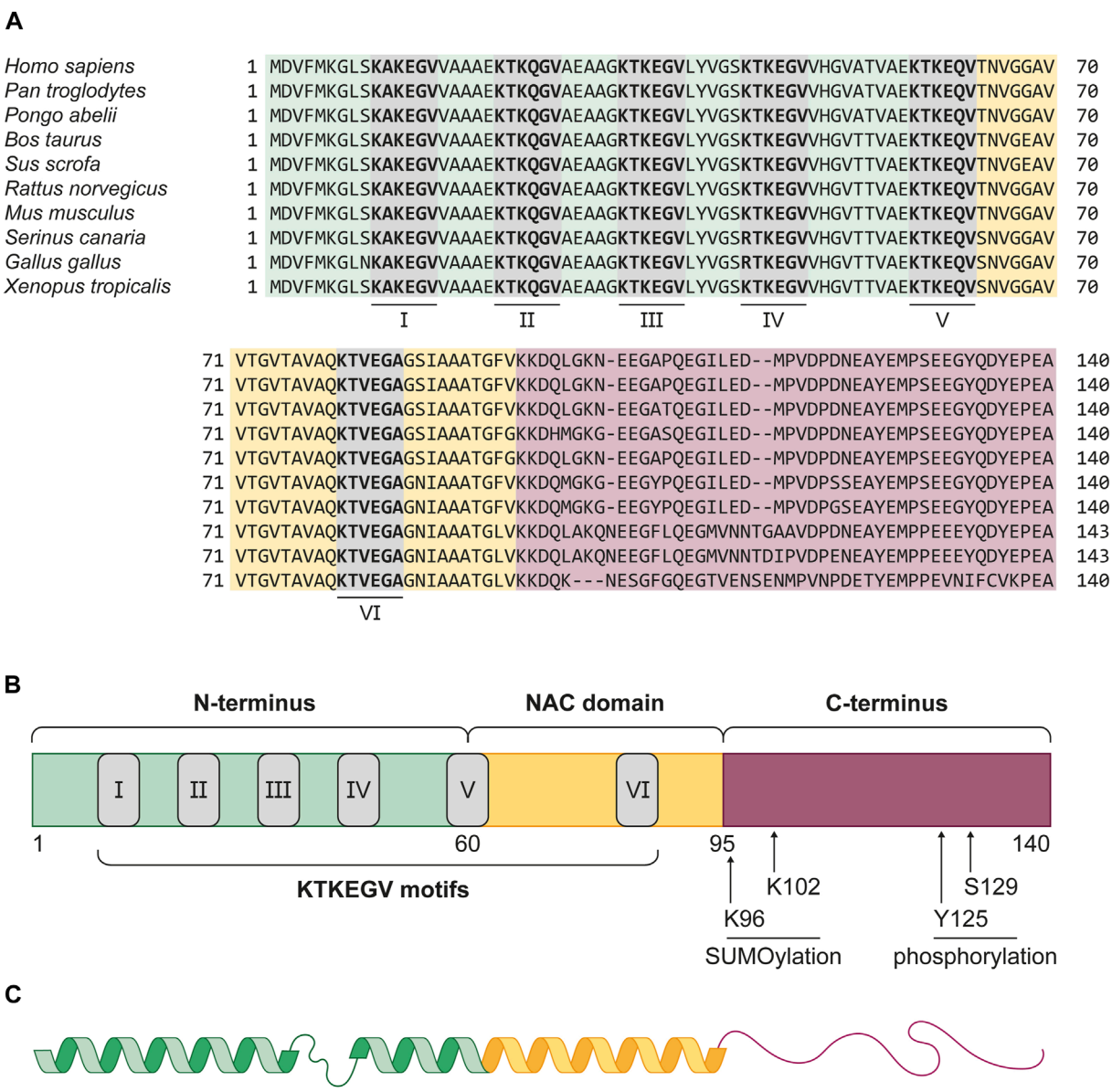

FIGURE 1
Evolutionary conservation and structure of αSyn. **(A)** Protein sequence alignment of αSyn in vertebrae species *Homo sapiens* (human), *Pan troglodytes* (chimpanzee), *Pongo abelii* (sumatran orangutan), *Bos taurus* (cattle), *Sus scrofa* (wild boar), *Rattus norvegicus* (common rat), *Mus musculus* (house mouse), *Serinus canaria* (atlantic canary), *Gallus gallus* (chicken), and *Xenopus tropicalis* (western clawed frog). The alignment shows a high conservation of the protein across all listed species, especially in the amphipathic N-terminus (green) and NAC domain (yellow). The six KTKEGV motifs (grey boxes), numbered I-VI, show close similarity, with only two differences. In cattle, the first arginine residue in the third motif (III) replaces the chemically very similar lysine residue. The same is observed for the first aa of the fourth KTKEGV motif (IV) in both bird species. In birds, the αSyn protein is also three aa longer than in the other listed organisms. **(B)** αSyn can be structurally divided into the amphipathic N-terminus (green, 1–60 aa), the aggregation promoting NAC-domain (yellow, 61–95 aa) and the acidic C-terminus (red, 96–140 aa) which facilitates protein-protein interactions. The grey boxes depict the KTKEGV motifs, which promote membrane association. At the C-terminus, four post-translational modifications, K96 and K102 SUMOylation, as well as Y125 and S129 phosphorylation, are displayed. These post-translational modifications are suggested to serve physiological functions of αSyn inside the cell. Phosphorylation at S129 is also associated with αSyn pathology. **(C)** Representation αSyn's secondary structure in the presence of membrane lipids. The N-terminus and NAC domain form an interrupted α-helix which binds to highly curved membranes. The proline-rich C-terminus is considered as intrinsically disordered and flexible.

