Neurobiology of Disease 166 (2022) 105663

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments

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ARTICLE INFO

Keywords:
Parkinson disease
α-synuclein
Lysosome
Autophagy
Lipid
Neuroinflammation
Glucocerebrosidase

ABSTRACT

Dysfunction of the endolysosomal system is implicated in the pathogenesis of both sporadic and familial Parkinson disease (PD). Variants in genes encoding lysosomal proteins have been estimated to be associated with more than half of PD cases. The most common genetic risk factor for PD are variants in the *GBA* gene, encoding the lysosomal enzyme glucocerebrosidase (GCase), which is involved in sphingolipid metabolism. In this review we will describe the clinical symptoms and pathology of GBA-PD, and how this might be affected by the type of *GBA* variant. The putative mechanisms by which GCase deficiency in neurons and glia might contribute to PD pathogenesis will then be discussed, with particular emphasis on the accumulation of α-synuclein aggregates and the spread of pathogenic α-synuclein species between the cell types. The dysregulation of not only sphingolipids, but also phospholipids and cholesterol in the misfolding of α-synuclein is reviewed, as are neuroinflammation and the interaction of GCase with LRRK2 protein, another important contributor to PD pathogenesis. Study of both non-manifesting *GBA* carriers and GBA-PD cohorts provides an opportunity to identify robust biomarkers for PD progression as well as clinical trials for potential treatments. The final part of this review will describe preclinical studies and clinical trials for increasing GCase activity or reducing toxic substrate accumulation.

1. GBA-Parkinson disease

Bi-allelic mutations in the *GBA* gene cause the lysosomal storage disorder Gaucher disease (GD). Following clinical observations that people with GD were at increased risk of developing Parkinson disease (PD) (Neudorfer et al., 1996; Turpin et al., 1987), several large-scale genetic studies demonstrated that heterozygote *GBA* variants are the most important genetic risk factor for developing PD identified to date, accounting for 5-30% of PD cases depending on population and age (Cilia et al., 2016; Duran et al., 2013; Senkevich and Gan-Or, 2020; Sidransky et al., 2009).

More than 100 *GBA* variants have been associated with PD. However, the pathogenicity of many GBA missense variants remain unknown. Overall the odds ratio for developing PD is approximately 3.5 - 6 (Neumann et al., 2009; Sidransky et al., 2009). However, some 'severe' *GBA* variants that cause type II/III GD (e.g., p.L444P, c.84GG) have a greater risk of disease (odds ratio 10.3), while 'mild' variants (e.g., p.N370S) have an odds ratio less than five. Two *GBA* variants (p.T369M and p.E326K) that do not cause GD, but increase PD risk (hereinafter referred to as 'risk' variants), have the lowest odds ratio (Cilia et al., 2016; Senkevich and Gan-Or, 2020). As the estimated lifetime risk of developing PD with a heterozygote *GBA* variant is relatively low (up to 30%), other factors are likely to contribute, including other genetic variants, haplotypes, mosaicism; environmental and age-related factors (Blauwendraat et al., 2020; Mokretar et al., 2018; Schierding et al., 2020; Senkevich and Gan-Or, 2020).

Abbreviations: AAV, adeno-associated virus; ALP, autophagy lysosome pathway; BBB, blood brain barrier; CBE, conduritol β-epoxide; CSF, cerebrospinal fluid; CMA, chaperone mediated autophagy; CNS, central nervous system; ER, endoplasmic reticulum; ERAD, ER associated degradation; ETC, electron transport chain; EV, extracellular vesicles; GCase, glucocerebrosidase; GCS, glucosylceramide synthase; GD, Gaucher disease; GlcCer, glucosylceramide; GlcChol, glucosylated cholesterol; GlcSph, glucosylsphingosine; GPNMB, glycoprotein nonmetastatic melanoma protein B; HMW, high molecular weight; HSP70, heat shock protein 70; iPS, inducible pluripotent stem cells; KD, knock down; KI, knock in; KO, knock out; LD, lipid droplet; LRRK2, leucine rich repeat kinase 2; mDA, midbrain dopaminergic neurons; NFKB, nuclear factor $_{K}$ B; NRF2, nuclear factor erythroid 2-related factor 2; PC, phosphatidylcholine; PD, Parkinson disease; PE, phosphatidylethanolamine; PFFs, preformed α-synuclein fibrils; PGRN, progranulin; PS, phosphatidylserine; RCT, random controlled trial; RT-QuIC, real time quaking conversion; TFEB, transcription factor EB; TLR, toll like receptor; TRIP12, thyroid hormone receptor interacting protein 12; UPR, unfolded protein response.

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https://doi.org/10.1016/j.nbd.2022.105663
Received 5 December 2021; Received in revised form 30 January 2022; Accepted 15 February 2022
Available online 17 February 2022

Age of onset for *GBA*-PD is approximately five years earlier than sporadic PD (Avenali et al., 2021; Neumann et al., 2009; Sidransky et al., 2009), with carriers of a severe variant manifesting symptoms even earlier (Cilia et al., 2016; Lerche et al., 2021). *GBA* variants increase the burden of non-motor symptoms such as rapid eye movement sleep behaviour disorder, autonomic dysfunction, and cognitive decline in GBA-PD cohorts (Brockmann et al., 2011; Gan-Or et al., 2018; Petrucci et al., 2020; Winder-Rhodes et al., 2013). Both motor and non-motor decline is reported to be faster in non-manifesting *GBA* carriers (Avenali et al., 2019; Beavan et al., 2015). It should also be noted that *GBA* variants increase the risk of developing dementia with Lewy bodies (DLB) with odds ratio greater than for PD (Bras et al., 2014; Nalls et al., 2013).

Lewy body pathology in *GBA*-PD brains has been reported to be similar to that of sporadic PD (Neumann et al., 2009; Parkkinen et al., 2011), with perhaps more diffuse neocortical Lewy body pathology present in *GBA*-PD brains compared to sporadic PD (Neumann et al., 2009). No differences in soluble or insoluble α-synuclein species (either monomeric or high molecular weight (HMW)) have been detected by western blotting in Lewy body disease brains with or without *GBA* variants (Gegg et al., 2012; Kurzawa-Akanbi et al., 2021). Total levels of α-synuclein in cerebrospinal fluid (CSF) have been reported to be decreased in GBA-PD, when compared to sporadic PD (Lerche et al., 2021), but not all cases (Brockmann et al., 2021; Huh et al., 2021). Levels of α -synuclein levels in brain extracellular vesicles (EV) from Lewy body disease brains were also similar between wild-type and *GBA* variants in the small number of samples measured (Kurzawa-Akanbi et al., 2021). Exosomes isolated from plasma of PD patients with *GBA* variants also had similar α -synuclein content as that of sporadic PD (Avenali et al., 2021). Although there was no change in plasma exosomes, the amount of α -synuclein in peripheral blood mononuclear cells was significantly higher than sporadic PD samples.

2. GCase activity in the brain

GBA encodes the lysosomal enzyme glucocerebrosidase (GCase) and catalyses the final step of glycosphingolipid and ganglioside catabolism, breaking down glucosylceramide to glucose and ceramide. Homozygote or compound heterozygote *GBA* variants cause the accumulation of glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph).

