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AMBROXOL'S POTENTIAL THERAPEUTIC EFFECTS COMBATING AGAINST NEUROLOGICAL DISORDERS: A REVIEW

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ABSTRACT
The FDA has approved ambroxol hydrochloride as a medicinal chemical for use as an expectorant. People currently use it as a cough suppressant and a drug to manage asthma. Ambroxol has mucolytic properties and also demonstrates antioxidant, anti-inflammatory, and anaesthetic features. The CNS's consequences are the subject of a continuing investigation. Research has demonstrated that ambroxol can inhibit the growth of microglial cells and decrease the levels of proinflammatory substances in the brain. It has the ability to cross the blood-brain barrier, suggesting potential benefits in protecting the central nervous system (CNS) from various conditions such as spinal cord injury, nervous system inflammation, Parkinson's disease (PD), amyotrophic lateral sclerosis, and Gaucher syndrome. This study aims to assess Ambroxol's impact on the central nervous system (CNS) and its prospective as a therapeutic intervention for neurological disorders. Amyotrophic lateral sclerosis (ALS), It is the most prevalent type of motor neuron disease., primarily impacts found on adults. This condition is characterized by a significant metabolic aspect that influences its progression and leads to the deterioration of the neurons containing of both upper and lower motor neurons. In about two-thirds of ALS patients, metabolic issues play a role in worsening their symptoms. Additionally, ALS disrupts the function of complex lipids called glycosphingolipids, a phenomenon observed in other brain-wasting diseases. This interruption might enable successful therapy. In mice with the SOD1G86R ALS model, the enzyme glucocerebrosidase (GBA 2), which breaks down glucosylceramide, is active more than usual in their central nervous systems. Researchers have shown that ambroxol, a molecule acting as a chaperone to block GBA2, slows down the disease's progression in these mice. Clinical trials are currently testing Ambroxol for Parkinson's disease and Gaucher disease, and exploring it as a potential treatment for ALS.

KEYWORDS: Ambroxol, Neurodegerative disease, Glucocerebrosidase, α Sinuclein, Gcase.

Neurodegenerative diseases

Neurodegenerative disorders are permeate by the impairment of the neurological system and death of neurons as they progress. Variations in the participation of functional systems contribute to a wide range of clinical symptoms, which vary from one condition to the next. Several clinical manifestations are associated with these variations. An important feature is the buildup of proteins that have altered physicochemical properties; these kinds of proteins are also known as misfolded proteins. Misfolded proteins represent a category of accumulated proteins. According to the concept of conformational diseases, the basic structure of a physiologic protein may change, resulting in a change in function or potentially dangerous accumulation either within or outside of the cell. This can occur within or outside of the cell's circumstances.

With regard to neurodegenerative diseases, the categorization of these conditions is based on the following criteria.

1. The anatomical location identifies clinical symptoms that indicate a malfunction in the neural system.
2. Proteins display a range of biochemical alterations, accumulating either within neuronal or glial cells (intracellular environments) or externally (extracellular environments).

It is therefore possible to characterise anatomical, cellular, and protein susceptibility patterns in situations that are associated with neurodegeneration.[1]

Neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). These diseases' symptoms largely depend on damage to central nervous system (CNS) tissue. These disorders share

common molecular changes and pathways, which offer potential course of action for research across different neurodegenerative diseases. However, it's important to recognise that each neurodegenerative illness is different in terms of its underlying causes, intensity of symptoms, and rate ofdevelopment.[2]

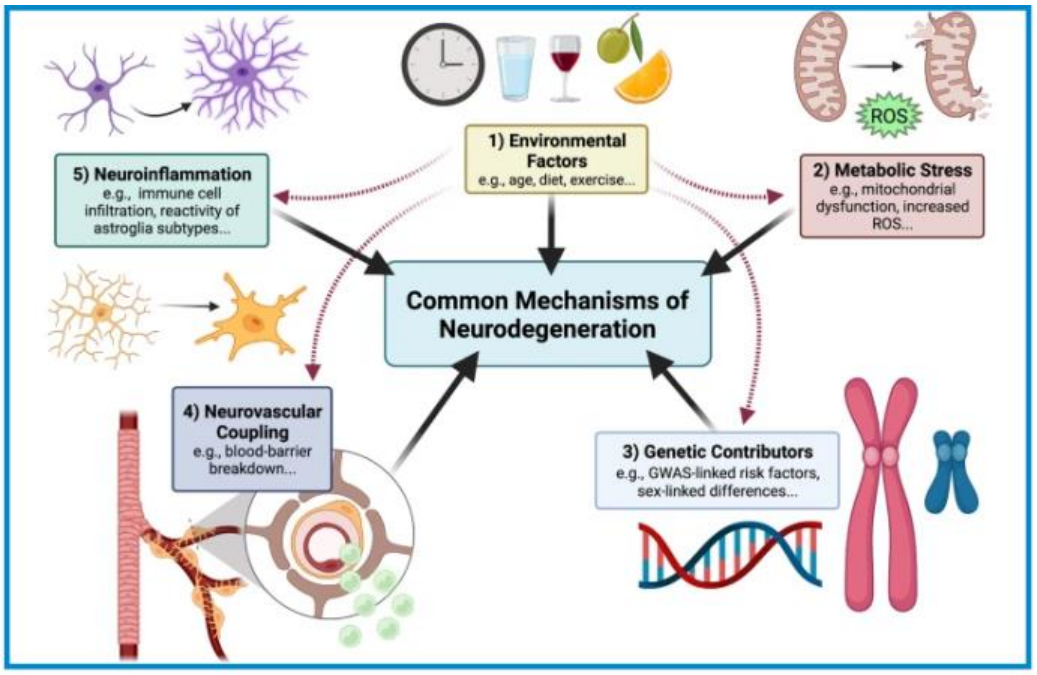


Fig No. 1 Common mechanisms of neurodegeneration.

Source: Wareham, L.K., Liddelow, S.A., Temple, S. *et al.* Solving neurodegeneration: common mechanisms and strategies for new treatments. *Mol Neurodegeneration* 17, 23 (2022).