transport chain (ETC), which is most likely due to its cardiolipin-rich environment (Paradies et al., 2014). The physiological function of αSyn at the ETC is not fully understood, but several lines of evidence suggest that αSyn might stabilise complex I-III electron transfer (Ellis et al., 2005; Devi et al., 2008).

One of the most important processes that αSyn interferes with is vesicular trafficking between the endoplasmic reticulum (ER), the Golgi apparatus (Golgi), and the endosomal shuttle network (Thayanidhi et al., 2010; Teixeira et al., 2021). In several PD models, αSyn was found to interact with membrane fusion

factor Rab1 and its homologues, which are associated with ER-Golgi trafficking (Cooper et al., 2006). While the study from Cooper et al. (2006) mainly focused on the detrimental interplay of αSyn with proteins involved in ER-GA transport, previous studies suggested a physiological function of αSyn for *soluble N-ethylmaleimide-sensitive-factor attachment receptor* (SNARE)-dependent membrane fusion events (Burré et al., 2010; Yoo et al., 2023). Accordingly, experiments in *S. cerevisiae* expressing human αSyn showed that the Rab1 homologue Ypt1 colocalises with cytosolic αSyn-accumulations (Soper et al., 2011). Human wild-type αSyn also co-localises with several other yeast Rab proteins, involved in intra-Golgi trafficking, such as Ypt6, Ypt31, and Ypt32 (Soper et al., 2011). In the endo-lysosomal system, αSyn was found to be in close proximity to transport vesicles (Lee et al., 2011; Huang et al., 2019) as well as important factors, such as RAB5A, RAB7, and RAB11A, which play a role in endosomal trafficking (Hasegawa et al., 2011). αSyn being involved in this pathway is supported by the high amounts of anionic, phosphorylated phosphoinositides that comprise endosomal transport vesicles, to which αSyn demonstrates an exceptionally high affinity (Jacob et al., 2021b; Choong et al., 2023).

One of the earliest discovered key functions of αSyn is its involvement in synaptic vesicle trafficking and exocytosis at the pre-synapse (reviewed in (Sharma and Burré, 2023; Nordengen and Morland, 2024)). In fact, the majority of αSyn is found at pre-synaptic axon terminals in adult animals (Maroteaux et al., 1988; Hsu et al., 1998). In order to reach its destination, αSyn is transported along the axon via the slow component b (SCb) (Tang et al., 2012). Besides αSyn, SCb was shown to mainly transport proteins critical for axon growth and regeneration, as well as synaptic function (Roy et al., 2007). Interestingly, the translocation of αSyn to the synapse is also dependent on its association with lipid rafts (Fortin et al., 2004).

At the axon terminal, αSyn was found to play an important, but not essential, role in the life cycle of synaptic vesicles (SV), primarily, but not exclusively, in dopaminergic neurons (reviewed in (Nordengen and Morland, 2024)). During preparation of SV secretion, αSyn participates in different steps, such as monoamine transmitter loading, vesicle docking and - priming (Pifl et al., 2014; Huang et al., 2019). In vesicle priming, αSyn was shown to interact with different proteins that facilitate the fusion of SV and the plasma membrane, e.g., SNARE proteins and the previously mentioned Rab proteins (Burré et al., 2010; Lou et al., 2017). In these processes, the N-terminus of αSyn is proposed to remain in close proximity to the SV membranes, due to its high affinity to anionic and highly curved membranes, while the C-terminus is thought to interact with other proteins (Jensen et al., 1999; Payton et al., 2004; McFarland et al., 2008). Recent data in different cell types show that the localisation of αSyn to the plasma membrane is highly dependent on the abundance of phosphatidylinositol polyphosphates, namely, phosphatidylinositol bisphosphates (PIP2) and phosphatidylinositol trisphosphates (PIP3) (Jacob et al., 2021b). Subsequently, αSyn is also involved in the fusion of SVs and, thereby, the release of neurotransmitters. The presence of αSyn was shown to expand the exocytotic fusion pore at the synapse, favouring full membrane fusion over the faster "kiss-and-run" mechanism (Khounlo et al., 2021). In order to keep the SV pools balanced, αSyn was suggested to aid with endocytosis by introducing higher curvature to the synaptic plasma membrane (Westphal and Chandra, 2013).