Following translation, GCase folds in the endoplasmic reticulum (ER) and then passes along the secretory pathway from the ER to the Golgi, undergoing several glycosylation steps on the way before being trafficked to endosomes and finally lysosomes. GCase binds to the transporter LIMP-2 in the ER for trafficking to the lysosome (Reczek et al., 2007) and requires enzymes such as phosphatidylinositol 4-kinase IIα in the Golgi for sorting into the correct vesicles (Jović et al., 2012).

Some GCase variants such as L444P and N370S fail to fold correctly in the ER activating the unfolded protein response (UPR) and ER stress (Fernandes et al., 2016; Ron and Horowitz, 2005; Sanchez-Martinez et al., 2016). Progranulin (PGRN), heat shock protein 70 (HSP70) and HSP40 have been implicated in the correct folding and trafficking of GCase to the lysosome (Arrant et al., 2019; Fog et al., 2018; Jian et al., 2016; Lu et al., 2010; Tan et al., 2014; Zhou et al., 2019). When GCase is unable to be refolded in the ER by chaperones, it undergoes ER-associated degradation (ERAD) utilising ubiquitin E3 ligases such as ITCH and thyroid hormone receptor interacting protein 12 (TRIP12) to direct unfolded GCase to be degraded by the proteasome (Maor et al., 2013; Seo et al., 2021). Therefore, *GBA* variants can result in a loss of GCase activity by a variety of mechanisms: loss of transcription/translation, misfolding in the ER followed by ERAD, incorrect trafficking and loss of critical amino acid in the enzyme domains required for catalytic activity.

GCase activity in GBA-PD brains was found to be decreased by 58% in the substantia nigra (Gegg et al., 2012) with other areas also affected to a lesser extent, including the putamen, amygdala and cerebellum (Gegg et al., 2012). GCase activity was also found to be decreased in the substantia nigra, putamen and frontal cortex in Lewy body disease cohorts (Kurzawa-Akanbi et al., 2012; Moors et al., 2019). The lower enzyme activity was coincident with a decrease in protein expression of GCase (Gegg et al., 2012; Kurzawa-Akanbi et al., 2012). The size of all three cohorts was too small to draw any conclusions as to whether the genotype correlated with GCase activity. However, a much larger study on CSF from two GBA-PD cohorts has indicated that people with severe *GBA* variants had significantly less activity than mild or risk variants (Lerche et al., 2021).

GCase activity has been reported to be significantly decreased in sporadic PD brains from several different cohorts (Chiasserini et al., 2015; Gegg et al., 2012; Huebecker et al., 2019; Moors et al., 2019; Murphy et al., 2014; Rocha et al., 2015a). Notably GCase has been found to decrease with age in healthy controls (Huebecker et al., 2019; Rocha et al., 2015a). Decreased GCase activity has also been reported in CSF and blood from sporadic PD patients when compared to age-matched healthy controls (Alcalay et al., 2015; Parnetti et al., 2014).

Once again, the decreased GCase activity in sporadic PD brains was coincident with lower GCase protein expression (Gegg et al., 2012; Murphy et al., 2014). While three reports suggested that this was not in tandem with a significant decrease in *GBA* mRNA levels (Gegg et al., 2012; Moors et al., 2019; Murphy et al., 2014), one study has found a significant decrease (Chiasserini et al., 2015). In addition to ageing, impaired endolysosomal trafficking of GCase may account for the decreased activity (discussed further below), as might dopamine oxidation-mediated damage (Burbulla et al., 2017).

Analyses of activities and protein expression of other endolysosomal proteins in sporadic PD brains have proved mixed, with some reports showing that the decrease in GCase activity is relatively selective in the substantia nigra (Gegg et al., 2012; Moors et al., 2019), while another reported decreases in several other lysosomal hydrolases (Huebecker et al., 2019). Data regarding other endolysosomal proteins such as the cathepsins evaluated in various regions and CSF of sporadic PD brains remains variable (reviewed by Moors et al., 2016; Paciotti et al., 2019), with GCase being the only one consistently reported to be decreased.

3. Glucocerebrosidase and lipid homeostasis

Bi-allelic *GBA* mutations causing type II/III neuronopathic GD result in a significant accumulation of GCase substrates GlcCer and GlcSph in the brain (Nilsson and Svennerholm, 1982; Orvisky et al., 2002). Very few studies have investigated GCase substrate accumulation in Lewy body disease brains with heterozygous *GBA* variants or sporadic PD brains. Neither GlcCer nor GlcSph was increased in the putamen of heterozygous GBA-PD brains (Gegg et al., 2015). Two different studies on Lewy body disease brains with *GBA* variants also reported no accumulation of GlcCer in the frontal cortex (Kurzawa-Akanbi et al., 2021) or primary motor cortex (Clark et al., 2015).

GlcCer and GlcSph have been found to be significantly increased in the substantia nigra of sporadic PD brains (Huebecker et al., 2019; Rocha et al., 2015a). It should be noted that these increases are modest compared to neuronopathic GD brains. However, this does not exclude the contribution of substrate accumulation to PD pathogenesis. All analyses were performed on tissue homogenates and local increases in particular types of neurons (e.g., the A9 dopaminergic neurons most susceptible to neurodegeneration in the substantia nigra), glia or localised intracellular locations (e.g., endolysosomal membranes) may have a pronounced effect on cell function.

The disparity in substrate accumulation between GBA-PD and sporadic PD might reflect the different brain regions and analytical techniques used as well as the small cohort sizes. In the case of GlcCer, the significant increase in sporadic PD brain was observed in people in their eighties (Huebecker et al., 2019), therefore age might have contributed to these results. A larger study on CSF from GBA-PD and sporadic PD indicated a small significant increase in total GlcCer levels in GBA-PD

versus sporadic PD. (Lerche et al., 2021). GlcCer was also found to be significantly increased in GBA-PD patients when compared to healthy controls in the Parkinson's Progressive Markers Initiative (Huh et al., 2021; Lerche et al., 2021). However, depending on the study, there was either higher total GlCer in GBA-PD when compared to sporadic PD (Huh et al., 2021), or similar levels (Lerche et al., 2021).

Lipidomic analyses of other sphingolipids in the brains containing wild-type or mutant *GBA* have yielded mixed results. In the substantia nigra of sporadic PD brains with significantly decreased GCase activity and substrate accumulation, an increase in total glycosphingolipids and a decrease in gangliosides were observed (Huebecker et al., 2019). Given that GCase activity was not the only lysosomal enzyme involved in sphingolipid metabolism to be impaired in these samples, it cannot be concluded, which, if any, are due to GCase deficiency specifically. Ceramide has been reported to be increased in Lewy body disease brains either specifically in brains with *GBA* variants (Clark et al., 2015) or independent of genotype (Kurzawa-Akanbi et al., 2021). Total sphingomyelin has been reported to be unchanged in the putamen of GBA-PD brains compared to healthy controls (Gegg et al., 2015). In CSF, total sphingomyelin levels have been found to be decreased in GBA-PD patients versus healthy controls and sporadic PD (Huh et al., 2021). However analyses of particular sphingomyelin species from the same cohort indicated that some species (e.g., C24:0) were significantly increased in CSF of GBA-PD patients (Lerche et al., 2021). When these results were stratified even further, carriers of mild or severe *GBA* variants had significantly higher levels of these particular species, compared to *GBA* risk variants (Lerche et al., 2021).