The pathway that put up to the development of neurodegenerative illnesses is depicted in the ray diagram in Figure 2 below.

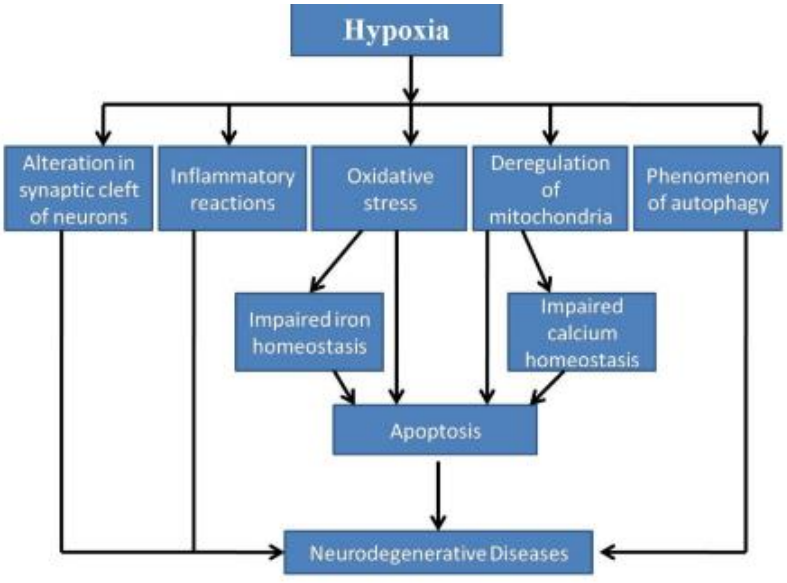


Fig No. 2: pathway that contributes to the development of neurodegenerative diseases.

Source: Sachchida Nand Rai, "Recent Advances in the Treatment of Neurodegenerative Disorders", Bentham Science Publishers (2021).

A number of tests are now emerged and commonly used in the medical practice for the detection of various brain disorders, which help to find out the correct diagnosis for the NDDs and their correct management as shown in Table no. 1 and 2.[3]

Table No. 1: Diagnostics tests of neurodegenerative diseases.

Sr. No.	Name of test	Purpose
1.	Addenbrooke's cognitive examination Frontal assessment battery Trog test Peabody vocabulary test Token test	For the screening of neurodegenerative diseases
2.	Wechsler test of adult reading National adult reading test	For the testing of function of pre-morbidity
3.	Boston or graded naming test Pyramids and palm trees test	For the testing of the languages
4.	Visual and object space perception battery Benton line orientation test Birmingham object recognition battery Behavioral inattention test.	For the testing of visuoperceptual functions
5.	Wechsler adult intelligence scale	For the testing of intelligence
6.	List learning tests Recognition memory test Doors and people test Autobiographical memory interview Wechsler memory scale Adult memory and information processing battery Rivermead behavioural memory test	For the testing of memory
7.	Trail making test Stroop test Hayling and Brixton test Verbal fluency Behavioural assessment desexcutive syndrome Deliskaplan executive function system Wiskonsin card sorting test	For the testing of executive functions and attention

Table No. 2: Medical management for neurological diseases.

Sr. No.	Neurological disease/sign and symptoms	Medical Management
1.	Parkinson disease and movement disorders	Dopaminergic drugs
2.	Cognitive disorders	Cholinesterase inhibitors
3.	Behevioral and psychological symptons of dementia	Antipsychotic drugs
4.	Pain and fatigue	Analgesic drugs
5.	Associated infections	Anti-inflammatory drugs and antibiotics
6.	Tremor and refractory movement disorders	Deep brain stimulatory drugs
7.	Cerebellar ataxia and Huntingtons's disease	Riluzole

Current scenario for treatment of neurodegenerative diseases

Allopathic drug

1. Parkinson's Disease: Physicians often prescribe drugs like donepezil, rivastigmine, galantamine, and memantine to improve mental abilities and manage behavioral issues. Yet, these medications do not stop the disease from advancing.
2. Multiple Sclerosis: We utilise treatments that modify the disease course (DMTs) to decrease the occurrence and intensity of flare-ups and to slow down the disease's advancement. Additionally, symptomatic treatments are available to efficiently address particular symptoms, including muscle tightness and tiredness.
3. Amyotrophic Lateral Sclerosis (ALS): Doctors prescribe medications like riluzole and edaravone to slow down the disease's progression and manage its symptoms. The treatment also includes physical therapy, support for breathing, and the use of devices to assist with daily activities.

Herbal drug

1. Ginkgo biloba: Although the research findings have been varied, there is some evidence that supports the hypothesis that ginkgo biloba extract may enhance cognitive function and memory in people with Alzheimer's disease.
2. Curcumin, the key component of turmeric, its having the anti-inflammatory and antioxidant properties. That features could aid in lowering inflammation and oxidative stress within the brain, possibly offering advantages for ailments such as Alzheimer's disease.
3. Researchers have investigated Ashwagandha, an adaptogenic plant, for its potential neuroprotective

properties and its ability to alleviate stress. These findings may have implications for neurodegenerative illnesses.

4. Green tea: Research has focused on the polyphenols found in green tea, particularly epigallocatechin gallate (EGCG), because of their neuroprotective properties and potential benefits for cognitive function.[13]

Neurodegenerative conditions burden individuals worldwide with substantial expenses related to public health and healthcare. The primary neurodegenerative conditions consist of Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), among others. Additionally, several other conditions are considered to be part of this group. The occurrence and prevalence of these conditions significantly rise with age, leading to a forecasted increase in their numbers in the coming years. Various nations have consistently observed an increase in life expectancy. In general, there are relatively few deviations from the fundamental principle that the understanding of causal impacts from environmental and genetic components is limited. Cellular epidemiological techniques have demonstrated their usefulness in various domains. Some of these are improving disease diagnosis, learning more about disease prognostic factors, finding genes linked to a higher risk of neurodegenerative disorders in parents, looking into genetic variations that may show susceptibility to non-familial forms of these diseases, and figuring out how much exposure people get from their environment. The integration of molecular methodologies, including proteomics, genomics, and assessments of environmental toxicant body loads, has the potential to greatly enhance our comprehension of the mechanisms that drive disease progression and pinpoint certain risk factors, especially for the non-hereditary variations of these diseases. This chapter offers brief summaries of the epidemiological characteristics of Parkinson's disease and amyotrophic lateral sclerosis (ALS).

