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# NEURODEGENRATIVE DISORDERS: CURRENT STATUS AND FUTURE PROSPECTIVE

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## ABSTRACT

In neuroscientific research the field of neurodegeneration is most important in respect to both medical and associated social issues. Neurodegenration is a broad term used for the progressive loss of structure or function of neurons or sometime death of neurons. Current therapies available for Parkinson's disease significantly improve the quality of life for patients suffering from this neurodegenerative disease, yet none of the current therapies has been convincingly shown to slow or prevent the progression of disease. A lot of studies is going on discovering the pathophysiology of Parkinson's disease in recent years, and these discoveries offer a variety of potential targets for protective therapy. Mechanisms implicated in the disease process include oxidative stress, mitochondrial dysfunction, protein aggregation and misfolding, inflammation, excitotoxicity, and apoptosis. At the same time, the involvement of these diverse processes makes modeling the disease and evaluation of potential treatments difficult. In addition, available clinical tools are limited in their ability to monitor the progression of the disease. In this review, we summarize the different pathogenic mechanisms implicated in Parkinson's disease and neuroprotective strategies targeting these mechanisms currently under clinical study or under preclinical development, with a view towards strategies that seem most promising.

**KEYWORDS:** Neurodegenration, Parkinson's disease, Current Therapy, Neuroprotection.

## NEURODEGENRATIVE DISEASE

A neurodegenerative disease is a disorder caused by the deterioration of certain nerve cells neurons, and become function abnormally, eventually bringing about death of the nerve cells. It includes a wide range of diseases that consist of the common characteristics of progressive loss of structure or function of neurons in brain and spinal cord. Neurodegenerative diseases are chronic and slowly progressive process. A recent study has evaluated that the each year about 16–19 people per 100,000 are diagnosed with PD. Disease prevalence is age-associated, with approximately 1% of the population being affected at 65 years, increasing to 4–5% in 85-year-olds. The occurrence of PD in India is 70 out of 100,000.[1] They are characterized by more or less selective neuronal degenerations including neurological syndromes, and affect both sensory-motor areas and cognitive functions.

Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons normally don't reproduce or replace themselves, so when they become damaged or die they cannot be replaced by the body.[2] Neurons or cells in neurodegenerative diseases are affected by neuronal dysfunction at the level of synaptic transmission, synaptic contacts, and axonal and dendritic degeneration. In different neurodegenerative diseases, neurons degeneration and cell loss of neurons are present within specific neurotransmitter populations. In addition, numbers of functional neurons in brain in adults altered or decreased with increasing ages.