Although GCase is the last step in the catabolism of sphingolipids and generates ceramide, the building block of sphingolipids, there is growing evidence that other lipid species and cholesterol are affected by GCase deficiency in cell and animal models (discussed below). However, lipidomic analysis for these species in mutant *GBA* brains is limited. Total cholesterol levels were reported to be unchanged in the putamen of GBA-PD brains (Gegg et al., 2015). Studies in the blood have indicated either a decrease in cholesterol and low density lipoprotein in GBA-PD patients (Macías-García et al., 2021) or cholesterol levels to be unchanged (Guedes et al., 2017). Since cholesterol synthesis and catabolism is largely separate between the brain and the periphery, it is unclear if any changes in blood cholesterol levels are reflective of what is occurring in the brain.

Increased levels of glycerophosphoethanolamine, the breakdown product of the phospholipid phosphoethanolamine (PE), has been found to be increased in the putamen of GBA-PD brains (Brockmann et al., 2012). To complement this, the levels of PE in the cortex of Lewy body disease brains with *GBA* mutations was decreased, as was another major phospholipid subclass phosphatidylcholine (PC) (Clark et al., 2015). A few studies have reported decreased PE levels in sporadic PD brains (reviewed by Patel and Witt, 2017), but in the one case where glycerophosphoethanolamine levels were reported, they were found to be decreased (Hattingen et al., 2009).

Phosphatidylyserine (PS) levels were also increased in Lewy body disease brains with *GBA* mutations (Clark et al., 2015). PS can be made from PE and PC, but it is unknown if this pathway contributes to the imbalance in the major classes of phospholipids in mutant *GBA* brains or if other mechanisms are involved.

4. The relationship between GCase and α-synuclein

4.1. GCase deficiency and α-synuclein metabolism

Loss of GCase activity is coincident with an increase in intracellular α-synuclein levels in a variety of cell and animal models. Increased α-synuclein levels have been reported in human dopaminergic cell lines (Kim et al., 2018; Magalhaes et al., 2016), human dopaminergic midbrain neurons (mDA) differentiated from induced pluripotent stem cells (iPS) (Aflaki et al., 2016; Mazzulli et al., 2016a; Schöndorf et al., 2014), and human midbrain organoids (Jo et al., 2021). Similarly, α-synuclein accumulates in the midbrain of mouse models with knock-in (KI) heterozygote human p.L444P *GBA* mutations (Migdalska-Richards et al., 2017; Yun et al., 2018), or mice treated with the specific GCase inhibitor conduritol β-epoxide (CBE) (Rocha et al., 2015b). Increased α-synuclein levels are not confined to GCase deficient midbrain dopaminergic neurons *in culture* or *in vivo*, and include cortical and hippocampal neurons (Li et al., 2019a; Magalhaes et al., 2016; Migdalska-Richards et al., 2017; Osellame et al., 2013; Sardi et al., 2011).

Knock-out *GBA/Gba1* models (Jo et al., 2021; Kim et al., 2018) or the use of CBE (Magalhaes et al., 2016;Rocha et al., 2015; Zunke et al., 2018) suggests that GCase loss of function is sufficient for α-synuclein accumulation (Fig. 1). Activation of the UPR and ER stress by mutations such as L444P may also contribute to α-synuclein pathology or other aspects of PD pathogenesis, and might explain why severe variants tend to have an earlier age of onset and greater symptomatic decline than other *GBA* variants and sporadic PD.

Many studies have reported an increase in detergent soluble monomeric α-synuclein in GCase deficient cell models by western blotting (Magalhaes et al., 2016; Mazzulli et al., 2011; Schöndorf et al., 2014). Size exclusion chromatography of detergent soluble extracts have also indicated the presence of high molecular weight (HMW) α-synuclein species (Mazzulli et al., 2011; Zunke et al., 2018). The native state of α-synuclein has been proposed to be a tetramer, which is not as susceptible to aggregation to oligomers/fibrils as monomers (Bartels et al., 2011). The ratio of tetramer and related multimers to monomer has been reported to be decreased in *GBA* knock out (KO) SH-SY5Y cells and mDA from GBA-PD patients, suggesting that destabilisation to more monomeric species will increase the pathogenic oligomerisation of α-synuclein (Kim et al., 2018).

Of relevance to Lewy body pathology, proteinase K-resistant α-synuclein aggregates have been reported in brain sections of mutant GCase mouse models (Rocha et al., 2015b; Sardi et al., 2011, 2013). Insoluble α-synuclein has also been observed in cell models treated with CBE (Zunke et al., 2018), but not in all cases (Gegg et al., 2020). *GBA* KO midbrain organoids also exhibit insoluble and HMW α-synuclein species and increased kinetics of α-synuclein aggregation in seeding assays (Jo et al., 2021).

While the accumulation and aggregation of α-synuclein are well established, the conformation of oligomers and fibrils in GCase deficient cultured neurons and brains remains unclear. It is also unknown if these species are different 'strains' to that observed in sporadic PD. Fibrillar species of α-synuclein that can seed monomeric α-synuclein to aggregate in a prion-like fashion have been shown to have different conformations and seeding ability depending on the type of synucleinopathy (Peng et al., 2018). This will likely depend on the type of *GBA* mutation and the cellular conditions this engenders. Accumulation of the GCase substrates GlcCer and GlcSph; imbalances of sphingolipid, phospholipid and cholesterol in cellular membranes; impairment of the autophagy-lysosome pathway (ALP) and calcium dysregulation, perhaps as a response to particular *GBA* mutations unfolding in the ER may all contribute to α-synuclein aggregation (Fig. 1). Real time quaking conversion (RT-QuIC) experiments that measure the seeding potential of misfolded α-synuclein have been performed on CSF from sporadic PD and DLB patients or PD/DLB with *GBA* variants (Brockmann et al., 2021). Seeding was observed in 85% of sporadic PD and 86% of sporadic DLB patients. This rose to 93% for PD and 100% for DLB if the patient carried a severe *GBA* variant. Furthermore, there was a shorter lag phase, a larger area under the curve and maximal fluorescence indicating the kinetics of seeding was also quicker with severe *GBA* variants. As a comparison, only 75% of PD patients with *LRRK2* mutations and 59% of recessive *PARKIN/PINK1* PD patients were positive for RT-QuIC (Brockmann et al., 2021).