Along with, it provides examples of how molecular epidemiology techniques have contributed to a greater comprehension of the underlying processes and risk factors associated with various illnesses. This information holds the potential to enhance medical treatment and, ultimately, prevent the onset of the illnesses under discussion. The chapter concludes with a number of recommendations for potential future studies in the field of molecular epidemiology.[4]

Introduction of ambroxol in neurodegenerative diseases

Ambroxol is a synthetic derivative of vasicine, and the chief chemical constituent of the Adhatoda vasica plant. In ancient India vasicine used to treat the respiratory disorders. Bromhexine's metabolite ambroxol has comparable effects and applications.[5] Ambroxol, is over-the-counter expectorant, is commonly used as expectorant. It is use for the treatment of respiratory disorders by decreasing excessive mucus production and thickness reduction. Ambroxol has mucolytic characteristics, but it also has anaesthetic, anti-inflammatory, and antioxidant qualities.[6] Ambroxol has available over-the-counter in many European countries, the UK, the US, and other industrialized nations. It is used as an antitussive because of its excellent safety record, even at high doses. When taken orally, it has a bioavailability of 70–80% and can easily crossing the blood-brain barrier (BBB). Discovered in 2009, ambroxol acts as a mild pharmacoperone for recombinant glucocerebrosidase (GCase). It has the potential to be a future treatment to modify Parkinson's disease (PD) by increasing GCase protein levels.[7]

Ambroxol's half-life has 1.3 hours. When ambroxol is broken down in the body, dibromoantranilic acid is produced.[8] The efficacy of ambroxol as a Parkinson's disease medication is being investigated in ongoing Phase II clinical studies. The GBA1 gene encodes GCase and is the site of homozygous mutations that cause GD.[9] As a helper molecule, ambroxol has been shown to reduce the symptoms of cellular stress, prevent dementia, and improve the activity of glucocerebrosidase (GCase) that is not folded correctly. Moreover, it has shown potential for alleviating Parkinson's disease symptoms. Research on animal models of Parkinson's disease has revealed that ambroxol decreases the buildup of alpha-synuclein and boosts GCase function. In the amyotrophic lateral sclerosis (ALS), which mainly impacts the neurons that control unwanted muscle movements, recent studies suggest ambroxol might offer neuroprotective benefits. Ambroxol could achieve this by improving the removal of improperly folded proteins and lowering oxidative stress. Studies have also shown the potential of ambroxol to guard against other neurological diseases such as Gaucher's disease, neurological damage, and Alzheimer's disease.[10] It does this because of its ability to raise gluco-cerebrosidase (GCase) levels. This review focuses on its neuroprotective qualities.[13] To a certain extent, drug-based helpers assist in the proper assembly of faulty proteins, restoring some of their activity inside lysosomes. Researchers have discovered that Ambroxol (ABX), a drug known for its ability to break down mucus, functions as a drug-based helper for glucocerebrosidase (GCase). There are six different versions of GCase with mutations, including p.Asn227Ser (also called p.Asn188Ser), (p.Arg120Trp), Arg159Trp, (p.Gly193Trp), (p.Gly202Arg), (p.Phe213Ile), Gly232Trp, Gly241Arg p.Phe252Ile and Asn409Ser (p.Asn370Ser), which have all responded to ABX at different levels from 0.3 to 30 μmol/L.

Importantly, ABX can pass through the blood-brain barrier (BBB), suggesting it could be a promising method for treating conditions in the brain and central nervous system.[14]

Fig. 3 represents the role of abroxol.

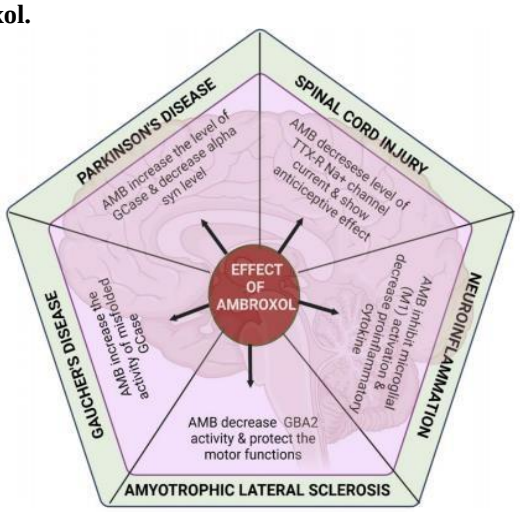


Fig No. 3: Ambroxol against neurodegeneration.

Source: P. Dhanve et al Ambroxol: A potential therapeutics against neurodegeneration., Health sciences review, June 2023.

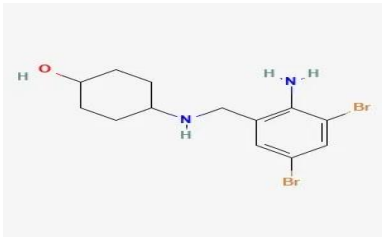
History and Discovery

The German pharmaceutical firm Boehringer Ingelheim was responsible for discovering and synthesizing ambroxol. during the 1960s. Initially, the Boehringer Ingelheim created ambroxol through chemical synthesis as a byproduct of bromhexine, another substance that breaks down mucus. Scientists were studying variations of bromhexine when they found that ambroxol had more potent mucolytic capabilities and greater tolerability compared to its original form. Ambroxol pharmaceutical development began in the late 1960s and early 1970s. The 1970s saw the launch of ambroxol under various brand names, including Mucosolvan, Mucobrox, and Mucoangin, which varied depending on the country and producer. Ambroxol has undergone extensive research to determine its effectiveness and safety in treating respiratory diseases. Nowadays, doctors commonly prescribe it to treat respiratory tract illnesses that involve excessive mucus production.[14]