αSyn demonstrates a high variety of localisations and putative physiological functions across the neuron, from soma to axon terminal (Summarised in Figure 2). In PD and LBD, aggregated forms of αSyn that contribute to disease pathology were found to be in close proximity to the beforementioned organelles and pathways (Miraglia et al., 2018; Moors et al., 2021). This underlines the importance of a strict regulation of putative physiological functions of αSyn in affected cellular compartments. Even though interactions with multiple organelles and transport pathways may appear arbitrary at first glance, a shared characteristic unites these diverse localisations of αSyn. αSyn seems to play a key role in general vesicle organisation and membrane fusion events. This was especially observed in highly curved membrane regions rich in anionic phospholipids, such as SVs, general endolysosomal vesicles, or even mitochondria with externalised cardiolipin (Ryan et al., 2018). Given that the above described αSyn-membrane interactions play such a considerable role in αSyn's putative impact on a variety of neuronal functions, dysregulation of these interactions might be likely to contribute to the generation and/or progression of αSyn related neurodegenerative diseases.

4 Synucleinopathies and lipids

4.1 PD and lipid changes

The most common synucleinopathy is PD, which is commonly associated with neurodegeneration of dopaminergic neurons in the substantia nigra (SN) and the formation of LBs (Kalia and Lang, 2015). Analyses of patient tissue have revealed that the lipid composition of the brain is changed. These changes include, for example, an increase of diacylglycerols (DAGs) in the frontal cortex of PD patients (Wood et al., 2018). Lipidomic analysis of the visual cortex of PD patients revealed a dramatically altered lipid profile when compared to control brains. These changes include a decrease of unsaturated phosphatidylethanolamine (PE) and differences in the amount of phosphatidylinositol (PI), depending on its fatty acid (FA) chain lengths (Cheng et al., 2011). Similar observations were made when lipidomic analyses were performed upon expression of αSyn in several model systems, where an increase in DAG together with a decrease of several membrane lipid species such as phosphatidylserine (PS) and PI was found (Fanning et al., 2019). Taken together, this suggests that αSyn (-aggregation) may change the lipid composition of the brain.

It is also known that αSyn-lipid interactions depend on the membrane lipid composition. For example, it was shown that increasing the amount of negatively charged gangliosides (GMs) of small unilamellar vesicles (SUVs) *in vitro* increased membrane binding of αSyn (Man et al., 2021). Further *in vitro* studies revealed that the amount of anionic lipids is crucial for αSyn-membrane interactions (Davidson et al., 1998; Andersson et al., 2024) and that more αSyn is able to bind to anionic deformable SUVs, showing that the charge, the flexibility, and the curvature of membranes influence αSyn binding (Andersson et al., 2024; Makasewicz et al., 2024). Furthermore, the interaction of αSyn with membrane lipids was proposed to contribute to aggregate formation (Auluck et al., 2010;