Several markers of ALP dysfunction have been found to be coincident with GCase deficiency and α-synuclein accumulation. Inhibition of macroautophagy flux has been found in GCase deficient neurons

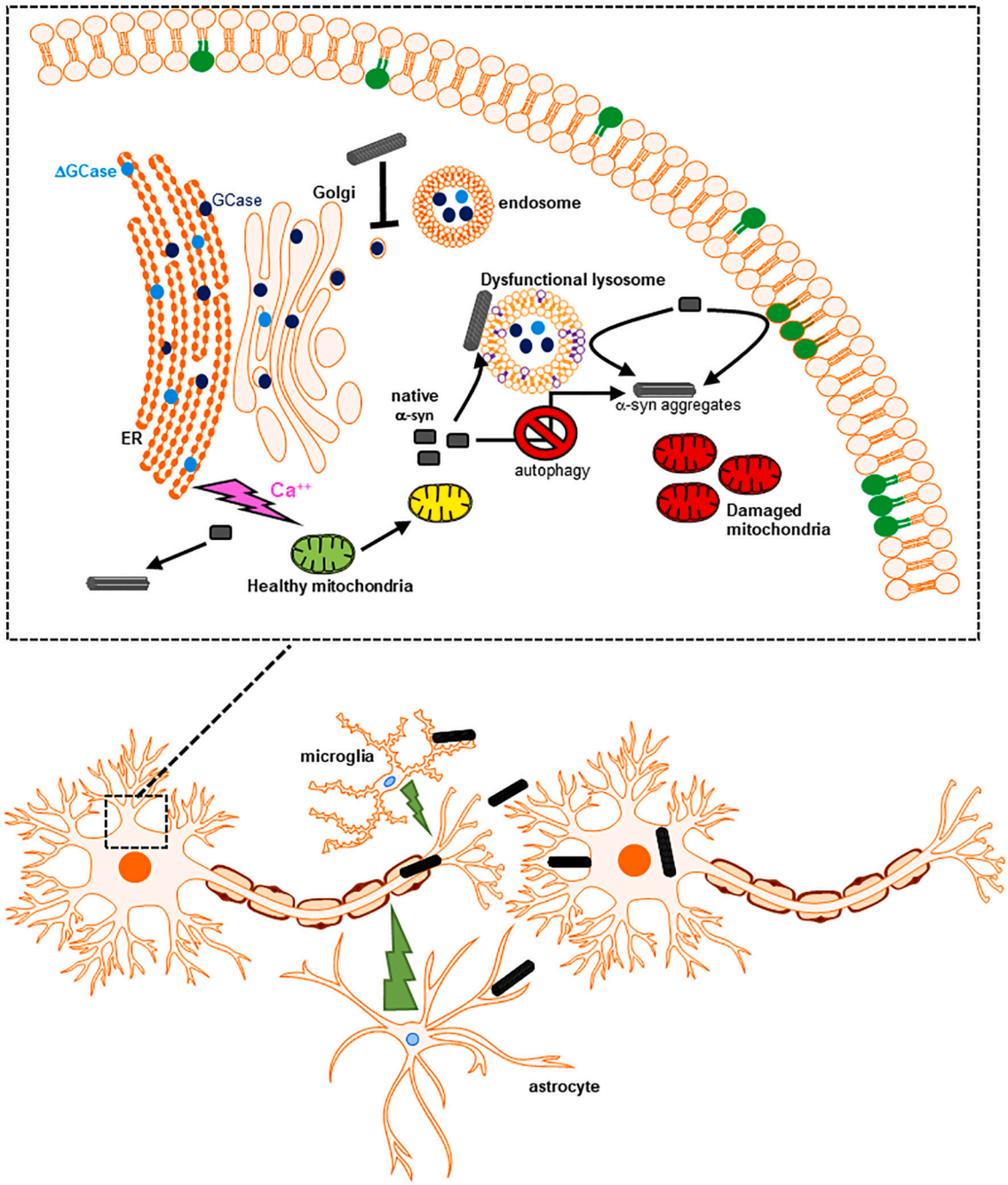

Fig. 1. Putative pathogenic mechanisms in GBA-PD. GCase deficient neurons accumulate α-synuclein that aggregates to form higher molecular weight species (grey fibrils). Neurons also increase the release of α-synuclein fibrils, which are taken up by neighbouring neurons, and cause the spread of α-synuclein pathology through the brain. Astrocytes and microglia can also bind and phagocytose α-synuclein, perhaps increasing neuroinflammation and impairing trophic support to neurons (green lightning) and exacerbating neurodegeneration. Inset: Loss of lysosomal GCase activity results in inhibition of autophagy affecting the degradation of both native α-synuclein (grey rectangles) and misfolded/aggregated α-synuclein. This would result in the accumulation of α-synuclein and old/damaged organelles such as mitochondria. Accumulation of GCase substrates (GlcCer and GlcSph; purple lipids in lysosome) may also cause α-synuclein to misfold and aggregate, as may changes in the lipid content (both sphingolipids and phospholipids) of other cellular membranes (green lipids) as a result of decreased lysosomal function. Some GCase mutations (Δ; light blue circle) cause the protein to misfold in the ER, activating the UPR and causing ER stress (pink lightning) which may also affect α-synuclein folding and mitochondrial function (yellow mitochondria). The trafficking of wild-type GCase (dark blue circle) through the secretory pathway can be inhibited by increased α-synuclein levels, including fibrils, and may contribute to the loss of GCase activity in sporadic PD brains.

(Fernandes et al., 2016; Li et al., 2019b; Magalhaes et al., 2016; Schöndorf et al., 2014). Macroautophagy impairment has also been reported in KO animal models (Keatinge et al., 2015; Kinghorn et al., 2016; Osellame et al., 2013). In both cellular and animal models the number of autophagosomes are generally increased following reduction of GCase activity suggesting that macroautophagy impairment is a result of decreased fusion of autophagosomes with the lysosome, resulting in decreased degradation of cargo such as α-synuclein and old or damaged mitochondria. In accordance with this, the proteolysis of long-lived proteins via ALP is decreased following GCase deficiency (Mazzulli et al., 2011), as are reports of increased lysosomal pH (Magalhaes et al., 2016; Sanyal et al., 2020), impaired reformation of lysosomes

(Magalhaes et al., 2016) and increased lysosomal content with evidence of undegraded cargo (Fernandes et al., 2016; Kinghorn et al., 2016; Magalhaes et al., 2016).

Chaperone mediated autophagy (CMA) also degrades α-synuclein via hsc70 and the lysosomal protein LAMP2A, and is decreased in sporadic PD (Alvarez-Erviti et al., 2010). It is unknown if CMA is impaired in GCase deficient cells as no specific assays exist to measure this. However, the activity and/or expression of cathepsins B and D have consistently been found to be decreased in neurons and astrocytes containing homozygous or heterozygous *GBA* variants (Aflaki et al., 2020; Blauwendraat et al., 2020; Sanyal et al., 2020; Yang et al., 2019). Both of these cathepsins have been shown to be involved in the degradation of α-synuclein (McGlinchey and Lee, 2015) and decreased proteolytic activity could affect macroautophagy and CMA.

While there is plenty of evidence for ALP impairment in GCase deficient cells the mechanism remains unclear and might be a result of localised accumulation of substrate in the lysosome. GlcSph has been reported to activate mTORC1 in GD neurons, inhibiting lysosomal biogenesis and autophagy (Srikanth et al., 2021). GCase deficiency may also have a broader effect on the sphingolipid balance of cellular membranes that may directly affect the maturation and fusion of vesicles and organelles (e.g., autophagosomes, endosomes) and/or recruitment/retention of proteins to particular membrane domains for macroautophagy and CMA to correctly proceed.