Name Origin

The chemical configuration of the substance informs the coining of the term "ambroxol". We form the word by combining the prefix "ambro-" with the suffix "ol." Greek mythology sometimes links the prefix "ambro-" to the term "ambrosia." In this context, the gods consume ambrosia, a meal or drink renowned for its heavenly scent and ability to grant immortality. Chemical compounds frequently use the suffix "-ol" to indicate that they are alcohol. Hence, the term "ambroxol" may refer to a chemical that possesses advantageous characteristics similar to those found in ambrosia. The selection of the name "Ambroxol" was likely based on its chemical structure, pharmacological qualities, and marketing aspects rather than any connection to mythology. Ambroxol has emerged as a crucial medicine for treating respiratory illnesses, and its discovery and development have had a substantial impact on managing ailments characterised by excessive mucus production.[14]

Structure of ambroxol



Ambroxol's protein folding and degradation role

structures, which ultimately leads to a shift in function. Ambroxol is responsible for activates autophagy, which aids in the removal of misfolded proteins. It guards against the formation of plaques and protein aggregation, two common occurrences in neurodegenerative diseases.[16] There is some evidence that ambroxol contributes to protein misfolding, which is associated with ER stress and lysosome dysfunction. The processes that result in protein degradation include both of these components. Studies have demonstrated the involvement of ambroxol in protein misfolding. Folding, modifying, and transporting proteins are all functions of the endoplasmic reticulum (ER), a cellular component. An excessive number of misfolded proteins bombard the ER, causing Endoplasmic Reticulum (ER) stress. Research has shown that ambroxol may help the ER (endoplasmic reticulum) maintain appropriate protein folding even when the ER is under stress. The endoplasmic reticulum (ER) induces stress, which it alleviates by preventing the build-up of fragmented proteins. Stress arises when the ER's capacity to fold proteins is exceeded, resulting in the accumulation of improperly folded proteins. As a result, cellular malfunction and eventual cell death may result from the accumulation of misfolded proteins. Studies have demonstrated that ambroxol can significantly boost ER-associated degradation (ERAD), a mechanism that specifically targets misfolded proteins to disintegrate them. Improper protein folding leads to the

formation of aberrant cellular structures through the process of protein misfolding. This process facilitates the elimination of molecules from the endoplasmic reticulum (ER) thanks to its aid.[17]

Lysosomes are organelles found inside cells that contain enzymes that recycle and breakdown a wide variety of biological elements, including misfolded proteins. Studies have showed that Ambroxol enhances lysosomal activity and accelerates the clearance of protein clumps, thereby proving its effectiveness in cases of lysosomal dysfunction.[18]

The lysosome has the capability to break down, leading to the buildup of protein clumps, a typical characteristic seen in various neurodegenerative conditions. Researchers have shown that ambroxol can make lysosomes work better by stopping the production of proteins like beta-hexosaminidase and cathepsin D. Moreover, ambroxol helps in the merging of lysosomes and autophagosomes, boosting the destruction of proteins for reuse.

In summary, ambroxol can reduce stress on the endoplasmic reticulum (ER) and lysosomal issues, aiding in the proper folding and removal of proteins.[16]

Role of Ambroxol in Glucocerebrosidase

Certain proteins, such as the lysosomal enzyme glucocerebrosidase (GCase), are produced by polyribosomes attached to the endoplasmic reticulum (ER). ER Quality Control (ERQC) oversees the folding states of newly synthesized proteins after they translocate into the ER. The lysosome only transports molecules that have undergone proper folding at specific locations.[19] The endoplasmic reticulum (ER) retains mutant glucocerebrosidase (GCase) molecules that fail ER quality control (ERQC) to facilitate subsequent refolding attempts. After multiple unsuccessful folding attempts, the ubiquitin-proteasome system retrotranslocates certain proteins from the ER to the cytoplasm. We refer to this entire process as ER-associated degradation (ERAD). Researchers have shown that ambroxol can improve the activity of the lysosomal enzyme glucocerebrosidase (GCase) by doing tests on animals and in the lab. This enzyme is very important for break down of the glycolipid glucocerebroside, which builds up in the lysosomes of people who suffering from the Gaucher's disease. While the exact mechanism by which ambroxol increases GCase activity remains somewhat unclear, there are a few suggested theories to explain this effect. One theory suggests that, the ambroxol might directly bind to GCase, making the enzyme more robust and safeguarding it from degradation.[21] Ambroxol has been shown in studies to activate the Nrf2 transcription aspect, which regulates genes involved in detoxifying and antioxidants metabolism. One hypothesis is that ambroxol may increase glucocerebrosidase (GCase) function by altering the pH of lysosomes, allowing enzymes to function more effectively. Another hypothesis is that ambroxol may boost GCase production by stimulating TFEB, a transcription element that regulates the activity of genes involved in autophagy and lysosomal biogenesis. TFEB binding to the GCase gene promoter region increases the activity of the glucocerebrosidase enzyme.[23]

Role of Ambroxol Glucocerebrosidase in PD

Glucocerebrosidase (GCase) acts as a catalyst in the decomposition of substances, assisting in the degradation and reutilization of different proteins. The body synthesizes beta-glucocerebrosidase from the GBA gene. Alterations in the GBA1 gene can result in autosomal recessive lysosomal storage conditions, such as Gaucher disease (GD). Importantly, alterations in the GBA1 gene significantly increase the genetic risk of developing Parkinson's disease.[24] GCase is a membrane-associated protein that has 497 extra amino acids in addition to a leader sequence with 39 amino acids and five glycosylation sites.[25] The process of glycosylation and protein synthesis both take place in the endoplasmic reticulum (ER). The enzyme goes into an active state within the acidic lysosome lumen.[26] Migdalska-Richards A's 2017 research linked the glucocerebrosidase 1 (GBA1) gene to Gaucher disease (GD) and Parkinson's disease (PD), two incurable neurological illnesses. In both cases, the gene GBA1 encodes the glucocerebrosidase (GCase) enzyme, and its absence correlates with the disease. Researchers have found that the small chemical chaperone ambroxol may be able to get through the blood-brain barrier in microorganisms to increase GCase activity and decrease the amount of alpha-synuclein protein present. Researchers investigated the impacts of ambroxol on GCase activity among non-human primates in good health. Furthermore, studies have demonstrated that regular ambroxol therapy increases brain GCase activity.[28]

GBA1 mutations can alter the structure of the glucocerebrosidase (GCase) protein, leading to various dysfunctions.

