Exploring Ambroxol's Potential as a Repurposed Treatment Avenue for Parkinson's Disease

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Parkinson's Disease (PD) is a neurodegenerative disease diagnosed in over 90,000 patients per year in the United States alone in 2022. A biological characterization of PD is the accumulation of Lewy bodies (LBs) in the central nervous system (CNS), causing disruption of neurotransmitter signaling and the death of dopaminergic neurons. This leads to both motor and non-motor symptoms including tremors, rigidity, slowness, depression, and bowel difficulties. The accumulation of alpha-synuclein (alpha-syn) protein is involved in forming LBs and therefore has been highlighted as a target for the treatment of PD. Glucocerebrosidase (GCase) is an enzyme that can potentially lower alpha-syn accumulation and, consequently, reduce LB formation. Ambroxol (ABX), a commonly used cough medicine, has been found to bind to mutant GCase and act as a molecular chaperone to increase its activity, reducing alpha-syn accumulation and marking it as a possible treatment for PD. This review highlights the relationship between the enzyme GCase and the formation of LBs to posit how ABX could be an efficient treatment for PD through its role as a pharmacological chaperone.

Keywords: Parkinson's Disease, Ambroxol, Glucocerebrosidase, Alpha-synuclein, GBA 1 Mutation

Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder[1] that primarily affects movement. PD was diagnosed in nearly ninety thousand people in 2022 just in the United States- a fifty percent increase from previous years[2]. PD has a slight male predominance and individuals become more susceptible with increasing age[3], but it does not affect the lifespan of a patient.

PD is characterized by the accumulation of insoluble forms of the protein alpha-synuclein (alpha-syn) into Lewy Bodies (LBs) that lead to the death of dopamine-producing neurons[4]. Dopamine is a neurotransmitter responsible for neural communication that coordinates movement, motivation, and memory functions. Patients with PD experience movement difficulties that include slowness, tremors and rigidity, stiffness, and impaired balance[5]. Dopamine deficiency also results in non-motor symptoms including bladder and bowel dysfunction, changes in the skin, and communication or sleep difficulties[6]. Consequently, PD is known to increase patients' development of anxiety and depression.

There is currently no cure for PD, however, there are a variety of treatments that work to control symptoms or provide supportive therapies. The current first-line drug standard care for individuals with PD is Levodopa, a medication that replaces deficient amounts of dopamine in the CNS, ultimately aiming to restore dopaminergic neurotransmission[7]. However, a major limiting factor in Levodopa therapy is patient susceptibility to developing motor complications such as dyskinesias and motor fluctuations[8].

Current treatments for PD work to remedy insufficient activity of Glucocerebrosidase (GCase), a lysosomal enzyme that hydrolyzes anionic lipids ultimately preventing LB formation. Enzyme replacement therapy (ERT) is another common treatment avenue that involves the use of intravenous infusions to correct GCase deficiencies in PD and its related disorders such as Gaucher Disease (GD). However, ERT has negligible neurological effectiveness due to the inability of the enzyme to cross the blood-brain barrier[9,10]-a semipermeable membrane that regulates the flow of substances between the brain and blood. ERT is also an expensive treatment, costing $250,000 to $500,000 per year[11]. Substrate reduction therapy (SRT) is another approved treatment that lowers levels of substrates such as glycolipids to balance the deficiency of certain enzymes, i.e GCase[12]. This treatment works to prevent glycolipid storage of PD that is known to increase the presence of LBs. SRT has had some success in clinical trials[13], however, certain SRTs have failed to show significant benefits for neurologic manifestations overall[9,14]. Pharmacological chaperone therapy (PCT), is emerging as a new approach for PD. Pharmacological chaperones are small molecules that bind to misfolded proteins and assist their proper folding, restoring normal protein function[15]. In PD patients, PCT aids in reinstating normal GCase activity[16].

Ambroxol (ABX) is a cough medicine with high efficacy and

safety ratings that has been used since the 1970s to treat airway mucus hypersecretion[17,18]. Studies have suggested that ABX can assist in the proper protein folding of GCase to reinstate normal enzymatic function. The mechanisms of action of ABX mark it as a potential therapy for GCase enzyme dysfunction in PD, highlighting its potential as a repurposed drug. This literature review aims to explore ABX's potential as a treatment for PD by discussing the disease's pathogenesis and ABX's mechanisms to potentially counter disease-causing pathways.