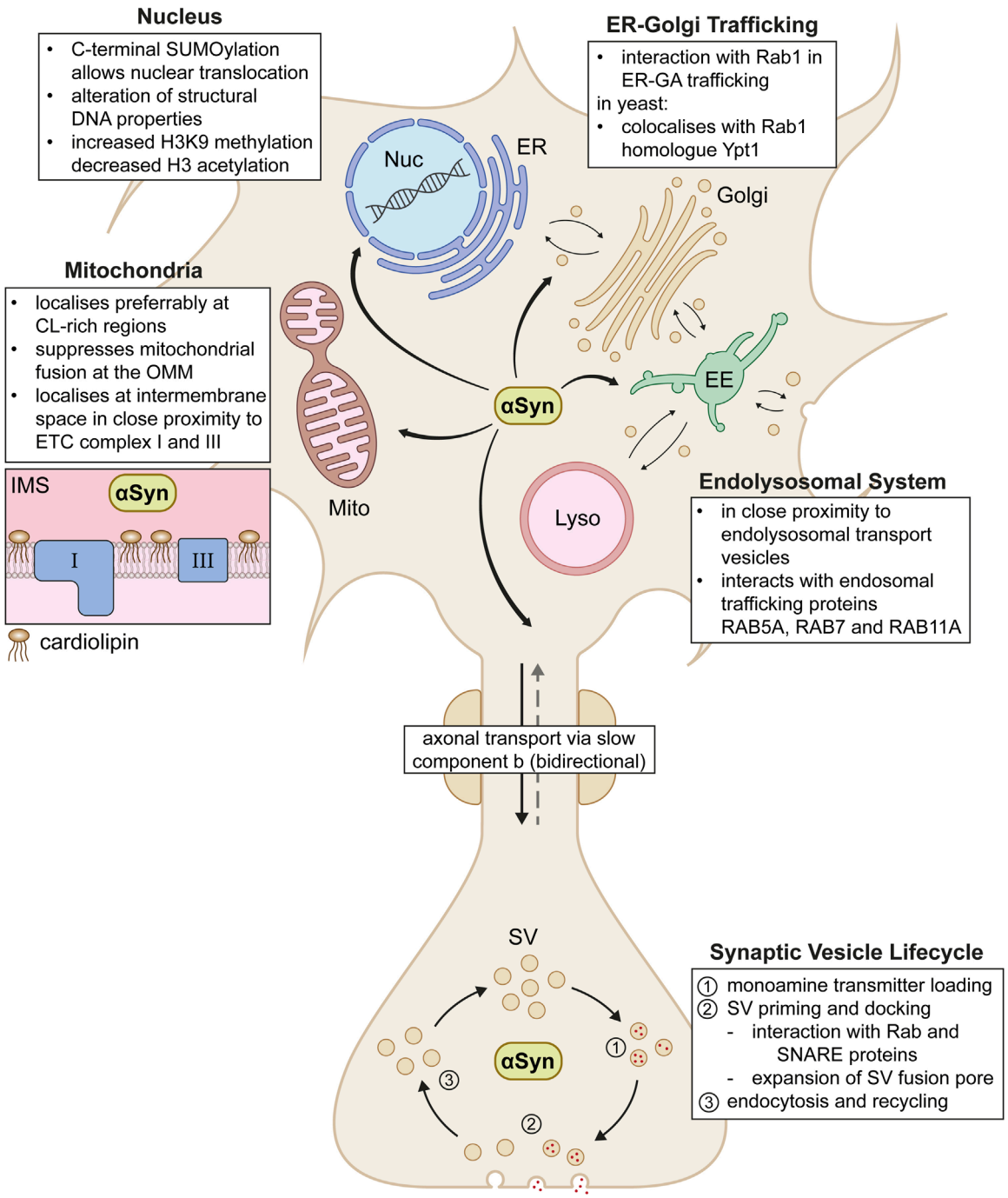

FIGURE 2
Proposed physiological interactions of αSyn across the neuron. In the cell, αSyn acts in various compartments including the nucleus (Nuc), endoplasmic reticulum (ER), Golgi apparatus (Golgi), early endosomes (EE), lysosomes (Lyso) and mitochondria (Mito). In mitochondria, αSyn localises in the intermembrane space (IMS) in close proximity to electron chain complex I and III (box on the left). αSyn shuttles between soma and synapse via axonal transport via the slow component b. At the synapse, αSyn plays a role in various steps of the entire life cycle of synaptic vesicles (SV). Further interaction details are depicted as text boxes in the figure.

Galvagnion et al., 2015). However, other studies have shown that this interaction can prevent αSyn fibril formation (Zhu and Fink, 2003; Martinez et al., 2007). It is important to note that these studies have all been conducted *in vitro* and in correlation with different lipid compositions. While the ratio of PS, phosphatidylcholine (PC), and PE contributed to amyloid aggregation (Galvagnion et al., 2015), interaction with the ganglioside GM1 inhibited it (Martinez et al., 2007). Indeed, GM1 levels were shown to be decreased in brains

of PD patients (Hadaczek et al., 2015). Studies on mice deficient for the GM2-synthase, were shown to exhibit PD-like symptoms, which could be alleviated by treatment with LIGA-20, an analogue of GM1 that is able to cross the blood brain barrier (BBB) (Wu et al., 2011). Therefore, the overall lipid composition might not only have a great influence on αSyn membrane interaction but also on αSyn oligomerisation and fibril formation, by either inducing or preventing it. Interestingly, PD-associated mutations of αSyn have been shown to exhibit differential membrane interaction properties (Battis et al., 2023).

Furthermore, some genetic risk factors for PD that are involved in membrane lipid metabolism continue to be identified. One of the most prominent examples are mutations of the *GBA1* gene, coding for the hydrolase glucocerebrosidase (GCase) (Aharon-Peretz et al., 2004; Neumann et al., 2009; Galper et al., 2022; Flores-Leon and Outeiro, 2023). *GBA1* mutations include T369M, T297S, and E326K, among others and cause a reduced activity of the lysosomal GCase (Dos Santos et al., 2024). This is associated with an increased risk for PD (Flores-Leon and Outeiro, 2023; Dos Santos et al., 2024). The GCase hydrolyses glucoceramide to glucose and ceramide in the lysosome and, thus, plays a role in sphingolipid metabolism (Gegg et al., 2022). However, the exact mechanisms of how this leads to PD are still unclear. It is thought that a reduced activity of the GCase inhibits lysosomal function and, thereby, leads to an increased amount of protein aggregation, including aggregation of αSyn (Johnson et al., 2020). It was further shown that αSyn aggregation depends on the FA chain length of GCase substrates; only FA chains longer than C22 induced aggregation (Fredriksen et al., 2021). Conversely, GCase activation enhanced lysosomal activity, which induced clearance of αSyn aggregates (Mazzulli et al., 2016). Interestingly, homozygous mutations of *GBA1* are known to cause Gaucher's disease (GD), in which symptoms overlap with symptoms known in PD (Johnson et al., 2020).