Increased cellular levels of GlcCer and GlcSph might also have a direct effect on the misfolding and aggregation of α-synuclein, in addition to the impairment of the ALP to remove these species. *In vitro* experiments have shown that GlcCer and GlcSph can induce monomeric α-synuclein to form oligomers and fibrils (Paul et al., 2021; Taguchi et al., 2017; Zunke et al., 2018). Furthermore, the α-synuclein aggregation seen in GCase deficient cells can be reversed using compounds targeted to reduce the accumulation of GCase substrate such as GlcCer synthase inhibitors (Cosden et al., 2021; Kim et al., 2018; Sardi et al., 2017; Zunke et al., 2018). It is tempting to speculate that this misfolded α-synuclein forms and accumulates on lysosomal membranes, but this has yet to be proven. However, it should be noted that all these are modelling GD rather than PD, with KO, homozygous *GBA* mutations or CBE inhibition, and have notable accumulation of GCase substrates. Whether smaller substrate increases observed in some heterozygote *GBA* neuronal models (Fernandes et al., 2016; Schöndorf et al., 2014) or older sporadic PD brains (Huebecker et al., 2019) will have the same direct effect on α-synuclein aggregation remains uncertain.

Changes in the lipid composition of membranes can affect the aggregation of α-synuclein (reviewed in Fanning et al., 2020; Galvagnion, 2017). Loss of GCase activity not only changes the levels of GlcCer, GlcSph and other sphingolipids, but also phospholipids and cholesterol in cellular and animal models (Galvagnion, 2017; Brekk et al., 2020; García-Sanz et al., 2017; Kinghorn et al., 2016; Magalhaes et al., 2016). The ALP is a process by which the cell can regulate lipid metabolism, with the turnover and recycling of lipids in membranes and organelles such as lipid droplets (LD). Increased neutral lipids (e.g., phospholipids, triglycerides) have been reported to be increased in dopaminergic neurons and microglia in the substantia nigra of mice treated with CBE in a similar fashion to that observed in sporadic PD brains (Brekk et al., 2020). LD store triglycerides and cholesterol esters and are a source of fatty acids for metabolism when required, either via recruitment of lipases, or turnover by autophagy (Teixeira et al., 2021). Excess fatty acids are stored in LD to prevent oxidation to toxic species that can damage mitochondria, and can also be formed following mitochondrial dysfunction, oxidative and ER stress. Formation of LD can mediate α-synuclein toxicity and promote α-synuclein aggregation (Fanning et al., 2019). Cholesterol esters are increased in *Gba* KO mouse embryonic fibroblasts (MEFs) (Magalhaes et al., 2016), while RNA sequencing of CBE-treated mice brains has indicated a large upregulation in LD associated proteins (Blumenreich et al., 2021). Perturbed α-synuclein metabolism and the increased number of LD reported in a PD mouse model were reversed following delivery of human GBA by adenovirus (Glajch et al., 2021). These observations suggest that GCase plays a role in LD homeostasis.

In addition to increased cholesterol esters, the levels of total cholesterol are increased in *Gba* KO MEFs, human fibroblasts with heterozygote *GBA* variants and mouse cortical neurons treated with CBE (García-Sanz et al., 2017; Magalhaes et al., 2016). This accumulation was coincident with impaired macroautophagy and altered lysosomal content (Magalhaes et al., 2016), and in the case of human fibroblasts, cholesterol accumulated in lysosomes (García-Sanz et al., 2017). Cholesterol affects the dynamics of lipid membranes and in combination with sphingomyelin form lipid rafts/detergent resistant membranes regulating vesicle trafficking, signal transduction cascades and synaptic transmission (García-Sanz et al., 2021). The activity of CMA is regulated by the movement of LAMP2 in and out of lipid rafts (Kaushik et al., 2006), and this could be directly affected by GCase deficiency leading to accumulation of α-synuclein. Furthermore, cholesterol can bind α-synuclein, while lipid rafts also act as aggregation sites for α-synuclein (García-Sanz et al., 2021). Variants in *APOE*, which is a lipoprotein involved in cholesterol homeostasis, have been shown to be involved in progression of PD (Liu et al., 2021), while APOE$^{-/-}$ cerebral organoids exhibit aggregation of α-synuclein, dysregulation of cellular lipid content and accumulation of LD (Zhao et al., 2021).

GCase has been linked with the metabolism of glucosylated cholesterol (GlcChol) (Marques et al., 2016). GCase can degrade GlcChol under normal conditions, however upon excessive lysosomal accumulation of cholesterol (e.g., the lysosomal storage disease Nieman Pick C) GCase can also transglucosylate excessive cholesterol. GlcChol is detectable in the brain (Marques et al., 2016), but it remains unclear if GlcChol dyshomeostasis plays a role in GBA-PD. No changes in GlcChol were observed in the plasma of people with heterozygous N370S variants, with or without PD (Surface et al., 2021).

4.2. GCase and pathological spread of α-synuclein through the brain

The formation of intracellular α-synuclein oligomers and fibrils and its accumulation in Lewy bodies is likely to play a central role in PD pathogenesis. Increasing evidence suggests that the transfer of α-synuclein fibrils between neurons may promote the spread of α-synuclein pathology through the brain as PD progresses (Karpowicz et al., 2019), as first proposed by Braak and colleagues (Braak et al., 2002). Fibrillar α-synuclein can act in a prion-like fashion promoting monomeric wild-type α-synuclein to misfold and aggregate to form oligomers and fibrils, eventually forming Lewy body-like inclusions in cultured neurons and animal models (Luk et al., 2012; Mahul-Mellier et al., 2020; Recasens et al., 2014). Injection of recombinant pre-formed α-synuclein fibrils (PFFs) at specific locations in the brain like the striatum result in the spread of Lewy body-like pathology along interconnected neuronal circuits (Gómez-Benito et al., 2020; Luk et al., 2012).

This spread of α-synuclein fibrils may be via release of free fibrils, in EV such as exosomes or via nanotubes (reviewed by Karpowicz et al., 2019). In addition to the accumulation of α-synuclein within GCase deficient neurons, the increased release of both monomeric α-synuclein (Fernandes et al., 2016; Magalhaes et al., 2016) and fibrillar species (Gegg et al., 2020) has been reported. The mechanism for this release is still unclear. However, it is well known that both impaired ALP and altered ceramide metabolism result in increased release of exosomes (Alvarez-Erviti et al., 2011; Kurzawa-Akanbi et al., 2021). Both these mechanisms may play a role in GBA-PD. Increased release of extracellular vesicles have been reported from fibroblasts with *GBA* variants (Cerri et al., 2021), and animal models with KO or mutant *GBA* (Papadopoulos et al., 2018; Thomas et al., 2018). In a *Drosophila dGba* KO model increased extracellular vesicles containing aggregated proteins was associated with depletion of ceramide levels (Jewett et al., 2021). However, as yet, there have been no reports of increased α-synuclein in exosomes from GBA deficient neurons or in the CSF. Levels of

α-synuclein in plasma exosomes were similar between sporadic and GBA-PD (Avenali et al., 2021).