1. It may fail to exit the endoplasmic reticulum (ER).
2. It might not bind properly to its trafficking transporter, LIMP2.
3. The protein could be misfolded and unstable, leading to degradation by proteasomes.
4. It may not be able to properly exit the Golgi apparatus.
5. Reduced enzymatic activity could occur if the enzyme becomes inactive.
6. Alterations in Saposin C, a protein that interacts with GCase, can also affect GCase activity.

These dysfunctions can impair GCase function and contribute to the pathogenesis of diseases such as Gaucher disease and Parkinson's disease.[27]

The buildup of glucocerebrosidase and β-synuclein is linked in Parkinson's disease

Dopaminergic neurons die and persistent β-synuclein fibrils build up in the brain's substantia nigra as Lewy bodies and neurites. These are signs of Parkinson's disease.[29]

In cells, α-synuclein exists in two forms: soluble in the cytoplasm and attached to the cell membrane. Undissolved fibrils and aggregates may develop when there is an excess of δ-synuclein, a protein that has the ability to self-assemble. As with misfolded prion proteins, synuclein has the potential to self-seed, leading to a rise in the amount of insoluble forms. This is due to the fact that the presence of existing aggregates enhances aggregation.[30] in It was in the 1990s, when Parkinson's disease began to manifest in patients with Gaucher disease, that the link among GBA1 alterations and the onset of the condition was first identified. Both disorders were linked to one another.[31] About 7% to 12% of people with Parkinson's disease have a mutation in the GBA1 gene, a prevalence significantly higher among Ashkenazi Jews where the mutation rate exceeds 15%. Research suggests that individuals with mutant alleles linked to Gaucher disease have an increased risk of developing Parkinson's disease. Studies have shown that people carrying the GBA1 mutation are at a six to eleven times higher risk of developing Parkinson's disease compared to those without the mutation. Importantly, the overall prevalence of Parkinson's disease remains consistent whether individuals carry the GBA1 mutation as a homozygote (two copies) or a heterozygote (one copy).[32] In fact, GCase deficiency has been linked to Parkinson's disease development in a major way by experts. The glucocerebrosidase (GCase) gene, GBA1 mutations, are a major hereditary cause for Parkinson's disease. Decreased GCase activity may lead to lysosomal dysfunction and alpha-synuclein buildup, two important aspects of the pathophysiology of Parkinson's disease. This relationship emphasises GCase as a possible therapeutic target for disease modifying techniques and emphasises the significance of cytosolic dysfunction in the aetiology of Parkinson's disease.[33] This was possible because the researchers looked at the amounts of alpha-synuclein in animal models and found a link among GCase activity and those levels. Through histology studies, it was found that the olfactory bulb, hippocampus, brain, the striatum, and nigra of the brain of mice lacking GCase had a lot of alpha-synuclein buildup. After doing study, the scientists found that lower GCase activity causes more alpha-synuclein to clump together, and that high amounts of alpha-synuclein cause nerve cells to die in Parkinson's disease.[34] Figure 2 shows that glucocerebrosidase (GCase) is thought to control the amount of alpha-synuclein (α-syn), and dopaminergic neurons are killed when there are too many of these proteins. Many studies have established a connection between decreased GCase activity and an elevated risk of Parkinson's disease, primarily attributed to the buildup of alpha-synuclein.[35]

Role Ambroxol in Parkinson diseases

Mutations in the glucocerebrosidase gene (OMIM number 606463) cause Gaucher disease, an autosomal recessive lysosomal storage disorder. These mutations represent the most notable hereditary threat factor along with the development of Parkinson's disease, with a penetrance ranging from 10% to 30%. Their prevalence varies from 5% to 15% in the Caucasian population, approximately 25% in the Ashkenazi Jewish population, and about 1% in the general population without Parkinson's disease. There seems to be a two-way street among the levels of α-synuclein and the event of the β-glucocerebrosidase (G Case) enzyme in both GBA1 cell and animal models. The connection enables α-synuclein to accumulate more effectively. People with Parkinson's disease (PD) and GBA1 mutations both exhibit reduced G Case activity in their brains, but the GBA1 mutant patients have it at a lower level. There is a link between increased levels of α-synuclein and reduced G Case activity in the brain. Furthermore, decreased levels of G Case activity were seen in the cerebrospinal fluid (CSF) of both GBA1-mutant and non-mutant Parkinson's disease (PD) patients relative to healthy subjects. An increase in cerebral cytosolic/lysosomal G Case expression in Parkinson's disease (PD) patients, regardless of whether they have GBA1 mutations or not, could potentially result in decreased α-synuclein levels and neuroprotective benefits. Since the 1970s, ambroxol treatment has been used as a cough linctus without any adverse effects (a description of product features may be found in Methods 1 in Supplement for further information). A disruption in the gastrointestinal tract and a little risk of anaphylaxis are the most significant side effects of this substance. Based on the results of a high throughput chemical study, it was determined that ambroxol promoted a rise in G Case activity that was dependent on pH.

Research conducted in both laboratory settings and live organisms has shown that injecting ambroxol may increase GCase activity while decreasing α-synuclein levels. The inhibitory chaperone ambroxol releases the mutant G Case, trapped in the endoplasmic reticulum. The process involves attaching to the enzyme's active site and inhibiting it, resulting in a conformational change that enables the enzyme to transit to the lysosome.