Another risk factor for PD that is associated with lipid metabolism is Synaptojanin 1 (SYNJ1), which is a PIP-phosphatase (Krebs et al., 2013; Quadri et al., 2013; Olgiati et al., 2014; Ben Romdhan et al., 2018; Schechter and Sharon, 2021). SYNJ1 is part of several pathways involving vesicular structures such as endocytosis (Perera et al., 2006), endosomal trafficking (Watanabe et al., 2018), and autophagy (George et al., 2016; Vanhauwaert et al., 2017). Mutations in SYNJ1's PIP-phosphatase domain but also other domains are associated with an increased risk for developing PD (Ben Romdhan et al., 2018; Taghavi et al., 2018; Schechter and Sharon, 2021). Again, the exact mechanisms that cause an increased risk for PD are still unclear. It is thought that synaptic dysfunction, caused by SYNJ1 mutations, may trigger neurotoxicity (Brooker et al., 2024). Additionally, mutations of *SH3GL2*, which encodes for the SYNJ1 binding partner endophilin A1, have also been identified as risk factors for PD (Nalls et al., 2019; Brooker et al., 2024). Similarly, mutations in *LRRK2*, a protein kinase that phosphorylates SYNJ1 and is involved in endocytosis (Pan et al., 2017; Schechter and Sharon, 2021) and autophagy (reviewed in (Madureira et al., 2020)) have been identified as risk factors for PD (Summarised in Table 1). Again, detailed molecular mechanisms remain unclear. Taken together, dysregulation of lipid homeostasis, whether directly or indirectly, is likely to affect cellular function and, thus, contributes to PD formation and/or progression.

As most data on αSyn and lipid homeostasis exist in the context of PD, little is known about lipid changes, maybe even in other brain regions, that may also be altered in other synucleinopathies. The question here is whether similar changes in lipid composition might be a common factor in all synucleinopathies and whether changes occur in different regions of the brain, which might explain the differences between the synucleinopathies. Lastly, whether and how the lipid composition influences aggregate conformation known to vary in different synucleinopathies still needs to be investigated.

4.2 DLB and lipid changes

Formation of LBs and a loss of dopaminergic neurons of the SN, together with a reduction of cortical neurons and neurons of the limbic system, are commonly associated with DLB (Outeiro et al., 2019). In DLB, LBs can also be found in different regions of the brain besides the SN, such as the neocortex and the limbic system (Outeiro et al., 2019). There is still very little data connecting changes in lipid homeostasis to DLB but a few genetic risk factors are known that overlap with risk factors for PD.

The most common genetic risk factors for DLB, shared with PD, are mutations of *GBA1*, causing changes in the functionality of the GCase, a dysregulation of sphingolipid metabolism, and changes in autophagy function (see above) (Lee et al., 2021). It was suggested that mutations of *GBA1* may even have a stronger association to DLB than to PD (Nalls et al., 2013; Lee et al., 2021). Another risk factor involved in lipid homeostasis that is associated with DLB is the presence of the *APOE ε4* isoform of the apolipoprotein E (APOE) (Tsuang et al., 2013; Bras et al., 2014). APOE has three isoforms (ε2, ε3, and ε4) and is mainly expressed in astrocytes. It plays a role in cholesterol and lipid transport across the brain, which is important for neuronal function (Yamazaki et al., 2019; Jin et al., 2022). Interestingly, the presence of the *APOE ε4* isoform has also been associated with Alzheimer's Disease (AD) (Lee et al., 2021; Pires and Rego, 2023; Fortea et al., 2024; Lozupone and Panza, 2024). An inefficient lipid transport from astrocytes to neurons is known to change neuronal lipid composition (Lefterov et al., 2019; Miranda et al., 2022). Interestingly, it was found in the context of AD, that carriers of the *APOE ε4* allele have reduced levels of PIP2, which was explained by a decreased degradation of the *SYNJ1* mRNA (Zhu et al., 2015). As mentioned above, mutations in *SYNJ1* itself are known risk factors for PD (Krebs et al., 2013; Quadri et al., 2013; Olgiati et al., 2014; Ben Romdhan et al., 2018; Schechter and Sharon, 2021), however, whether this is also the case for DLB is still unclear. Further research into a possible connection of *SYNJ1* mutations and DLB would help to clarify this. Maybe unsurprisingly, DLB is often not clearly distinguishable from AD (dementia only) or PD (Parkinsonism with dementia) (Noe et al., 2004; Jellinger and Korczyn, 2018; Nedelec et al., 2023) (Summarised in Table 1).

In general, the presence of αSyn itself is already changing the cellular lipid composition (see above), and, thus, it might be likely that this is also the case in other synucleinopathies. The combination of genetic factors that change the cellular lipid profile might be one of the factors leading to or accelerating disease progression.

TABLE 1 Summary of lipid-related connections to αSyn pathology in PD, DLB, and MSA.