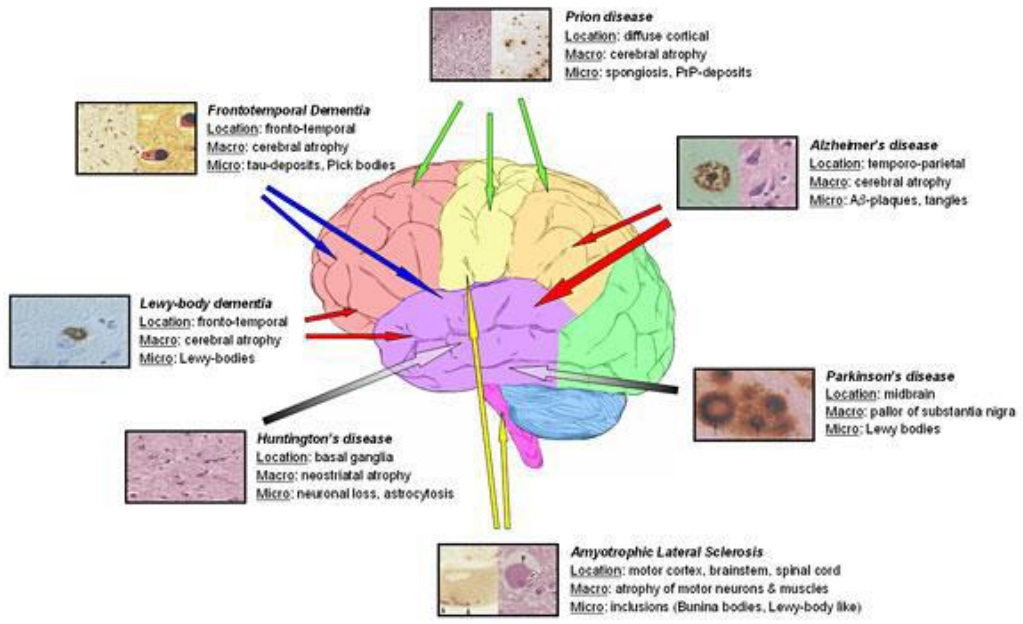


**Figure 1**: **Various kind of Neurodegenerative Disease and Location of Disease.**

This Neurodegenerative disease is associated with the nerve cells malfunctioning due to accumulation of misfolded proteins into microscopically visible aggregates in the brain.[4] These aggregates contain fibrillar structures that are mainly composed of disease specific misfolded proteins, such as α-synuclein in Parkinson's disease, amyloid-b and tau in Alzheimer's disease, superoxide dismutase (SOD) in Amyotrophic lateral sclerosis (ALS), and mutant huntingtin in Huntington's disease (Fig 2).[5-7] There is still controversy about the role of the aggregates but the prevalent hypothesis is that they represent a cellular protection mechanism against toxic aggregation intermediates.[8, 9]

This article consists of overview of Parkinson's disease it's causing factors, Pathophysiology and current Treatment in Parkinson's disease.

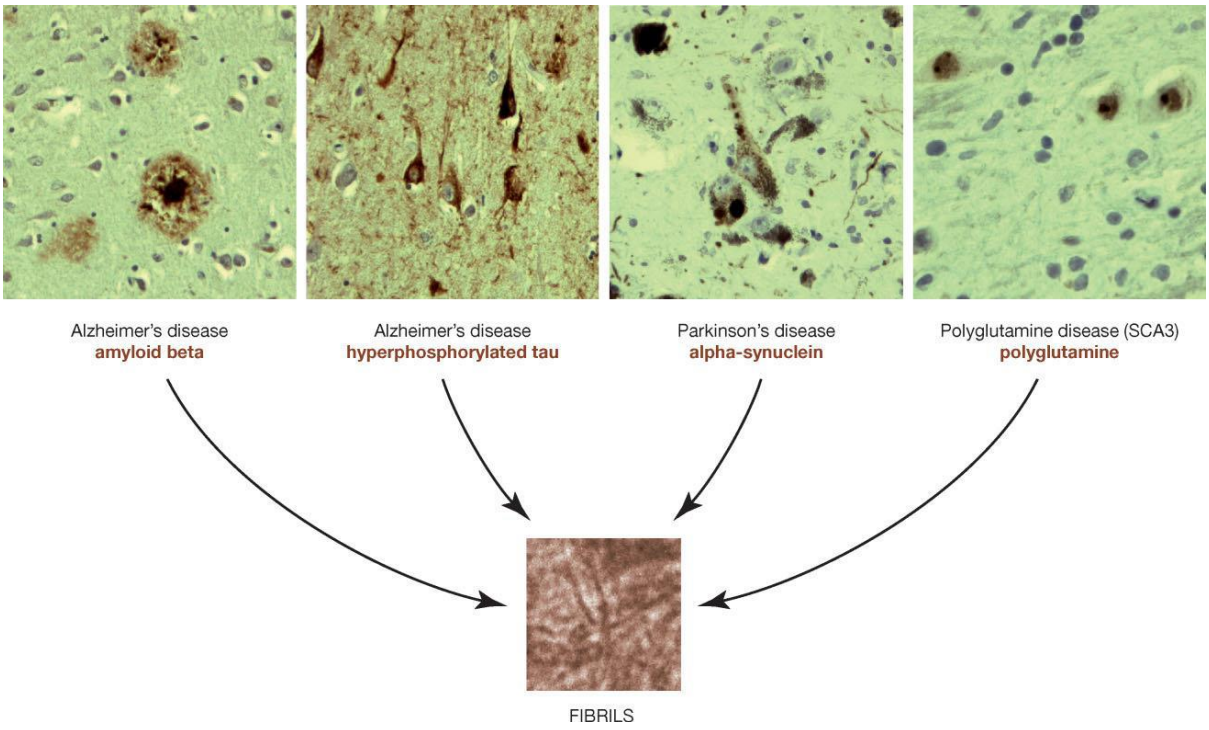


**Figure 2**: **Protein aggregation in neurodegenerative disease.**

Examples of aggregation in brains of patients with neurodegenerative disorders (disorders in dark blue). Typically, these aggregates contain amyloid-like fibrils composed of specific disease proteins (disease proteins in brown).