Literature Review

The Accumulation of Lewy Bodies and Decrease of Dopaminergic Neurons Leads to PD

Alpha-syn is a neuronal protein that is involved in various CNS pathways. It is involved in the regulation of synaptic transmission and neurotransmitter release[19], and plays a role in the compartmentalization, storage, and recycling of neurotransmitters[20]. In addition, alpha-syn participates in several signaling pathways that regulate cell differentiation, synaptic plasticity, and cell survival. Alpha-syn can be overexpressed due to genetic multiplication and impairment of normal protein clearance mechanisms[21]. This can lead to alpha-syn deposition in the CNS, and ultimately the formation of LBs.

LBs are made up of abnormal alpha-syn protein aggregates. They form when insoluble forms of alpha-syn accumulate inside nerve cells in a stepwise manner (Figure 1). First, unfolded proteins turn into fibril formations called oligomers. The initially soluble oligomeric forms of alpha-syn are termed protofibrils, which are not by themselves harmful. However, protofibrils gradually become insoluble and combine into amyloid fibrils[22]. These insoluble alpha-syn oligomers that compose LB are directly involved in motor dysfunction in PD as they are associated with the progression of degeneration and death of dopaminergic neurons[23] (Figure 2).

The accumulation of LBs in neurons leads to the death of dopamine-producing cells (dopaminergic neurons) in the substantia nigra[24,25], a region of the midbrain that supplies dopamine to areas in the brain responsible for voluntary motor control. Reduced dopamine levels disrupt the neural communication pathways that coordinate voluntary movement, which is thought to lead to PD symptoms[22].

Multiple Factors Promote Alpha-syn Aggregation

The aggregation of alpha-syn is promoted by various factors. Alpha-syn forms amyloid fibrils at a faster rate in the presence of anionic lipids, such as glycuosylceramide (GlcCer)[26]. This is because anionic lipids can stabilize the unfolded alpha-syn protein and promote interactions with lipid membranes, both known to facilitate fibril formation[27].

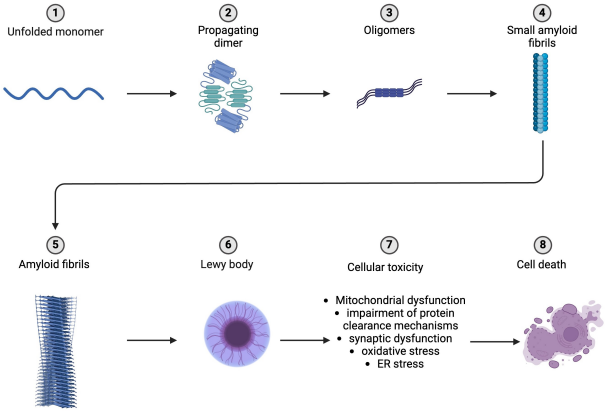

Fig. 1 Alpha-synuclein aggregates to form Lewy bodies that cause cell death through a temporal sequence. Alpha-synuclein begins as a soluble, unfolded monomer that is found in presynaptic terminals of the brain (1). The aggregation process begins with the formation of a propagating dimer (2) and that eventually forms small aggregates called oligomers (3). As confrontational changes continue to occur, oligomers, now termed small amyloid fibrils (4), enter a growth phase where they increase their size through the addition of more alpha-synuclein monomers, becoming larger amyloid fibrils (5). Eventually, mature fibrils become highly stable and insoluble and continue to form larger aggregates such as Lewy bodies (6). The presence of Lewy Bodies leads to increased cellular toxicity in neurons by disrupting protein clearance methods, synaptic and mitochondrial function, and ER homeostasis (7). Eventually, neurons that are exposed to prolonged toxicity die and disrupt neural function (8). Created with BioRender.com