Cell culture models suggest that GCase deficiency can modestly increase the spread of a-synuclein fibrils, inducing insoluble α-synuclein phosphorylated at Ser 129 and HMW species (Gegg et al., 2020; Henderson et al., 2020). *In vivo*, the spread of α-synuclein pathology following injection of PFFs into the striatum was increased in WT/L444P KI mice (Migdalska-Richards et al., 2020) and CBE-treated mice (Henderson et al., 2020), although in the latter study only in brain regions with lower endogenous α-synuclein expression. However, fibril injection into the olfactory bulb of WT/D409V GBA mutant mice did not worsen α-synuclein pathology or behavioural phenotypes after 6 months, when compared to wild-type littermates (Johnson et al., 2021).

It has been proposed that in some cases of PD, α-synuclein pathology originates first in the gastro-intestinal tract, and then spreads to the brain via the enteric nervous system and vagal nerve. Injection of PFFs in the gut results in α-synuclein pathology in the brain several months later, including the midbrain. This can be abolished when the vagal nerve is cut (Holmqvist et al., 2014; Kim et al., 2019; Uemura et al., 2018). The spread of α-synuclein is increased in aged animals (Challis et al., 2020; Van Den Berge et al., 2021). Recent papers have suggested spread of α-synuclein pathology can be bi-directional between the enteric nervous system and brain (Arotcarena et al., 2020; Van Den Berge et al., 2021). Accumulation of phosphorylated α-synuclein and dysfunction of the enteric nervous system following PFF injection of the gut has been shown to be decreased by viral overexpression of GCase in enteric neurons, reinforcing the importance of GCase in α-synuclein metabolism and spread of pathogenic species (Challis et al., 2020).

5. Interaction of GCase with PD-associated proteins

5.1. α-synuclein

In addition to the effect of GCase deficiency on α-synuclein metabolism and aggregation, increased α-synuclein levels have been shown to decrease wild-type GCase activity and protein expression. Lower GCase activity correlates with higher α-synuclein levels in sporadic PD brains (Murphy et al., 2014), while GCase activity is also decreased in neuronal cell models and the brain and gut of animal models in which α-synuclein proteins levels are increased (Challis et al., 2020; Gegg et al., 2012; Mazzulli et al., 2016b; Sardi et al., 2013). Treatment of hippocampal and cortical neurons or differentiated dopaminergic SH-SY5Y cells with PFFs, but not monomeric α-synuclein, decreased GCase activity (Gegg et al., 2020; Henderson et al., 2020). GCase expression was also decreased in the duodenum following PFF injection (Challis et al., 2020). Live GCase activity assays indicated that the deficiency was due to a decrease in lysosomal GCase activity (Gegg et al., 2020). This was coincident with activation of the UPR that might suggest that α-synuclein fibrils affect the trafficking of GCase through the endolysosomal system (Gegg et al., 2020). The correct trafficking of GCase and other lysosomal enzymes has also been reported to be impaired in neurons containing increased α-synuclein levels (Mazzulli et al., 2016a). Whether α-synuclein directly affects the trafficking of GCase via the ER and/or Golgi (Cooper et al., 2006; Mazzulli et al., 2016b; Winslow et al., 2010), or a more general dysfunction of the endolysosomal system (Hoffmann et al., 2019) remains to be determined. Regardless of the mechanism, impairment of lysosomal GCase by α-synuclein raises the possibility that α-synuclein pathology and GCase deficiency spreads through the brain in tandem.

5.2. Leucine rich repeat kinase 2

A relationship between GCase activity and leucine rich repeat kinase 2 (LRRK2/PARK8) has recently been identified (for review see (Lee et al., 2021). Autosomal dominant mutations in the LRRK2 gene are the most common familial form of PD. LRRK2 is a kinase, and PD-associated mutations such as p.G2019S increase enzyme activity. Midbrain dopaminergic neurons containing LRRK2 mutations exhibit decreased lysosomal GCase activity, while LRRK2 inhibitors increase GCase activity in both control and LRRK2 mutant cells (Ysselstein et al., 2019). LRRK2 KO or knock down (KD) mouse models also have increased GCase activity in the striatum (Albanese et al., 2021). These data suggest that the modulation of GCase activity by LRRK2 is dependent on its kinase activity. Rab8 and Rab10 are substrates of LRRK2 and the modulation of GCase activity by LRRK2 has been shown to be mediated by these proteins in neurons and astrocytes (Sanyal et al., 2020; Ysselstein et al., 2019). Rab10 is involved in endolysosomal trafficking and may therefore affect GCase trafficking to the lysosome. Inhibition of LRRK2 in GCase deficient astrocytes lowers lysosomal pH towards control levels and restores cathepsin B activity further suggesting that its modulation of the endolysosomal system (Sanyal et al., 2020). However, while LRRK2 mutations appear to decrease GCase activity in cultured cells, PD patients with both *LRRK2* and *GBA* mutations appear to have a milder phenotype, compared to patients with *GBA* mutations alone (Omer et al., 2020; Ortega et al., 2021). It has been suggested that modification of the peripheral inflammatory cascade related to the microbiome and enteric α-synuclein synthesis is reduced by LRRK2, and ameliorates the effects associated with reduced GCase activity (Menozzi et al., 2021). Further studies will elucidate the interplay between the two genes, and the ultimate effect on clinical phenotype.

6. The role of GCase in glia

Most studies investigating GCase deficiency and PD pathogenesis have focused on neurons. However, several RNA sequencing studies in mice have indicated *Gba* transcripts to be higher in glia than neurons (brainrnaseq.org; holt-sc.glialab.org; astrocyternaseq.org). Human *GBA* mRNA reports are mixed with both lower (brain-map.org) and higher expression of *GBA* in glia (brainrnaseq.org).

Microglial activation has been reported in the brains of non-manifesting *GBA* carriers (Mullin et al., 2021), which might suggest that neuroinflammation is an early event in GBA-PD. Widespread neuroinflammation has also been observed in mouse models of neuronopathic GD (Enquist et al., 2007; Rocha et al., 2015b; Vitner et al., 2012). RNA sequencing of CBE-treated mice indicated large increases in interferon signalling, toll like receptor (TLR) and chemokines (Blumenreich et al., 2021). Further analysis of astrocytes indicated large transcript increases common to pan-reactive astrocytes as well as A1 and A2-reactive astrocytes. Increased glycoprotein nonmetastatic melanoma protein B (GPNMB) levels are observed during neuroinflammation and is associated with astrocytes, microglia and macrophages (Moloney et al., 2018). GPNMB expression is increased in the brains of CBE-treated mice, including the substantia nigra (Blumenreich et al., 2021; Moloney et al., 2018). GPNMB protein levels are increased in the substantia nigra of PD patients (Moloney et al., 2018). Selective KO of *Gba1* in mouse midbrain dopaminergic neurons and accumulation of substrate also results in activation of neighbouring microglia (Soria et al., 2017). *Gba* KO zebrafish also exhibit changes in microglia shape and miR-155, a master regulator of neuroinflammation (Keatinge et al., 2015). Increased miR-155 levels were also found in GBA KO mice and CBE-treated SH-SY5Y cells (Watson et al., 2019), although genetic ablation of miR-155 in zebrafish did not reverse neuroinflammation or increase survival (Watson et al., 2019). While evidence of neuroinflammation is observed in GD animal models, heterozygote *GBA* mouse models are mixed with increases in reactive astrocytes (GFAP) or microglia (Iba1) detected in the brains of aged heterozygote KI D409V mice (Clarke et al., 2019), but not in heterozygote KO mice or heterozygote KI L444P *GBA* mutations (Migdalska-Richards et al., 2017; Yun et al., 2018). However, increased activation of astrocytes was observed in heterozygote L444P mice following treatment with the dopaminergic neuron toxin MPTP (Yun et al., 2018).