**Parkinson's disease**

Parkinson's disease is a progressive and one of the major neurodegenerative Disorders of middle and old age, and was originally described by James Parkinson in 1817. It is most common hypokinetic disorder and the second most common late life neurodegenerative

Disorder of CNS that often impairs Motor skills and speech. It is characterized by symptoms—muscle rigidity, tremor and bradykinesia—but can also involve postural deficits and impaired gait, as well as dementia in a significant minority of patients.

It is the condition in which degeneration of dopamine producing neurones in the substantial nigra, in basal ganglia, deep in the lower region of the brain, on either side of the brain stem. Microscopic deposits known as Lewy bodies are formed within dopamine-producing neurons and are characteristic of the pathology of the condition. Clinical signs of Parkinson's are evident when about 80% of the dopamine-producing neurons are lost. Dopamine is a major neurotransmitter that promotes the functions of the basal ganglia, which is also where the dopamine is produced. The basal ganglia's role is to orchestrate the performance of well-learnt, voluntary and semi-automatic motor skills and movement sequences. Dopamine also contributes to other cognitive processes, such as maintaining and switching focus of attention, motivation, and mood, problem-solving, decision-making and visual perception. Parkinson's affects functional activities such as balance, walking, speech, handwriting, typing, fastening buttons, driving, and many other simple, or complex but familiar and routine activities, as they are usually controlled by the mechanisms of dopamine and the basal ganglia.

**SYMPTOMS**[10]

The basic motor symptoms are slowed movements called bradykinesia, resting tremor (shaking in an arm or leg when it is not being moved), muscle rigidity (stiffness), and postural instability. Symptoms typically begin on one side of the body (unilateral) and progress to include both sides.

**Table 1: Important Symptoms are listed below.**

| Motor Symptoms | Non-Motor symptoms |
|---|---|
| Tremor , Rigidity, Akinesia , Postural Instability, Bradykinesia/Hypokinesia, | **Neuropsychiatric Symptoms**<br>Dementia, Depression, psychosis, anxiety and Slowness of Thought.<br>**Autonomic Dysfunction**<br>Neurogenic Bladder, Erectile and urinary Dysfunction, Constipation, Orthostatic Hypotension.<br>**Sleep Disturbance**<br>**Sensory Symptoms**<br>Diminished Sense of Smell, pain ,numbness And Dizziness |

**Table 2: While scientist Hoehn and Yahr scale, in 1967 suggested the 5 Stages of Parkinsonism:**

| | |
|---|---|
| **Stage I** | Mild unilateral signs and symptoms. |
| **Stage II** | Bilateral symptoms with minimal disability. |
| **Stage III** | Equilibrium impairment; general dysfunction noted. |
| **Stage IV** | Severe symptoms; limited mobility; support necessary at home. |
| **Stage V** | Cachexia; dependent; immobile. |