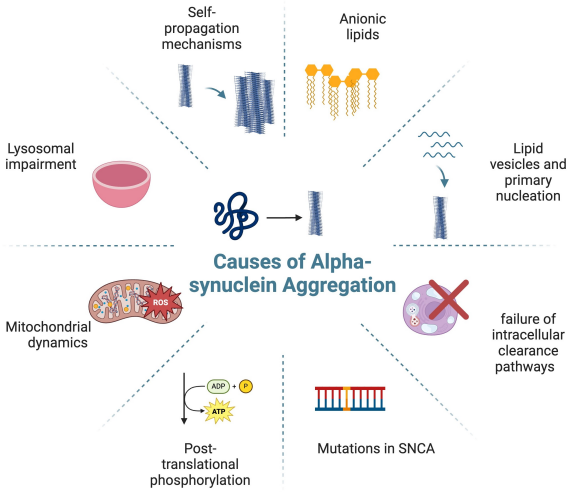

Fig. 2 Causes of Alpha-synuclein aggregation. Diagram showing the various factors that promote or lead to alpha-synuclein aggregation. Created with BioRender.com

The presence of pre-existing alpha-syn aggregates also en-

hances the aggregation process[28]. This is due to its ability to self-replicate and progressively spread between connected brain regions through cell-to-cell transmission techniques[29]. As a result, the accumulation of alpha-syn occurs at an exponential rate.

Under normal conditions, alpha-syn aggregates are disposed of by protein degradation pathways in small numbers[30]. However, dopamine normally functions as an inhibitor of maturing fibrils[31]. The decreased production and loss of neurons that produce dopamine, a characterization of PD, leads to a lack of protein degradation mechanisms for alpha-syn[30].

Alpha-syn is natively unfolded in solution and adopts an a-helical structure once it binds to membranes, changing the secondary structure of the protein[32,33]. Due to the predominantly unstructured form of alpha-syn, it becomes a target for post-translational modification, like phosphorylation. The accumulation of phosphorylated alpha-syn in the brains of PD patients is shown across studies[34–37]. The phosphorylation of alpha-syn in PD patients was found to promote oligomerization and fibrillization[37]. Over-phosphorylation is especially prominent after the initial formation of LBs[38].

Alpha-syn is composed of three domains (NAC): an N-terminal lipid-bonding alpha-helix, a non-amyloid-component, and an acidic C-terminal tail[39]. Point mutations in the N-terminal and C-terminal domains of alpha-syn have been pointed to as the cause of its misfolding and aggregation[40] likely because of the destabilization of the protein's conformation and consequent insolubility, leading to quicker aggregation[41–43].

Overall, many different external factors can lead to the over-accumulation of alpha-syn and the formation of detrimental LBs in PD. In examined PD Patients, there has not been a clear association of PD with changes in total cerebrospinal fluid (CSF) alpha-syn, however there has been consistent reduced levels of total CSF lpha-syn and increased oligomeric and phosphorylated alpha-syn[44]. Decreased levels of CSF alpha-syn could be the result of its intracellular accumulation into LBs, consequently reducing the amount of protein available for the release into the extracellular compartment[45]. Therefore, reduced CSF alpha-syn and increased oligomeric and phosphorylated alpha-syn could be a common phenotype of PD patients.

Alpha-syn Overexpression Leads to Cellular Toxicity

Alpha-syn overexpression not only leads to the formation of LBs but also contributes to the disruption of different cellular homeostasis pathways that are prominent in the progression of neural dysfunction in PD. As overexpressed alpha-syn accumulates, its oligomers can be detrimental to neuronal trafficking[22]. For example, aggregated alpha-syn has been shown to take away key components of protein complexes involved in protein trafficking, such as the fatty acid arachidonic acid from the SNARE complex, causing endoplasmic reticulum (ER) Stress[46–48]. Large alpha-syn oligomers have also demonstrated a role in the disruption of synaptic trafficking by inhibiting synaptic vesicle motility and dopamine release[49]. The overexpression of alpha-syn has been shown to lead to loss of presynaptic proteins, decrease of neurotransmitter release, enlargement of synaptic vesicles, and inhibition of synaptic vesicle recycling, all contributing to neural dysfunction[50–53].

Alpha-syn oligomers can also disrupt pathways needed for overall cellular function. Oligomers can inhibit protein degradation pathways such as the ubiquitin proteasome system and autophagy lysosomal pathway by causing proteasome dysfunction. When proteasomes are unable to degrade and remove misfolded proteins, these proteins can accumulate within the cell. The accumulation of insoluble proteins, including alpha-syn, in the ER interferes with protein folding and leads to ER stress and Golgi fragmentation[54], which lead to cell death.