Human astrocytes differentiated from iPS made from patients with

non-neuronopathic type 1 GD (with or without PD) and neuronopathic type II GD exhibited morphology changes and some markers of a proinflammatory phenotype under basal conditions, with no clear differences between the groups identified (Aflaki et al., 2020). In primary mouse cultured astrocytes with heterozygous or homozygous KI p. D409V *GBA* mutations, common proinflammatory markers (e.g. IL-1β, IL-6, iNOS) were decreased under basal conditions, when compared to controls (Sanyal et al., 2020). Stimulation with bacterial lipopolysaccharide did increase the expression of these markers but remained significantly lower than control.

The release of α-synuclein species from neurons not only affects neighbouring neurons but are also bound and taken up by neighbouring astrocytes and microglia. Binding of α-synuclein species (monomeric, oligomeric and fibrillar) to TLR-2 or 4 activate proinflammatory pathways such as the inflammasome, nuclear factor-κβ (NFKB), chemokine and cytokine production (Dutta et al., 2021; Hughes et al., 2019; Scheiblich et al., 2021). Astrocytes are also known to take up α-synuclein fibrils and degrade them by the ALP (Cavaliere et al., 2017; Choi et al., 2015; Loria et al., 2017) while also activating proinflammatory NFKB pathways (Choi et al., 2015). Co-culture studies have shown that activated astrocytes and microglia can increase the cell death of dopaminergic cells (Choi et al., 2015; Dutta et al., 2021). Recently GCase deficient microglia have been shown to decrease the activity of nuclear factor erythroid 2-related factor 2 (NRF2) in neighbouring neurons, a transcription factor involved in redox homeostasis, autophagy, lysosomal biogenesis and mitochondrial function (Brunialti et al., 2021).

Modulation of the activation status of microglia affects the spread of α-synuclein in cell and animal models (Dutta et al., 2021; George et al., 2019). The protective effects of astrocytes on α-synuclein accumulation in neighbouring neurons and the spread of pathology has also been shown to be reduced when the ALP is impaired by mutations in ATP13A2, a lysosomal protein, which when mutated, causes a familial synucleinopathy (Tsunemi et al., 2020). Given the role of GCase in the ALP it is likely that *GBA* mutations have a similar effect. However, to date, only a few reports have investigated this. In human GD astrocytes differentiated from iPS, increased α-synuclein aggregation was observed following PFF treatment, compared to control lines (Aflaki et al., 2020). Proinflammatory markers were not increased above basal levels in these cells. In mouse astrocytes containing heterozygote or homozygote D409V KI *GBA* mutations, the degradation of monomeric α-synuclein or PFFs were similar to wild-type cells, despite evidence of ALP impairment in the mutant *GBA* cells (Sanyal et al., 2020).

More studies are clearly needed to gain a better understanding of whether the turnover of α-synuclein is impaired in GCase deficient glia, and how this affects the spread of α-synuclein between neurons and glia, and vice versa. The impact of GCase deficiency in glia on the trophic and metabolic support to neurons would also be of interest.

7. GCase deficiency and organelle function

In addition to the lysosomal dysfunction associated with GCase deficiency, *GBA* mutations effect the function of other organelles within the cell. GCase mutations such as L444P and N370S that result in the protein unfolding in the ER and activating the UPR also cause the dysregulation of calcium from the ER in human fibroblasts (Kilpatrick et al., 2015a) and human midbrain neurons (Schöndorf et al., 2014). In addition to dysregulating many calcium-dependent signalling pathways, the UPR and ER stress has been linked with accumulation and aggregation of α-synuclein (Bellucci et al., 2011; Colla et al., 2012; Heman-Ackah et al., 2017).

Alongside α-synuclein accumulation, mitochondrial dysfunction is a hallmark of PD (Schapira et al., 1989; Schapira and Gegg, 2011). Loss of mitochondrial function has been observed in several models of GCase deficiency including cultured mouse and human neurons, astrocytes, animal models and human GBA-PD brains. Inhibition of complex I activity of the electron transport chain (ETC) similar to sporadic PD is commonly reported (Osellame et al., 2013; Schöndorf et al., 2018; Yun et al., 2018) as is decreased basal and maximal (uncoupled) mitochondrial respiration (Kim et al., 2021; Osellame et al., 2013; Schöndorf et al., 2018; Yun et al., 2018). Other complexes of the ETC have been reported to be decreased, as has decreased mitochondrial membrane potential, increased reactive oxygen species production and decreased ATP levels (Cleeter et al., 2013; Keatinge et al., 2015; Kinghorn et al., 2016; Osellame et al., 2013; Schöndorf et al., 2018). The morphology of mitochondria and the expression of proteins involved in the fission and fusion of mitochondria have also been reported, including GBA-PD brains (Kinghorn et al., 2016; Li et al., 2019a; Osellame et al., 2013; Schöndorf et al., 2018).

The degradation of mitochondria by macroautophagy (mitophagy) has been cited as a cause for the mitochondrial dysfunction observed in these models (Li et al., 2019b; Osellame et al., 2013). However other possible factors contributing to loss of function and morphology have been suggested, including changes in NAD+ metabolism (Schöndorf et al., 2018), mitochondrial calcium dysregulation, perhaps as a result of decreased expression of the mitochondrial calcium uniporter (Plotegher et al., 2020), and increased mitochondria-lysosome contacts due to a decrease in proteins mediating this process like TBC1D15, resulting in fewer mitochondria in the axons (Kim et al., 2021).

8. Therapeutic strategies in GBA-PD: current directions and challenges in clinical trials

8.1. GCase gene therapy

The significant reduction of GCase activity and protein expression in the substantia nigra of post-mortem brain tissues from *GBA*-PD and sporadic PD patients establishes a rationale to either enhance GCase activity or increase protein levels. Unfortunately, enzyme replacement therapy, one of the standard treatments for GD, is not central nervous system (CNS) penetrant and therefore not suitable for treatment of PD. *GBA* overexpression by adeno-associated virus (AAV) vectors has proved a good proof of principal for reducing α-synuclein accumulation in mouse brain by restoring GCase expression (Morabito et al., 2017; Rocha et al., 2015b; Sardi et al., 2011). PR001, an AAV9 viral vector delivering *GBA*, has also been shown to increase GCase activity, decrease glycolipid substrate accumulation, and improve motor abnormalities in *GBA*-PD models *in vivo* (Abeliovich et al., 2021). The effect of intra-cisternal PR001 administration is currently under investigation in a phase 1/2a randomised-controlled trial (RCT); the target population is moderate to severe PD with at least one pathogenic *GBA* mutation (NCT04127578).