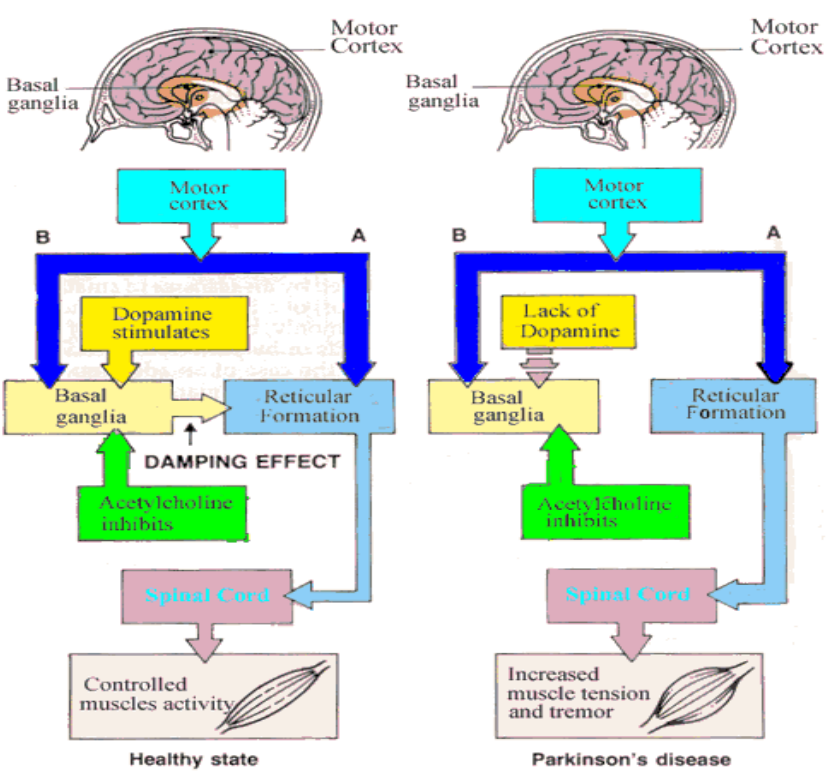


**Figure 3: Actual difference between the Healthy State person And Parkinson's Disease Patient.**

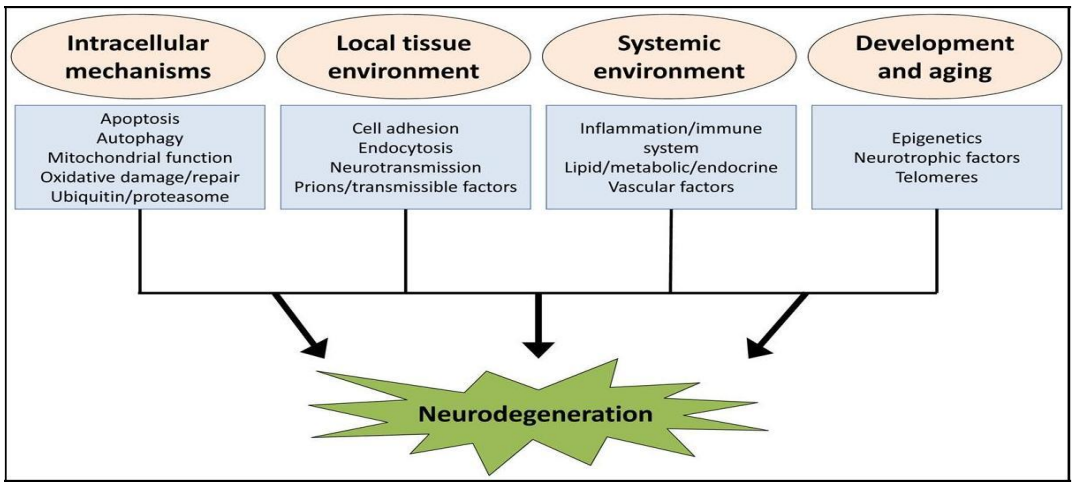


**Figure 4: Various kind of Neurodegenerative Mechanism.**

**Mechanisms of Parkinson's disease.**

Several mechanisms have been implicated as crucial to PD pathogenesis: oxidative stress, mitochondrial dysfunction, protein aggregation and misfolding, inflammation, excitotoxicity, apoptosis and other cell death pathways, and loss of trophic support Fig.4. None of the any one mechanism appears to be primary in all cases of PD, and these pathogenic mechanisms likely act synergistically through complex interactions to promote neurodegeneration.[11]

**Apoptosis[12]**

Apoptosis is one of the decisive process in neural development and to play a role in some forms of neural injury. Several pathological studies have revealed signs of both apoptotic and autophagic cell death in the SN of PD brains, although the extent is limited, perhaps because of the slow process of cell death which underlies PD.[13-16] Alterations in cell death pathways are the primary cause for PD, but both apoptotic and autophagic cell death pathways are hypothesized to become activated in PD through oxidative stress, protein aggregation, excitotoxicity, or inflammatory processes. Activation of these cell death pathways most likely represents end-stage processes in PD neurodegeneration.

Therefore, inhibitors of these cell death pathways have been proposed as potential neuroprotective agents regardless of the initial cause for neurodegeneration in PD. Two different compounds that inhibit apoptotic signaling have been recently tested in human PD trials.[20-21]

**Autophagy**

Autophagy is a highly mechanism for degradation of unnecessary or dysfunctional cellular components.[22-23] Controlled activation of autophagy may provide a strategy for clearance of long-lived, aggregated, or dysfunctional proteins which contribute to neurodegeneration24. There is a complex relationships between autophagic and other pathways involved in protein stress and response suggest that *in vivo* modulation of autophagy as a therapy for neu-rodegeneration may require fine-tuning to broader genetic and environmental profiles.