α-Synucleinopathy	Affected brain region	Connection to lipids (including genetic factors)	Aggregates found	References
Parkinson's Disease (PD)	• Dopaminergic neurons of the substantia nigra (pars compacta)	*Patient data* • Increase of DAG in the frontal cortex of PD patients • General change of the lipid profile of the visual cortex of PD patients including a decrease of unsaturated PE and FA-chain length dependent changes in the amounts of PI • Decrease of GM1 in brains of PD patients *In vitro studies* • αSyn has a higher binding affinity to negatively charged/anionic membrane lipids and to vesicular membranes • PS, PC, and PE to αSyn ratio contributes to amyloid aggregation • GM1 inhibits amyloid aggregation *In vivo studies* • Increase of DAG, decrease of PS and PI • GM2-synthase deficient mice show PD-like symptoms, which can be alleviated by GM1-analogue treatment *Genetic risk factors* • Mutations of *GBA1* • Mutations of *SH3GL2* • Mutations of *LRRK2*	• Formation of Lewy Bodies (LBs) and Lewy Neurites • Aggregates contain a Lewy fold: three layered aggregates comprised of residues 31–100 of αSyn that form a total of 9 β-sheet strands	Davidson et al. (1998), Aharon-Peretz et al. (2004), Martinez et al. (2007), Neumann et al. (2009), Cheng et al. (2011), Wu et al. (2011), Krebs et al. (2013), Quadri et al. (2013), Olgiati et al. (2014), Galvagnion et al. (2015), Hadaczek et al. (2015), Kalia and Lang (2015), Ben Romdhan et al. (2018), Wood et al. (2018), Fanning et al. (2019), Johnson et al. (2020), Man et al. (2021), Schechter and Sharon (2021), Galper et al. (2022), Gegg et al. (2022), Yang et al. (2022), Flores-Leon and Outeiro (2023), Andersson et al. (2024), Dos Santos et al. (2024), Makasewicz et al. (2024)
Dementia with Lewy Bodies (DLB)	• Neocortex • Limbic system • Dopaminergic neurons of the substantia nigra (pars compacta)	*Patient data* • Decrease of several phospholipids in brains of *APOEε4* carriers (in the context of AD) • In the context of AD: reduced levels of PIP2 *In vivo studies* • In the context of APOE ε4 KI mice: reduced levels of PIP2 and reduced degradation of *SYNJ1*mRNA *Genetic risk factors* • Mutations of *GBA1* • Carriers of *APOEε4*	• Formation of LBs and LNs • Aggregates contain a Lewy fold: three layered aggregates comprised of residues 31–100 of αSyn that form a total of 9 β-sheet strands	Nalls et al. (2013), Zhu et al. (2015), Lefterov et al. (2019), Outeiro et al. (2019), Lee et al. (2021), Yang et al. (2022)
Multiple System Atrophy (MSA)	• MSA-P (with parkinsonism): midbrain and basal ganglia • MSA-C (with cerebral ataxia): midbrain, cerebellum, and brainstem	*Patient data* • Low serum levels of cholesterol, LDL-C, HDL-C (lower in MSA-C patients), and TG are associated with both, MSA-C and MSA-P, but have no effect on disease progression *In vivo studies* • Transcriptome analysis of striatal astrocytes of a MSA mouse model revealed a downregulation of genes involved in lipid metabolism *Genetic risk factors* • inconclusive • weak connection to APOE ε4	• Formation of glial cytoplasmic inclusions (GCIs) in oligodendrocytes • Aggregates form asymmetrical Type I or Type II filaments • Type I filaments are made of two protofibrils: PF-1A is formed by residues 14–94 and contains 12 β-sheets and PF-1B is formed by residues 21–99 and contains ten β-sheets • Type II filaments are made of two protofibrils: PF-IIA is formed by residues 14–94 and also contains 12 β-sheets but has a different conformation to PF-IA. PF-IIB is formed by residues 36–99 and contains nine β-sheets	Lee et al. (2009), Cao et al. (2014), Robinson et al. (2018), Schweighauser et al. (2020), Poewe et al. (2022), So and Watts (2023), Schneider et al. (2024)

4.3 MSA and lipid changes

MSA is a rare neurodegenerative synucleinopathy and, in contrast to PD and DLB, associated with the formation of αSyn aggregates in oligodendrocytes referred to as glial cytoplasmic inclusions (GCIs) (Spillantini et al., 1998; Poewe et al., 2022). One of the hallmarks of MSA is a demyelination of neurons, which is connected to GCI-formation (Poewe et al., 2022). Myelin, multiple layers of membranes looped around the axon, contains a higher proportion of cholesterol and glycolipids (e.g., glycosylceramide) than other cellular membranes (Baumann and Pham-Dinh, 2001; Poitelon et al., 2020).

Little is known about the connections between GCI formation and the unique lipid composition of myelin sheaths in the context of MSA. It was shown that lower cholesterol levels and lower levels of LDL-C and HDL-C in patient serum have been connected to an increased risk of developing MSA (Lee et al., 2009; Cao et al., 2014). However, it is known that lipoproteins carrying cholesterol outside the central nervous system do not cross the blood brain barrier (BBB) and that cholesterol in the brain is mainly synthesised in astrocytes (Bleasel et al., 2014; Pifferi et al., 2021; Li et al., 2022). Thus, the connections between serum cholesterol levels and lipid changes in the brain during MSA remain elusive on a molecular level. In an MSA mouse model, transcriptome analyses of astrocytes implicated a dysregulation of cellular lipid metabolism (Schneider et al., 2024). This might point towards a changed lipid homeostasis in MSA but needs to be investigated more thoroughly.