The overexpression of alpha-syn in the mitochondria is associated with mitochondrial dysfunction, which can lead to cell death[54]. Alpha-syn oligomers can inhibit the import and interactions of proteins with its co-receptor in the mitochondria by interfering with the movement of molecules across membranes. As a result, decreased mitochondrial transmembrane potential leads to the production of reactive oxygen species (ROS)[49]. The irregular levels of ROS result in oxidative stress and cell death[49]. Overall, alpha-syn overexpression has been shown to be toxic to cells, not only through its role in forming LBs, but also by disrupting many pathways needed for neural communication and cellular homeostasis.

Glucocerebrosidase is Implicated in PD

GCase is an enzyme that assists in lipid homeostasis and is implicated in PD. GCase is synthesized in the ER, becomes activated by interacting with the protein Saposin C (SapC), and is then transferred into the acidic lumen of the lysosome with the help of Lysosomal Integral Protein 2 (LIMP2). In the lysosome, GCase maintains lipid homeostasis by hydrolyzing anionic lipids such as GlcCer[55]. Regulated levels of anionic lipids contribute to the structure, stability, and function of phospholipid membranes.

10 to 25 percent of PD patients have mutations in the GBA1 gene, which encodes GCase[56]. Heterozygous GBA1 mutations are considered the highest genetic risk factor for PD[57]. In one study, GCase activity was decreased by up to 58% in the substantia nigra in postmortem brain tissue of PD brains with heterozygous GBA1 mutations[58]. Common mutations include the N370S mutation and L444P, which both result in a decrease in the protein's catalytic activity[59]. Mutations can lead to the enzyme's inability to exit the ER and Golgi body or failure to link with the lysosomal membrane protein LIMP2 and activator Sap C. As a result, GCase is unable to function properly[60]. The inability of GCase to reach lysosomes and regulate anionic lipid metabolism leads to overall lysosome impairment in many cases

of PD, contributing to the disease's development[61].

The retention of mutated GCase variants in the ER and its susceptibility to degradation of its unstable form by the proteasome induces ER stress as it activates the ER-associated degradation system (ERAD) and the unfolded protein response (UPS)[28]. Increased ER stress is heavily implicated in PD as it initiates the activation of cell death and can further decrease GCase concentrations[62].

Reduced GCase activity can lead to mitochondrial dysfunction by causing the loss of the mitochondrial membrane potential needed for ATP production, inducing oxidative stress[63], which has been strongly implicated in the pathogenesis of PD as it plays a role in the degradation of dopaminergic neurons[64]. In one study, a decrease in GCase reduced action potential amplitudes and sodium and potassium currents in neural cells which led to the accumulation of oxidized dopamine and mitochondrial and lysosomal dysfunction[65]. Together, data has demonstrated that GCase is necessary for normal cellular function and its lack of activity is detrimental to regular neural abilities.

A Bidirectional Relationship between GCase and Alpha-syn Exists in PD Brains

The interaction of alpha-syn with GCase could promote the lysosomal degradation of alpha-syn, inhibiting alpha-syn aggregation[66]. Alpha-syn is predominantly degraded in the lysosome and mouse models of lysosomal storage diseases have shown slowed alpha-syn protein turnover, providing a link between GCase levels in the lysosome and alpha-syn clearance[67]. The reduced GCase activity in GBA1 mutated PD patients is also associated with increased concentrations of alpha-syn and formation of LBs[68].

High levels of oligomeric alpha-syn have also been shown to inhibit the lysosomal trafficking of GCase and its activity[69]. As alpha-syn concentrations increase, the susceptibility of GCase binding to alpha-syn at the surface of synaptic vesicles increases. This interaction was shown to decrease GCase activity as GCase becomes displaced from the lysosomal membrane surface[70]. Together, studies have shown that lowered levels of GCase and consequential higher aggregation of alpha-syn could lead to the formation of LBs, lead to loss of dopaminergic neurons through the formation of LBs[57,71].

Ambroxol is a Molecular Chaperone for GCase

ABX has been implicated as a molecular chaperone for mutant GCase (Figure 3), with *in vitro* studies demonstrating that ABX increases GCase levels and reduces alpha-syn levels[72]. ABX was found to increase the activity of GCase *in vitro* in macrophages derived from PD patients with GBA1 mutations[73]. ABX has been shown to bind to the active sites of mutant GCase molecules in ER, causing conformational change that stabilizes amino acid segments near the active sites and stimulates enzyme movement from the ER to the lysosome[72]. Once the enzyme-enzyme chaperone structure enters the lysosome, ABX displaces from GCase and allows the enzyme to hydrolyze lipid substrates in the lysosome[74].