The acidic lysosome facilitates the elution of ambroxol, thereby resuming normal catalysis and restoring lysosomal function. Ambroxol has the potential to influence α-synuclein levels through a variety of pathways. Research has shown that ambroxol may enhance GCase synthesis by activating lysosomal exocytosis and the gene expression factor EB pathway. This suggests that the GCase may play a direct role in the removal of -synuclein proteins. GBA1 mutations may disrupt the regular posttranslational folding process, potentially preventing the release of the enzyme to the lysosome.

Disruption in the process appears to cause the accumulation of α-synuclein in the endoplasmic reticulum, along with an unfolded protein response that can potentially lead to α-synuclein aggregation. Furthermore, there is evidence to suggest that ambroxol corrects posttranslational folding, hence reducing the overall response of unfolded proteins. Within the human volunteers, we explored the biological changes that were related with ambroxol treatment, as well as the effects that these changes had on the biochemical and clinical indicators of Parkinson's disease. The most important results were tests that looked at how safe and well the ambroxol drug was tolerated, how deep it went into the central nervous system (CNS), and how the glucocerebrosidase activity in the cerebrospinal fluid (CSF) changed from the start of the study to 186 days later.[36]

Parkinson's therapy

Parkinson's disease (PD) is the second most prevalent neurological disorder, impacting millions of individuals globally. Currently, available treatments focus on alleviating symptoms rather than halting or curing the disease.[37] Current conditions need the identification of a novel therapeutic target for Parkinson's disease. Dysfunction of dopaminergic neurons in the nigrostriatal segment is a hallmark of Parkinson's disease. Common symptoms of Parkinson's disease include rigidity, postural instability, bradykinesia, fatigue, and resting tremors. Another pathogenic feature of Parkinson's disease (PD) is the saturationn of alpha-synuclein in both the cerebral cortex and the subcortical areas of the brain.[38] Changes in the glucocerebrosidase (GBA1) gene cause problems with the glucocerebrosidase (GCase) enzyme inside cells, which in turn cause Gaucher disease. People may be either homozygous or heterozygous for the glucocerebrosidase changes, which rises the likelihood of acquiring Parkinson's disease.[39] We do not fully understand the precise mechanism by which GBA1 mutations substantially increase the risk of Parkinson's disease. The symptoms of idiopathic Parkinson's disease and PD-GBA1 patients are the same, which supports the idea that PD-GBA1 also has features like the buildup of alpha-synuclein and the death of dopamine-producing neurons in the substantia nigra.[40] According to the findings of studies conducted on animal models and cell cultures, ambroxol has the ability to raise the amounts of GCase protein while simultaneously lowering the levels of alpha-synuclein.[11] A little pharmacological chaperone drug called ambroxol helps the GCase enzyme function. It may raise GCase levels as a Parkinson's disease (PD) disease-modifying drug. Its small size and ability to cross the blood-brain barrier make it an excellent choice for treating Parkinson's disease associated with neuronopathic GD (nGD). the eleventh The current therapeutic modalities use the chemical chaperone, ambroxol. This increases GBA's lysosomal dispersion, which in turn increases its enzymatic activity. Phase II clinical studies involving ambroxol are currently underway to investigate its potential impact on the progression of Parkinson's disease (PD). Researchers are studying ambroxol because it boosts glucocerebrosidase (GCase) activity, an activity thought to be beneficial in Parkinson's disease (PD).[41]

GCase mutation and buildup of α-synuclein is represented in Fig No. 3 and pathophysiology of Parkinsons disease is expressed by ray diagram in Fig No. 4.

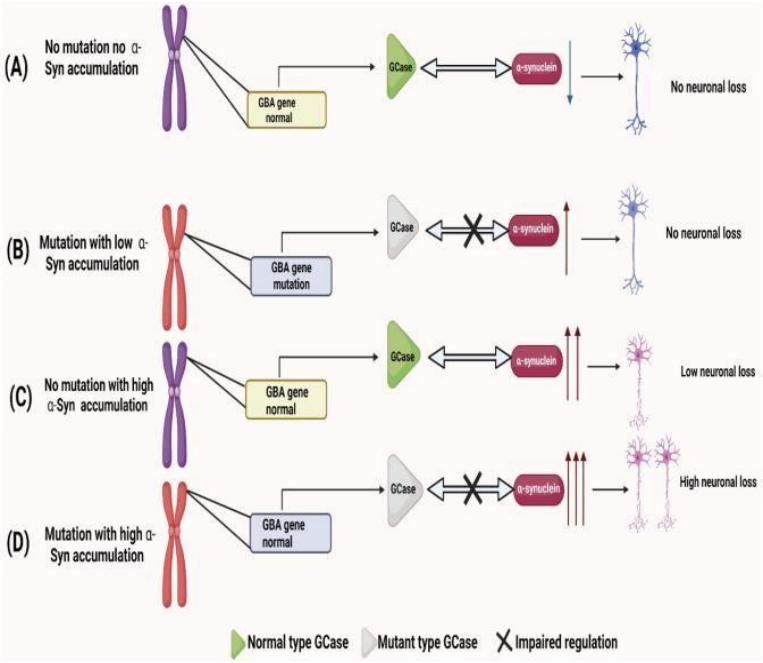


Fig. 4: GCase mutation and buildup of α-synuclein.

(A) The GCase enzyme controls the levels of alpha-synuclein. Therefore, under normal circumstances, No

dopaminergic neuronal death occurs due to the absence of alpha-synuclein buildup.(B) Mutant GCase only partially regulates alpha-synuclein levels, which results in alpha-synuclein accumulation without dopaminergic neuronal death. (C) Alpha-synuclein buildup may also cause mild dopaminergic neuronal death in those without GCase dysfunction. (D) A large build-up of alpha-synuclein is caused by the mutant GCase's inability to regulate the high levels of alpha-synuclein, which results in a notable loss of dopaminergic neurons.