Genetic risk factors for MSA that connect to lipid homeostasis are currently unknown. There are inconclusive studies on the genetic background of MSA (Poewe et al., 2022). Interestingly, one study suggests that the frequency of MSA-patients carrying the *APOE ε2* isoform is lower than the frequency of MSA patients carrying the *APOE ε4* isoform (Robinson et al., 2018) (Summarised in Table 1).

Taken together, MSA remains the rarest and, in terms of connection to lipids, the most elusive synucleinopathy, mostly due to the inconclusive evidence for a genetic background. Nevertheless, more research effort has to be directed towards understanding the differences or similarities between PD, DLB, and MSA.

5 Lipid changes in physiological ageing

Given that ageing is one of the biggest risk factors for developing neurodegenerative diseases such as PD, and that most neurodegenerative diseases occur sporadically, it is of great interest to understand lipid changes in the aged brain. While there has been a lot of research effort to better understand disease-related lipid changes in the brain, less is known about the possible lipid changes during physiological ageing. Very early studies analysing whole brains have described a general decline of total lipids with age (Rouser and Yamamoto, 1968; Mesa-Herrera et al., 2019). Later, analyses of white matter and cerebral cortices of the temporal and frontal lobes confirmed these findings (Svennerholm et al., 1991). More specific analyses of lipid classes revealed, for example, a reduction of polyunsaturated fatty acids (PUFAs) in the orbitofrontal cortex with age (McNamara et al., 2008). A more recent study has found that, while the overall lipid concentrations in the prefrontal cortex remain at a similar level with age, the lipid profile itself undergoes changes with a transition point of about 50–55 years of age. Some affected pathways were shown to be unsaturated fatty acid biosynthesis and glycerolipid metabolism, with differences between males and females (Yu et al., 2020). Interestingly, regional lipid profile diversity was also shown to change with age (Mota-Martorell et al., 2022). However, given the complexity of the brain, lipid changes in the physiologically ageing brain are still not clearly understood. Being able to differentiate between changes in healthy ageing and changes that might be part of, or even precede, pathological processes of neurodegeneration is of great importance to prevent and/or treat these diseases.

In an effort to find potential disease markers for PD, a significant amount of research has been focusing on lipidomic analyses of patient serum. For example, serum analyses of patients carrying the A53T mutation of *SNCA* revealed an increase of diacylglycerol, triacylglycerol, and PC (Avisar et al., 2022). Similarly, a decrease of serum levels of HDL-C was found in patients with PD (Choe et al., 2021). Furthermore, patients carrying a mutation in *LRRK2* showed changes in ceramide (Cer), TAG, sphingomyelin, PC, and lyso-phosphatidylethanolamine (LPE) (Galper et al., 2022). Analysis of samples from patients with idiopathic PD showed similar findings with lower levels of PS, some Cer species, and Sphingomyelin (SM) (Dahabiyeh et al., 2023). While these findings might pave the path to potential serum markers for disease, this is only the beginning of more extensive research to come. The challenge here is to find common markers that are reliably enough for all variants of PD, as it is a disease caused by multiple factors, many of which have not yet been completely understood.

6 Lipid interactions and possible influences on aggregate formation

Interestingly, it is known that different synucleinopathies exhibit different fibrillar αSyn conformations. These conformational differences are referred to as αSyn strains and, similarly to what is already known in prion diseases, they show different characteristics in terms of disease progression (Prusiner, 2012; Bousset et al., 2013; Peng et al., 2018; Woerman et al., 2019). When comparing LBs to GCIs from MSA patients, for example, the conformation of the accumulations was shown to be clearly distinct from each other (Peng et al., 2018; Shahnawaz et al., 2020). Indeed, two types of filaments were found in MSA patient brain extracts: Type I filaments were larger and showed a distinct folding when compared to the smaller Type II filaments. Both filaments were found to be asymmetrical and made of two protofilaments each. These protofilaments contain between 9 and 12 β-sheets (Schweighauser et al., 2020; So and Watts, 2023). αSyn filaments derived from patients with DLB or PD, on the other hand, showed identical conformations containing an ordered core called the *Lewy fold*, which is a three-layered aggregate with a total of nine β-sheets formed by residues 31–100 (Table 1) (Yang et al., 2022). *In vitro*, recombinant αSyn showed a larger variation in aggregate conformation, depending on chemical conditions under which the aggregations were formed (So and Watts, 2023). These variants exhibited different effectivities of prion-like seeding properties

(Walker and Jucker, 2015; Goedert et al., 2017), e.g., the propagation from cell to cell within the brain (Torre-Muruzabal et al., 2023).