ABX treatment significantly increased the lysosomal fraction and activity of mutant GCase, and reduced GlcCer storage in patient lymphoblasts[75]. ABX rescued some mutant GCase molecules from protein degradation pathways and restored the enzyme's functionality by 1.2-1.3 fold[75]. Thus, as ABX promotes GCase movement from the ER, it was found to help prevent the storage of mutant GCase in the ER and lowered levels of the unfolded protein response previously leading to ER Stress[72,76].

Results

in vivo evidence of ABX increasing GCase Levels and Decreasing Alpha-syn Levels

in vivo studies have demonstrated that ABX can increase GCase levels and decrease alpha-syn levels. A study in nonhuman primates demonstrated that GCase levels were increased by approximately 20% after oral ABX treatment for 28 consecutive days[77]. Increased GCase activity and decreased alpha-syn levels were shown in wild-type mice, transgenic mice with the heterozygous L444P mutation in GBA1 gene, and transgenic mice who were overexpressing alpha-syn, following administration of ABX[78].

To date, only one clinical study has been published demonstrating the use of ABX in PD patients[79]. 8 PD patients with GBA1 mutations and 9 without, were given an escalating dose of ABX (ending with 1.26g per day) and found high concentrations of the drug in the CSF, demonstrating the ability of ABX to enter the CSF. GCase, and CSF GCase expression increased by approximately 35%. As ABX crossed the blood-brain barrier and increased GCase enzyme protein levels, a 13% increase in CSF alpha-syn was also found, which can be interpreted as its increased metabolism through an increase of extracellular export of alpha-syn from the brain. However, a direct relationship between ABX and decreased alpha-syn aggregation was not found. These results were found in patients both with and without glucocerebrosidase gene mutations. Patients were evaluated using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), a comprehensive 50 question assessment that evaluates both non-motor and motor symptoms commonly associated with PD. Researchers found an average decrease of 8.7 points on the MDS-UPDRS, indicating improvement in PD symptoms. However, this clinical study was non-blinded and did not include a control group, which necessitates the use of caution when analyzing patient clinical outcomes.