Pathophysiology

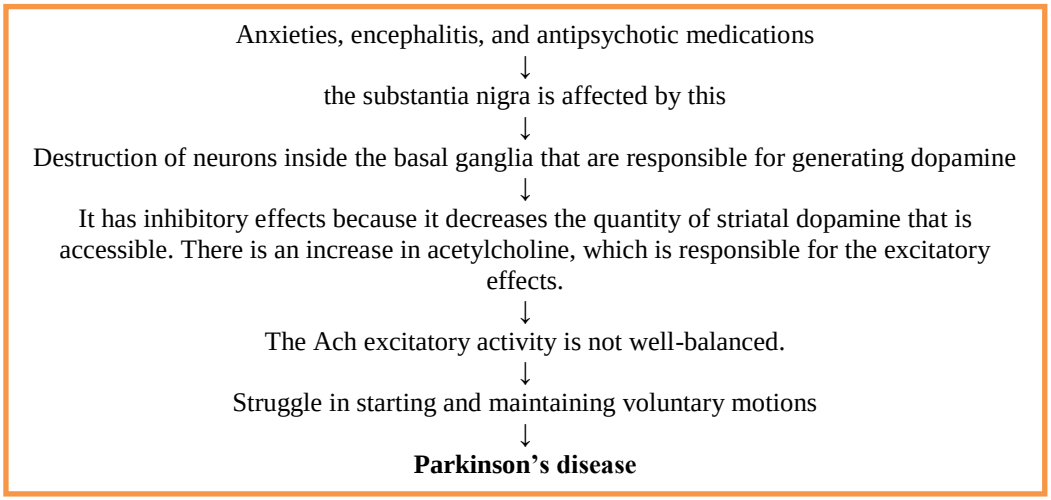


Fig No. 5 Pathophysiology of Parkinson's disease.

Ambroxol's function in Gaucher's illness

A pain reliever mucolytic, and antioxidant are the characteristics of the chemical known as ambroxol. Through crossing the blood-brain barrier (BBB), it may increase GBA1 activity in cells from people with Gaucher disease and wild-type mice, both in living things and in the lab. According to research by Maegawa et al. (2009), ambroxol improves GBA1 enzymatic activity by regulating its conformation and reduces glucosylceramide buildup in fibroblasts from Gaucher disease patients.

In fibroblasts from Parkinson's disease patients, ambroxol has been demonstrated to enhance GBA1 activity and decrease α-synuclein aggregation. When ambroxol was given to transgenic and wildtype mice overexpressing human α-synuclein, the brain's GBA1 mRNA along with enzyme activity increased along with α-synuclein levels falling. Lastly, after receiving ambroxol therapy, non-human primates exhibit considerable improvements in the activity of GBA1 and β-hexosaminidase. Our group has shown that ambroxol in the setting of ALS prolongs the survival of Sod1G86R mice, delays the onset of the illness, and avoids the loss of muscular strength. Furthermore, both in vivo and in vitro, ambroxol stimulates axonal development and neural network complexity. Overall, in a variety of mice models of neurodegeneration, ambroxol seems to be quite successful in modifying GBA1 activity to provide neuroprotective benefits.[43] Ambroxol has shown promising results in treating neurological disorders by reducing myoclonus and epileptic fits, leading to improved motor function, pain relief, and ultimately enhancing standard of life for patients and their families.[44]

The enzyme glucocerebrosidase, found in the lysosome, which is responsible for breaking down glucocerebroside into glucose and ceramide. GBA1 gene mutations, responsible for encoding glucocerebrosidase (GCase), lead to the development of Gaucher's disease (GD). Gaucher's disease (GD) is an uncommon disorder associated with the accumulation of substances in lysosomes, and is connected to synucleinopathy and is passed down through generations in a recessive pattern. In GD, the endoplasmic reticulum (ER) stores misfolded or dysfunctional GCase proteins instead of reaching the Golgi apparatus and lysosomes, as is normal. This is due to GD's characteristic slow transport rate. Endoplasmic reticulum stress is caused by too many misfolded proteins, efforts to fix their structure, and getting rid of proteins that cause stress. It can hurt cells and set off programmed cell death. Ambroxol contributes to this by acting as a helper, boosting the function of misfolded GCase, alleviating cellular stress, and possibly stopping the progression of neurodegeneration. As a helper, ambroxol ensures the correct folding of GCase in the ER, assists in its transport to the lysosome, where it can then perform its usual role in degrading glucocerebroside.

Figure 5 illustrates the pathophysiology of Gaucher disease and how it affects cells.

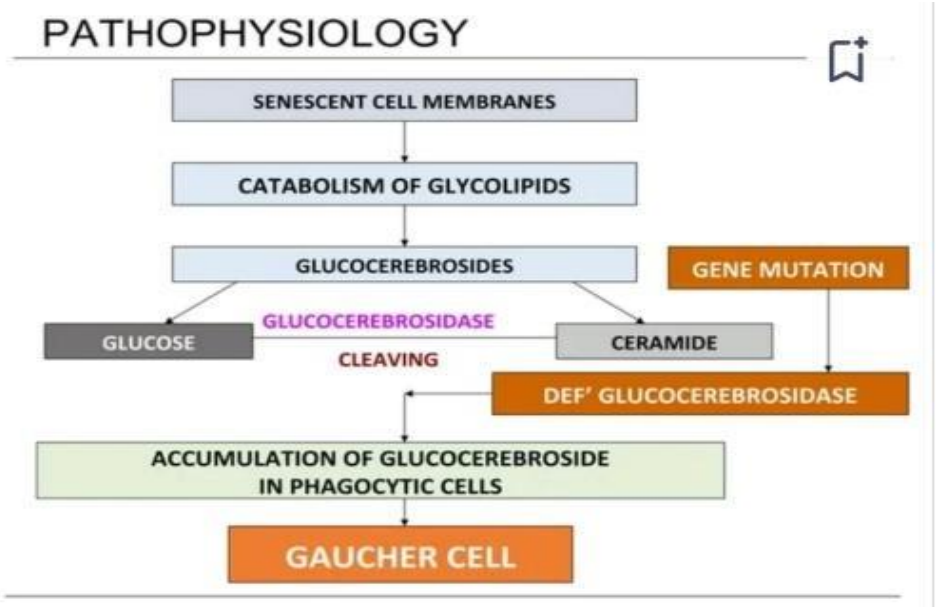


Fig No. 6: The Pathophysiology of Gaucher disease.