**Oxidative stress and mitochondrial dysfunction**

Oxidative stress contribute to the aetiology of variety of disorder of the CNS particularly PD. Oxidative stress results from an overabundance of reactive free radicals or a failure of cell buffering mechanisms that normally limit their accumulation. Excess reactive species can react with cellular macromolecules and thereby disrupt their normal functions. Oxidative

damage to proteins, lipids, and nucleic acids has been found in the SN of patients with PD.[25-27] Both overproduction of reactive species and failure of cellular protective mechanisms appear to be operative in PD. Dopamine metabolism promotes oxidative stress through the production of quinones, Peroxides and other reactive oxygen species(-ROS).[28-29] Mitochondrial dysfunction is another source for the production of ROS, which can then further damage mitochondria. The mechanisms responsible for mitochondrial dysfunction in PD are not well understood, but inherited or acquired mutations in mitochondrial DNA may contribute.[30-32] Increased iron levels seen in the SN of PD patients also promote free radical damage, particularly in the presence of neuro-melanin. Antioxidant protein glutathione is reduced in post-mortem PD nigra. Several of the genes linked to familial forms of PD appear to be involved in protection against oxidative stress, including PTEN-induced putative kinase (PINK1) and DJ.[36-37]

Several different strategies have been proposed to limit oxidative stress in PD. These strategies include inhibitors of monoamine oxidase, a key enzyme involved in dopamine catabolism; enhancers of mitochondrial electron transport, such as Coenzyme Q10; compounds that can directly quench free radicals, such as vitamin E; and molecules that can promote endogenous mechanisms to buffer free radicals, such as selenium. The advantage of many of these agents is that they are well tolerated with few adverse effects, although convincing clinical evidence for the effectiveness of this approach is still lacking.

**Ubiquitin-proteasome System[11]**

This system is responsible for targeted degradation of misfolded, aggregated, or otherwise abnormal proteins. The first step in activating this pathway involves ubiquitin labelling of a protein to direct it to cylindrical proteasomes in the nucleus, endoplasmic reticulum, and other compartments,which recognize ubiquitin-labeled proteins and contain protease enzymes for protein degradation. In contrast to autophagy, which can also degrade proteins in addition to whole organelles, ubiquitin-mediated proteasomal degradation is thought to be highly selective.[38]

For almost all neurodegenerative diseases marked by accumulation and aggregation of specific abnormal proteins, ubiquitin-proteasome pathways represent natural candidates for modulating pathology. Ubiquitin-positive inclusions in neurons and glial cells are also frequently identified in AD, PD, HD, FTD, and other neurodegenerative disorders and may

be occurs due to variation in sequence genes including GRN (progranulin) and MAPT among others.[39]

**Cell adhesion**

Cell adhesion involves the binding of a cell to another cell or to an extracellular surface. In healthy brains, cell adhesion pathways are important for maintenance of synaptic contacts and blood-brain barrier integrity as well as efficient neurotransmission and intracellular signalling 40. Altered expression of cell adhesion genes is a consistent finding in AD and PD.[12]

**Endocytosis**

The process in which extracellular molecules are engulfed into membrane-bound vesicles. This internalization is important for gathering nutrients, facilitating molecular interactions and protein degradation in a protected environment, and recycling ligands and receptors. Several AD- and PD-associated genes have central roles in endocytic pathways. For example, LRRK2 similarly regulates the recycling and/or degradation of α-synuclein and is a key influence on the endocytic formation of synaptic vesicles containing neurotransmitters. Targeting of endocytic pathways may also be a viable approach to combat PD. The PD-associated-coated gene GAK (cyclin G associated kinase) is a key mediator of endocytic vesicle trafficking by regulating interactions with adaptor proteins and later driving disassembly of the vesicle clathrin coat.

**Neurotransmission**

Neurotransmitters are endogenous substances used to relay signals across a synapse. Initial hypotheses about AD and PD focused on disease-associated neurotransmitter deficits. The loss of dopaminergic neurons from the substantial nigra understood to be important for motor functioning led to the hypothesis that dysfunction of dopaminergic neurotransmission was a primary cause of PD. As a result, modulation of cholinergic or dopaminergic neu-rotransmission forms the basis of several symptomatic therapies for AD and PD.