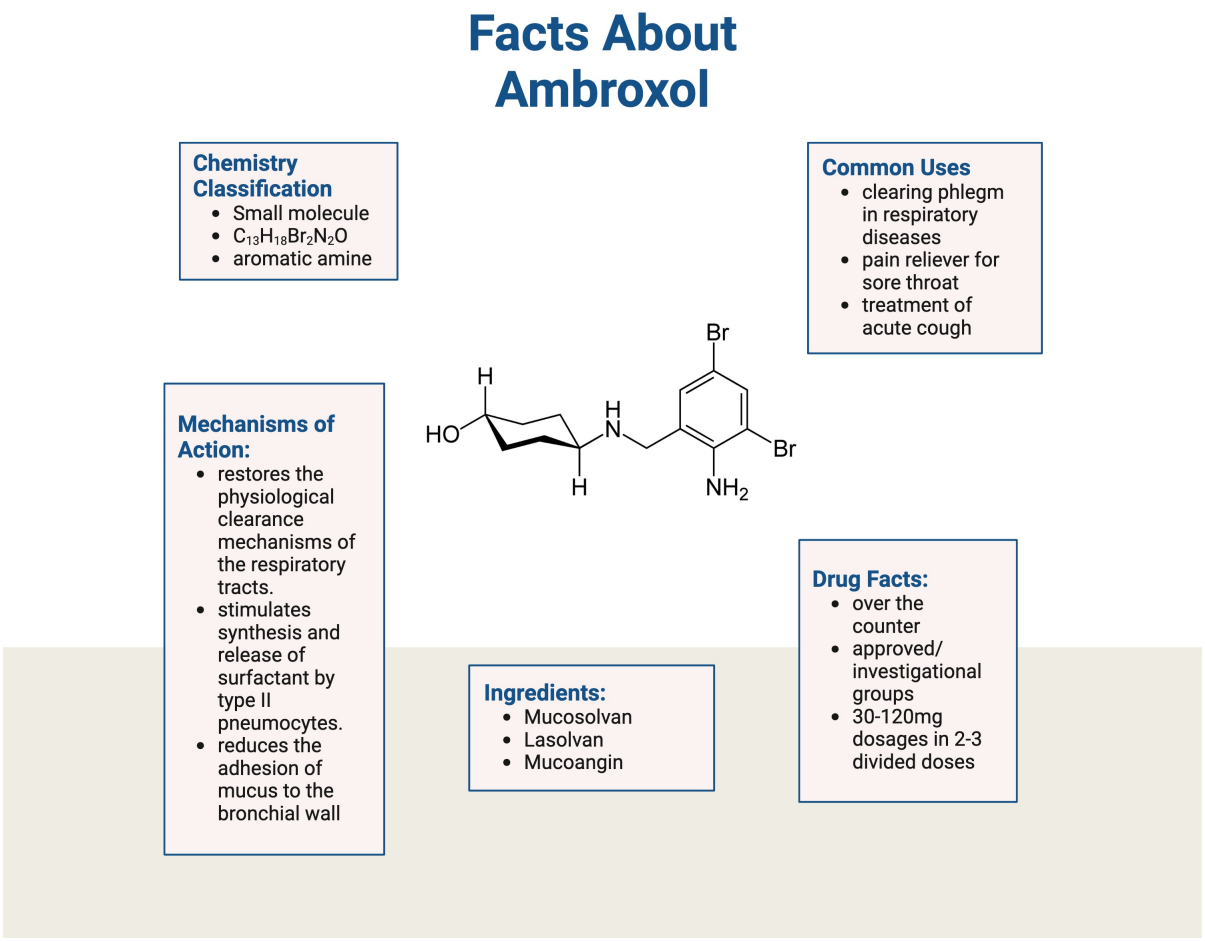

Fig. 3 Ambroxol is a drug that is primarily used to help clear mucus in respiratory diseases. Ambroxol (ABX) is classified as a small molecule drug and is typically administered in the form of tablets, capsules, or syrup. It can also be used to treat acute cough and act as a pain reliever for sore throats. ABX works by thinning mucus on the respiratory tract by stimulating the secretion of mucus-mobilizing enzymes and other structures that help the flow of mucus. Created with BioRender.com

Implications of ABX as a PD treatment

There are many advantages of using ABX as a pharmacological chaperone for PD. ABX is more widely accessible as an already established over-the-counter cough suppressant. Also, its small-molecule size enables its ability to cross the blood-brain barrier and effectively act on neurological dysfunction [19,78]. The binding of ABX to GCase is also PH dependent, binding best at the neutral pH of the ER where it is needed to assist in folding, and binding worst at the acidic pH of the lysosome, where it is no longer needed [70,75].

Due to the success of ABX in aiding biochemical changes in *in vitro* studies, clinical trials are testing its effects on PD patients. In the few recent studies of the effects of ABX on patients with PD with and without GCase mutations, it was consistently found that ABX successfully crossed the blood brain barrier and increased GCase levels and CSF alpha-syn levels, indicating positive effects in aiding neurological dysfunction in PD [79].

Limitations and Future Directions

Establishing evidence for the potential of ABX as a therapy for PD is still an ongoing process. However, *in vitro* results do not always translate to *in vivo* settings. Future *in vivo* and clinical studies of ABX and its interaction with GCase and alpha-syn amyloid formation will further reveal the mechanisms responsible for PD risk and provide insight into relevant therapeutic strategies.

The GRonigen EArly-PD Ambroxol Treatment (GREAT)