8.2. GCase enhancers

Small-molecule chaperones for GCase can bind and refold mutant GCase in the ER, thus facilitating trafficking and ultimately increasing GCase protein levels in the lysosome (Gegg and Schapira, 2018)

Within this class, ambroxol, a common over-the-counter expectorant, has been shown to increase GCase activity and protein expression, and reduce α-synuclein levels in several *in vitro* and animal models (Ambrosi et al., 2015; Maegawa et al., 2009; Magalhaes et al., 2018; McNeill et al., 2014; Migdalska-Richards et al., 2016; Yang et al., 2019) and human macrophages isolated from GD and GBA-PD patients (Kopytova et al., 2021). In *Drosophila*, ambroxol also decreases activation of the UPR and reverses loss of dopaminergic neurons (Sanchez-Martinez et al., 2016, Suzuki, 2013). Results from a proof-of-principle, phase 2, open-label study (NCT02941822) conducted on 17 patients with PD (with and without *GBA* mutations), showed that ambroxol (escalating dose to 1260 mg/day) crossed the blood brain barrier (BBB) and increased GCase protein levels and α-synuclein concentration in the CSF (Mullin et al., 2020). Importantly, improvement of motor function over 6-months was noticed, although the unblinded nature of the study should likely explain this. Nevertheless, this observation suggests

ambroxol does not interfere with concurrent dopaminergic medication. A phase 3 RCT of ambroxol (1260 mg/day versus placebo) is expected to commence in 2022, targeting PD patients with and without *GBA* variants. Another phase 2 RCT trial in individuals with mild to moderate PD dementia (Silveira et al., 2019), evaluating low (525 mg/day) and high doses (1050 mg/day) of ambroxol is currently ongoing (NCT02914366).

In addition to refolding GCase, ambroxol treatment may also have additional protective effects as a treatment for PD via the nuclear levels of transcription factor EB (TFEB)/PGC-1α axis. Ambroxol can increase TFEB in neurons (Magalhaes et al., 2018), a master regulator of lysosomal biogenesis (Sardiello et al., 2009), and through this pathway increase *GBA* mRNA levels, GCase activity and other lysosomal proteins in wild-type *GBA* cells (Ambrosi et al., 2015; Magalhaes et al., 2018; McNeill et al., 2014). Increasing TFEB expression has been shown to decrease α-synuclein misfolding in cultured cells and synucleinopathy mouse models (Arotcarena et al., 2019; Decressac et al., 2013; Kilpatrick et al., 2015b). Furthermore, TFEB can also affect mitochondrial biogenesis, lipid metabolism and oxidative stress as it can coordinate with PGC-1α signalling pathways (Ivankovic et al., 2016; Magalhaes et al., 2018; Settembre et al., 2013; Tsunemi et al., 2012).

Aside from ambroxol, other small molecule chaperones have been investigated, but are thus far supported by limited preclinical evidence. Non-inhibitory chaperone molecules such as NCGC00188758 or NCGC607, have been shown to enhance GCase activity, reduce α-synuclein accumulation, and reverse neurotoxicity in iPS derived neuronal lines derived from PD patients with different mutations, including *GBA* (Aflaki et al., 2016; Mazzulli et al., 2016b). Following a screen of 1280 FDA-approved drugs, the antipsychotic quetiapine has been shown to bind GCase, increasing wild-type GCase protein levels and activity, while partially reducing accumulation of α-synuclein in GBA-PD neurons differentiated from iPS and the brains of a heterozygote *GBA* mouse model (Burbulla et al., 2021). There is also interest in modulating the expression of PGRN and HSP70, chaperones that are involved in the folding of GCase. PGRN fused to a human transferrin receptor Fc domain for better CNS biodistribution increased GCase activity and lysosome function (Logan et al., 2021). Arimoclomol, a small molecule that increases levels of the HSP70 family, aids GCase refolding, maturation, and activity, but has not been tested in a PD clinical trial setting (Fog et al., 2018).

LTI-291 is a small molecule, acting as an allosteric modulator of GCase. By crossing the BBB, it has the potential to infiltrate the CNS and enhance GCase activity in the brain, without increasing its protein expression. (den Heijer et al., 2021). At the time of writing, publication of the details of LTI-291 increasing wild type GCase activity and restoring glycosphingolipid metabolism *in vitro*, *in vivo* and *ex vivo* was still awaited. Two phase 1 studies conducted on healthy subjects and middle-aged volunteers (trials NL6421 and NL6516) demonstrated safety and tolerability of the compound, but no evidence of increased GCase activity (den Heijer et al., 2021). A phase 1b randomized, placebo-controlled trial (NL6574) conducted on 40 *GBA*-PD patients, showed significant changes in glycosphingolipids biomarkers in the treatment arm although the relevance of this is uncertain, and a phase 2/3 pivotal trial is expected in 2022.

8.3. Substrate reduction accumulation

Glucosylceramide synthase (GCS) inhibitors are small molecules designed to reduce the production of glucosylceramide and thus the formation of glycosphingolipids. By correcting the aberrant flux of glycosphingolipids, these small molecules have a potential application in *GBA*-PD (Peterschmitt et al., 2021). An oral, CNS-penetrant GCS inhibitor, GZ667161, has been reported to reduce GlcCer and GlcSph levels and α-synuclein aggregation in mice expressing human mutant α-synuclein and GD mouse models (Sardi et al., 2017). GZ667161 also decreased neuropathology and neuroinflammation in a GD mouse model using CBE (Blumenreich et al., 2021). A similar compound, Venglustat, has been evaluated in a phase 2 RCT, targeting early-stage *GBA*-PD patients (MOVES-PD, NCT02906020). Venglustat consistently reduced glucosylceramide levels in both plasma and CSF of *GBA*-PD patients compared to placebo. However, a progressive and sustained deterioration in clinical outcomes was noticed over time in the treatment arm compared to placebo, leading to a premature interruption of the study. The deterioration was established at 13 weeks, and suggests the drug had some type of anti-dopaminergic activity, either endogenous or exogenous, rather than a direct negative impact of substrate reduction.

9. Conclusion

The accumulation of α-synuclein following loss of GCase activity and subsequent lysosomal dysfunction in neurons is well established. However, the mechanisms by which this occurs remain unclear, and are likely to reflect the type of *GBA* variant (mild/risk versus severe), the amount of substrate accumulation and overall lipid imbalance of the cell, in addition to other factors such as age and presence of other genetic changes. The interplay between neurons and glia in GBA-PD needs further investigation to clarify how this affects α-synuclein metabolism, spread of α-synuclein pathology through the brain, as well as the contribution of neuroinflammation and impaired trophic support. The gut-brain axis is a rapidly growing topic in PD and the role that *GBA* plays in the gastrointestinal tract will no doubt be of great interest, particularly given the emerging evidence GCase deficiency has on the spread of toxic α-synuclein species.

The recent failure of MOVES-PD clinical trial has shed light on how challenging the future of translational research in *GBA*-PD could be. Impressive results in GD mouse models with significant accumulation of GCase substrates may not fully reflect the pathogenesis of GBA-PD with heterozygote *GBA* mutations, where substrate accumulation might not play such an important role. Studying both prodromal *GBA* carriers and GBA-PD cohorts will hopefully aid discovery of reliable disease biomarkers that reflect the underlying pathological processes in GBA-PD, while stratification of patients according to *GBA* mutation status and/or clinical phenotype will help optimise disease modification strategies in future.

Acknowledgements

MEG was funded by a grant from Parkinson's UK (Principal investigator AHVS, G-1704). AHVS is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

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