Genetic and molecular studies support a role for neurotransmitter mechanisms in neurode-generative disease. Pathways related to calcium signaling, which are important for presynap-tic neurotransmitter release and postsynaptic signal transduction involving cyclic AMP (cAMP), protein kinase A (PKA), and cAMP response element binding protein (CREB), have displayed association to AD and PD. The gene COMT (catechol-O-methyltransferase)

encodes an enzyme that degrades dopamine and other catecholamine neurotransmitters, and COMT variants have been associated with dopamine levels in early PD and may contribute to cognitive and psychiatric deficits in AD through interactions with estrogen.

**Prions and transmissible factors**

Prion protein is a membrane-associated, protease-sensitive glycoprotein that is typically enriched in lipid rafts consisting of tightly packed signalling and trafficking molecules. As with other misfolded proteins, misfolded prion protein is normally susceptible to proteasome-mediated and other forms of protein degradation. However, accumulation of misfolded prion protein through inhibition of protein degradation pathways has been proposed to lead to the formation of protease-resistant, aggregated, infectious (i.e., transmissible) particles which can be released to neighboring cells and promote misfolded protein states in those cells. This mechanism is thought to underlie the development of fatal degenerative transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease (CJD), and it has been proposed as a unifying factor promoting neurodegeneration across multiple neurode-generative diseases including AD, PD, and ALS.[11]

**Systemic environment**

**Neuroinflammation**

The role of pathogenesis in the PD is unknown. Up-regulation of cytokines was found in the brain and CSF of brains. Neuroinflammation is a primary mechanism involved in PD pathogenesis. Activation of microglia has been demonstrated in SN and striatum from Post-mortem PD brains and in PD animal models. Pro-inflammatory cytokines, such As IL-1β, IL-6, and TNF-α, are elevated in the CSF and basal ganglia in PD patients. Also the complement proteins like Lewy bodies have been detected in PD. Both cytokines and α-syncline aggregation can promote microglia activation. In vitro, both aggregated and nitrated forms of α-syn can directly trigger a microglial response and release of cytotoxic factors. In mouse models, α-syn or modified forms of the protein can trigger both microglial and humoral responses, and inhibition of NF-KB signalling is neuroprotective.

**Lipid, metabolic, and endocrine factors**

Recent epidemiological and molecular studies are converging to support the hypothesis that loss of lipid homeostasis can prominently contribute to neurodegeneration. Findings that ath-erosclerosis and other cardiovascular diseases are impacted by APOE ε4 and can increase the risk of AD are complemented by studies suggesting that statin use to lower circulating

cholesterol may modestly reduce the risk of AD and PD. Importantly, neuronal membranes contain substantial amounts of cholesterol and other lipids, and disturbances in lipid pathways have been frequently proposed to impact synaptic signaling and neuronal plasticity and degeneration.

As the major lipoprotein of the brain, Apoprotein E transports key lipids and associated proteins to cells for uptake via receptor-mediated endocytosis. The degree of lipidation in ApoE is an important factor in maintaining lipid homeostasis and in mediating interactions with Aβ which can promote its endocytic clearance, and APOE allelic variants may affect both processes.

Recently, lipidomics analyses of the complete profile of lipids and their metabolites in tissue samples have provided initial unbiased views of lipid pathway disturbances in AD and PD. In PD, this approach identified changes in lipid metabolism in human primary visual cortex, a region that does not exhibit significant Lewy body pathology but may be important for visual symptoms in PD.

**Vascular changes**

Vascular pathology, including increases in vessel wall stiffness, changes in endothelial cell adhesion and metabolism, and dysfunction of the blood-brain barrier, can promote neurode-generation through yielding chronic, low perfusion.

Pathological changes to the blood-brain barrier have also been identified in PD through histological and molecular analyses and may explain the proposed modest protective effect of caffeine intake in these diseases.

**Neurodevelopment and biological aging**.

**Epigenetic changes**

Epigenetic factors provide mechanisms for genetic control that do not involve modifications to an individual's DNA sequence. These heritable changes, including RNA-associated silencing and methylation or acetylation of DNA or histones, can dynamically respond to environmental stimuli and also appear to increase in frequency with aging.

**Loss of trophic factors**

Neurotrophic factors (neurotrophins) are secreted growth factors that promote the development, functioning, and survival of neurons through regulation of gene transcription.