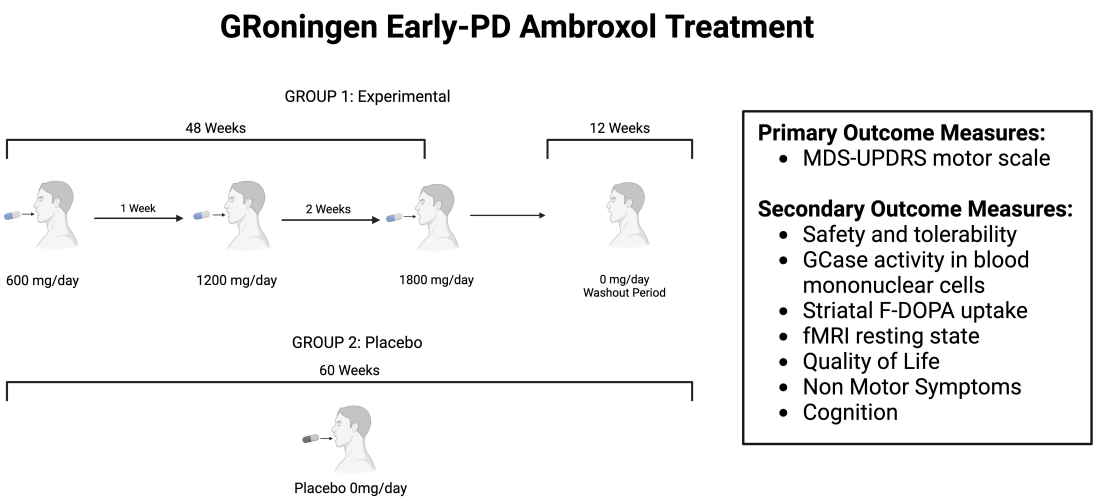

Fig. 4 The Groningen Early-PD Ambroxol (ABX) Treatment (GREAT) Clinical Trial Procedure. A graphic schematic describing the dosing schedule of ABX for the randomized, triple blind, placebo-controlled GREAT clinical trials for PD patients with a GBA1 mutation. The experimental group will receive an initial dosage of 600mg/day of ABX. After one week, the dosage will be increased to 1200 mg/day. After two weeks, the dosage will be further increased to 1800mg/day. ABX will be administered for an overall span of 48 weeks. Following the 48-week administration, a 12-week washout period will happen before final outcomes are measured through motor and cognitive tests, imaging, and blood tests that evaluate the effect of ABX in PD patients. Created with BioRender.com

Trial is a randomized triple-blinded clinical trial investigating the effects of ABX as a treatment for PD, and is expected to be completed in 2025. Approximately 80 PD patients with a GBA1 mutation will be split into two groups, with one group being given doses of ABX and the other a placebo (Figure 4). The primary outcome measure is patients' performances on the MDS-UPDRS. Secondary outcomes are used to see the overall effects ABX has on the pathophysiology of Parkinson's, and whether ABX is an efficient treatment for Parkinson's outside of its function as an enzyme chaperone for GCase. In addition, the study will evaluate the safety and tolerability of ABX, and glucocerebrosidase activity in blood mononuclear cells.

Discussion

PD is a progressive neurodegenerative disease that is characterized primarily by movement difficulties including tremors, stiffness, slowness, and balance impairment. A key factor that causes neural dysfunction in PD is the accumulation of LBs formed by insoluble alpha-syn aggregates. The lysosomal protein GCase was found to have an inverse relationship with the aggregation of alpha-syn, with decreased GCase activity leading to increased alpha-syn aggregation[80]. Heterozygous mutations in GBA1, the gene that encode GCase, is the most prominent genetic risk factor for the development of PD, as GBA1 mutations decrease GCase functionality.

The characterization of LBs in the pathophysiology of PD is crucial to understanding how ABX can work to reduce neural dysfunction. Patients in the early progression stage of PD have abnormal alpha-syn concentrations that aggregate into LBs which cause neurons to work less effectively and eventually die. LBs also lead to other disruptions in cells such as the impairment of normal protein clearance mechanisms[31], blocking of neural trafficking[22], induction of ER Stress, and mitochondrial dysfunction[54]. Together, LBs are harmful to the neural function of PD patients and result in cognition and movement difficulties.

LBs can form through multiple pathways. Primarily, unregulated levels of anionic lipids, such as GlcCer increase their formation. The unregulated storage of anionic lipids can provide alpha-syn more binding sites to lipid membranes, which increases alpha-syn's ability to undergo the necessary confrontational changes to form LBs. GCase is needed to function normally to maintain regulated levels of anionic lipids in cells as its main role is to hydrolyze lipid substrates in the lysosome. Together, the role of anionic lipids in promoting alpha-syn aggregation establishes the relationship between decreased GCase activity with increased alpha-syn aggregation.