Source: https://www.slideshare.net/slideshow/seminar-presentation-236643762/236643762#11

Ambroxol's Function in the Treatment of Amyotrophic Lateral Sclerosis

It is well-known that the neurodegenerative illness amyotrophic lateral sclerosis (ALS) causes the spinal cord, brainstem, and motor cortex to lose motor neurons, which in turn causes a gradual weakening of muscles, paralysis, and death. ALS affects adults primarily and also impacts peripheral organs in addition to the central nervous system. Current treatments provide only limited symptomatic relief, and there is no cure for ALS.

A significant dysregulation in the biosynthesis of glycosphingolipids, a type of complex lipid, has been observed in individuals with ALS. These lipids play critical roles in neuronal cell maturation, myelin sheath formation, and nerve impulse transmission. Dysregulated lipid metabolism, particularly involving ceramide, glucosylceramide, and gangliosides, appears to be linked to ALS pathogenesis. Glucocerebrosidase (GBA1 and GBA2) enzymes are responsible for breaking down glucosylceramide, a major precursor of glycosphingolipids. Studies have shown altered levels of these enzymes in ALS, suggesting their involvement in disease progression. Accumulation of sphingolipids, including glucosylceramide, has been implicated in motor neuron death in ALS animal models and human studies.

Ambroxol, a chaperone molecule, has shown therapeutic potential in ALS by inhibiting GBA2 activity, reducing glucosylceramide levels, and potentially slowing disease progression. Ambroxol can penetrate the blood-brain barrier, allowing for widespread distribution in the central nervous system (CNS). Studies in ALS models have demonstrated that ambroxol improves motor function, reduces myoclonus severity, and enhances GBA1 enzyme activity. Additionally, ambroxol's ability to inhibit GBA2 in the ER and plasma membrane further supports its role as a therapeutic chaperone in ALS.

In brief, disruptions in glucosylceramide metabolism seem to be heavily involved in ALS development, suggesting it as a potential focus for treatments like ambroxol.[47]

Ambroxol's function as an analgesic agent in the treatment of spinal cord injuries

Clinical studies using a double-blind, placebo-controlled design have demonstrated that ambroxol therapy reduces pain in patients with acute pharyngitis. Ambroxol's pain-relieving effects happen by slowing down the activity of TTXR sodium channels in neurons in the dorsal root ganglia (DRG). Researchers further explored this mechanism using rat models of peripheral nerve injury and inflammation, highlighting ambroxol's ability to alleviate pain. Studies using pain models caused by peripheral tissue damage have also shown that ambroxol has mucolytic and soothing effects, in addition to its antinociceptive properties.

Studies done in vitro show that ambroxol blocks voltage-gated sodium channels in DRG neurons. This supports its role in stopping the functions of nociceptor synapses and giving antinociceptive effects in vivo. Ambroxol's favourable clinical safety profile enhances its potential as an effective analgesic in therapeutic settings.

For a detailed overview of ambroxol's potential role in managing neurological disorders, including its mechanisms and therapeutic implications, please refer to the relevant literature.[48]

1. Parkinson's disease (PD)
The journal Brain published a 2014 study that explored the therapeutic potential of ambroxol for Parkinson's disease. The study used animals to show how PD works and found that ambroxol can increases the activity of glucocerebrosidase (GCase), which lowers the levels of α-synuclein.

2. Gaucher Disease (GD)
Researchers have investigated the possibility of Ambroxol in treating the neurodegenerative symptoms of Gaucher disease, a type of lysosomal storage disorder. Researchers have found that ambroxol can increase GCase activity and lower α-synuclein levels. This means that it might be possible to use it to treat the neurological symptoms of GD.

3. Alzheimer's Disease (AD)
Ambroxol may help decrease amyloid-beta (Aβ) pathology in people with Alzheimer's disease (AD), according to research. Ambroxol is shown to improve Aβ clearance in mouse brains, suggesting a possible therapeutic benefit in Alzheimer's disease, according to research published in the Proceedings of the National Academy of Sciences (PNAS).

4. Amyotrophic Lateral Sclerosis (ALS)
Researchers have studied ambroxol for its potential as a therapy for amyotrophic lateral sclerosis (ALS). Researchers have looked into how it affects the function of glucocerebrosidase (GCase), lowers glucosylceramide levels, and might change how quickly ALS models get worse. A research article published in the Journal of Neurology, Neurosurgery & Psychiatry investigated the impact of the substance on a specific kind of ALS called mutant SOD1-linked ALS, using a mouse model that had been genetically modified to have this condition. The study indicated that ambroxol has the potential to enhance motor function and increase survival rates in mice with ALS.

5. Huntington's Disease (HD)
Emerging research indicates that ambroxol may have potential benefits in treating Huntington's disease. Studies have demonstrated that it can improve autophagy and decrease mutant huntingtin clumping together, which may help alleviate the dysfunction and degeneration of neurons in Huntington's disease (HD).

6. Overall neuroprotective effects
Researchers have extensively researched ambroxol for its neuroprotective properties in various settings, in addition to its use in certain neurodegenerative illnesses. Evidence has demonstrated that it stimulates autophagy, diminishes oxidative stress, and regulates inflammatory responses, all of which are processes pertinent to neurodegenerative disorders. [Citation: Wu et al., 2020] Although preclinical research suggests that ambroxol holds promise for treating neurodegenerative illnesses, it is required to conduct clinical trials to assess its safety and effectiveness in humans. Furthermore, additional investigation is necessary to clarify the most effective schedules for administering doses and the potential adverse consequences associated with prolonged use in neurodegenerative disorders.[51]

CONCLUSION
This study discusses neurodegenerative diseases that could potentially benefit from ambroxol treatment. An extensive number of studies have shown that ambroxol is fruitful in treating neurodegenerative diseases; however, these studies have mostly employed cell lines and animals. In the membrane of the endoplasmic reticulum (ER), the chemical ambroxol binds to misfolded proteins, facilitating their transit to the lysosome. It may also be useful for future therapies for several neurodegenerative illnesses associated with protein misfolding because of its high BBB traversal capability.

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