However, the reason for these conformational differences that cause different disease phenotypes in synucleinopathies are not well understood. It is known that αSyn aggregation can be triggered by interaction with lipids (Makasewicz et al., 2024). Using *in vitro* membrane models including small unilamellar vesicles (SUVs), giant unilamellar vesicles (GUVs), and flat supported lipid bilayers, it was shown that lipid interaction of αSyn can induce nucleation of aggregates (Grey et al., 2011; Galvagnion et al., 2015; Makasewicz et al., 2021; Dear et al., 2024). These processes are dependent on the lipid composition of the vesicular structures investigated, the amount of negatively charged lipids, membrane fluidity, and membrane curvature (reviewed in (Makasewicz et al., 2024)).

Furthermore, familial variants of αSyn are found to be N-terminally acetylated in LBs (Anderson et al., 2006). Recently, it was shown that N-terminal acetylation of familial variants of αSyn can change the structure of the fibrillar aggregates and the lipid binding properties individually for each investigated variant (Bell et al., 2023). These findings point towards highly complex processes involved in the formation of synucleinopathies, implicating, among others, lipid composition, post-translational modifications, and possible mutations of *SNCA*.

Based on this, it might not be unlikely that changes in cellular lipid composition, occurring with age, through mutations in genes involved in lipid homeostasis, or through individual lifestyle and environmental factors, influence disease onset, variation, severity, and progression. Thinking a little further, this might even mean that differences of lipid compositions within a single brain (Mota-Martorell et al., 2022) could explain regional specificity of protein aggregates and symptom-phenotype variations. Indeed, it was recently found that distinct aggregate variants can be found in different brain regions (Wiseman et al., 2024). Taken together, understanding changes in the lipid composition of different brain regions and how this affects disease is likely to be one of the significant steps towards understanding the progression and onset of synucleinopathies. An improved understanding of the underlying processes will open new paths towards treatment or even disease prevention.

7 Discussion

The putative physiological functions and membrane binding properties of αSyn and processes during neurodegeneration are strongly connected to lipid changes in the brain. While synucleinopathies are all known to be multifactorial neurodegenerative diseases, it is possible that some of the factors currently recognised as contributing to disease development and progression might be rooted in changes in lipid metabolism or membrane lipid composition (Reviewed in (Flores-Leon and Outeiro, 2023)). For example, it was shown that a lack of the well-established risk factor for PD *PINK1* causes an accumulation of ceramides in the mitochondrial membrane, inhibiting β-oxidation and causing degradation of mitochondria via mitophagy (Vos et al., 2021; Flores-Leon and Outeiro, 2023). Even though the exact physiological roles of αSyn still remain to be determined, much progress has been made. With the help of advanced analytical methods, understanding the connection between lipid changes (storage, metabolism, lipid rafts, membrane composition) and αSyn is of importance to provide a deeper insight into the ever-increasing complexity of synucleinopathies.

Individual genetic risk factors, environmental and nutritional factors, and ageing, might all have an impact on the lipid composition of the brain. To date, very little is known about lipid-changes during physiological ageing although understanding these processes might be key to develop new research approaches for prevention or treatment of synucleinopathies. Furthermore, being able to distinguish between physiological lipid changes and alterations that contribute to disease progression will contribute substantially to future research of neurodegeneration. More progress is needed to understand regional lipid changes and their potential impact on disease development. Considering that these changes may result from a combination of several factors that are likely to be individual for each affected person, personalised assessments and treatments should be considered in the future. If different lipid compositions affect aggregate conformation and, with that, influence the rate of disease progression and spread throughout the brain, it might potentially open new ways of disease prevention or inspire novel therapeutical approaches.

A lot of research has already been conducted on future therapeutical or preventative treatments. One approach, for example, is the use of lipidic nanoparticles for drug delivery (Tsakiri et al., 2024), which could be adapted for targeting lipid changes in the brain, a concept referred to as *membrane lipid therapy* (Escriba et al., 2015). However, for that, we require a deeper understanding of the molecular mechanisms of lipid changes in synucleinopathies. Other major challenges that need to be addressed are ways to diagnose and classify neurodegenerative diseases such as synucleinopathies earlier and before the onset of clinical symptoms. Here, we can expand on the research efforts into finding reliable early biomarkers for PD such as, for example, αSyn seeding assays of cerebrospinal fluid (Orru et al., 2021; Rutledge et al., 2024).

Although a lot of factors connected to disease formation are already well understood, the influence of lipids on these processes have only recently gained more attention. Taken together, future research efforts should be made to (i) better understand differences between lipid changes that occur during physiological aging and lipid changes associated with pathological processes; (ii) to understand how regional differences in the lipid composition might contribute to aggregate localisation and conformation and, with that, influence the speed of disease progression and symptom variations; (iii) and to find reliable markers that can detect pathological processes earlier. Viewing synucleinopathies through the lens of lipid alterations alongside other well-established disease contributors possibly holds the potential to find novel approaches in disease diagnosis and therapy.

Author contributions

JS: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. TL: Visualization, Writing–original

draft, Writing–review and editing. CB: Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Hanna Bragard-Apfel Stiftung and the Peter-Beate-Heller-Stiftung des Stifterverbandes für die deutsche Wissenschaft.

Acknowledgments

We thank Fazilet Bekbulat for critical reading of the manuscript.

Conflict of interest

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