Decreased GCase function, resulting from GBA1 mutations, is the greatest genetic risk factor for the development of PD. Heterozygous mutations in GBA1 cause both its reduced expression and overall catalytic activity likely due to its improper folding[28]. Mutated forms of GCase are unable to leave the ER or link with its activators LIMP2 or Sap C, a crucial step in its ability to enter the lysosome and hydrolyze lipid substrates. With the decreased activity of GCase, lipid substrates accumulate in the brain. Therefore, alpha-syn aggregation is likely promoted

by decreased GCase activity. As mutated forms of GCase are unable to hydrolyze anionic lipids, anionic lipid concentration increases and so does Lewy body formation. Decreased GCase activity and unregulated high levels of alpha-syn concentrations are known to contribute to neural dysfunction by affecting mitochondrial, lysosomal, and protein degradation pathways, all of which contribute to the pathogenesis of PD.

ABX is a well-tolerated drug for children and adults in treating short-term respiratory symptoms such as excessive mucus. In *in vitro* studies, ABX was shown to increase GCase activity. The role GCase plays in hydrolyzing anionic lipid substrates marks it as a crucial factor in preventing alpha-syn aggregation and LB formation. As ABX binds to mutant GCase molecules, the molecules stabilize and become functional. The binding of ABX can allow for GCase movement from the ER to the lysosome, where GCase is able to function as a lysosomal enzyme and hydrolyze anionic lipid substrates. As GCase activity is promoted by ABX, anionic lipid storage decreases overall. As ABX works to upregulate GCase activity, it could also decrease alpha-syn aggregation and help counter the pathogenesis of PD.

Previous clinical studies for Gaucher Disease (GD) have suggested ABX is a promising treatment when used with enzyme replacement therapy or substrate reduction therapy[81]. GD is a genetic disorder that results from the buildup of lipids in organs due to the lysosomal deficiency of genetically mutated GCase. Therefore, GBA1 mutations are related to both PD and GD. In a clinical study of five GD patients that received high-dose oral ABX along with enzyme replacement therapy, it was found that ABX was able to permeate the blood-brain barrier, significantly increasing lymphocyte GCase activity, and decreasing lipid substrate levels in cerebrospinal fluid.

A clinical study has shown that ABX managed to cross the blood-brain barrier and bind to GCase, increasing the enzyme's concentrations in PD patients with and without GBA1 mutations. ABX administration also increased alpha-syn concentrations in CSF, which can be interpreted as its increased extracellular export. Overall, this clinical trial showed positive biochemical manifestations regarding GCase and alpha-syn in treating PD. However, this trial was not placebo-controlled. Thus, new clinical trials looking at ABX treatment for PD that are placebo controlled such as the GREAT trial will provide more concrete findings for clinical results.

Conclusion

PD is a progressive neurodegenerative disease that targets the nervous system and is characterized primarily by movement difficulties including tremors, stiffness, slowness, and balance impairment. ABX is a widely used drug that has the potential to be repurposed for PD, given by its involvement in multiple cellular pathways that are implicated in PD. One clinical trial examining ABX administration for PD patients with and without GBA1 mutations showed that ABX could cross the blood brain barrier and increase GCase levels within CSF. The GREAT clinical trial will provide crucial evidence for its use as a therapeutic treatment for patients with PD. The GREAT clinical trial offers a new PD treatment that could be readily available for use due to ABX's established safety profile exemplifying the importance of repurposing drugs for the future of treatment of diseases.

Methods

This review uses over 80 peer-reviewed studies or literature reviews to investigate the current understanding of Ambroxol's potential as a therapy for Parkinson's Disease. Articles were selected from credible, established scientific journals. Information on the GREAT clinical trial was obtained from ClinicalTrials.gov. Databases were relevantly used by filtering articles using keywords and date filters. The key words used were "Parkinson's Disease", "Ambroxol", "alpha-synuclein", and "GBA1". Publications from 2004 to 2022 were used throughout the review. Evidence for this review was extracted from literature by reviewing and comparing key findings and discussion synthesis across papers to establish how the natural mechanisms of ABX can potentially counter pathways of pathogenesis in PD. Not many clinical trials for Ambroxol for PD currently exist, so studies with mice for treatment if Ambroxol were examined in this review for evidence. Mice have been emerging with a prominent role in neuroscience research due to their large genetic toolbox. However, animal trials were used as evidence limitedly to preserve validity.

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