Neurotrophins typically affect transcription through binding receptors at neuron terminals to stimulate second messenger signalling cascades or to promote their internalization and direct transport along the axon to the nucleus. The loss of neurotrophic factors has been implicated as a potential contributor to cell death observed in PD. The neurotrophic factors brain-derived neurotrophic factor (BDNF), glialderived neurotrophic factor (GDNF), and nerve growth factor (NGF) have all been demonstrated to be reduced in the nigra in PD. As a result, treatment with growth factors has been proposed as a potential neuroprotective therapy in PD. Indeed, the patentability of these agents to stimulate growth and arborisation of dopaminergic neurons suggests that they may be useful neuroprotective treatments, even if deficiency of the factors is not the primary cause of the disease process. GDNF and a related growth factor, neurturin, are both protective against neurodegeneration in animal models. GDNF has been evaluated in human trials], and neurturin is currently being investigated in a phase II trial.

**Telomeres**

Telomeres are DNA sequences at the ends of chromosomes that provide protection against the loss of more proximal genetic material during DNA replication in mitosis. In germ-line and some somatic cells, the enzyme telomerase is responsible for maintaining telomere length and structure. However, most adult somatic cells do not express telomerase and as a result gradually lose telomere length and structure with each cycle of mitosis.

Although shortened telomere length in peripheral white blood cells has been associated with dementia and mortality in older adults, even after adjusting for APOE genotype. The relationship between telomere length in neurons and neurodegeneration is not yet clear.

**NEUROPROTECTION**

**Neuroprotection** *is* defined as the ability for a therapy to prevent neuronal cell death by intervening in and inhibiting the pathogenetic cascade that results in cell dysfunction and eventual death.

Up to date, no adequate clinical trial has provided definitive evidence for pharmacological neuroprotection. While many agents appear to be promising based on laboratory studies, selecting clinical endpoints for clinical trials that are not confounded by symptomatic effects of the study intervention has been difficult. As matters stand at present, neuroprotective trials of riluzole, coenzyme Q10 (Cow) and glial-derived neurotrophic factor (GDNF) do not support the use of any of these drugs for neuroprotection in routine practice. Although a

meta-analysis of seven observational studies suggests that dietary intake of vitamin E has a protective effect against PD, vitamin E did not have a neuroprotective effect in patients with PD. The sections below describe the neuroprotective use of drugs primarily known for their symptomatic effect.[47]

**Current Therapy of Parkinson's disease**

**Dopaminergic Agents**

Levodopa (precursor to dopamine)

**Dopamine agonists**

Apomorphine (Apokyn®)

Bromocriptine (Parlodel®)

Cabergoline (Not approved in the US)

Lisuride (Not approved in the US)

Pergolide (Permax® withdrawn from US market March 2007)

Pramipexole (Mirapex®)

Ropinirole (Requip®)

**COMT Inhibitors**

1. Entacapone (Comtan®)
2. Tolcapone (Tasmar®)

**MAO-B Inhibitors**

1. Rasagiline as Azilect®
2. Selegiline as Eldepryl® and Zelapar™

**Anticholinergics**

1. Trihexyphenidyl (Artane®)
2. Benztropine
3. Ethopropazine

**Amantadine** (Symmetrel®

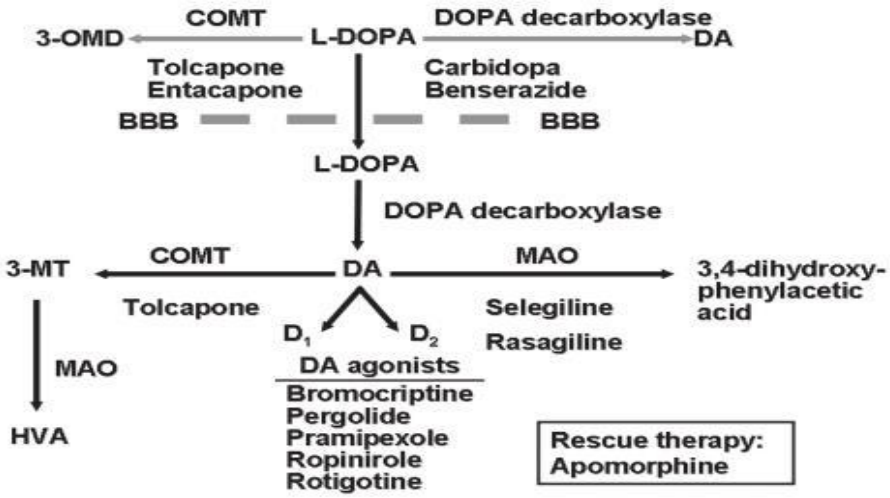


**Figure 5: Mechanism all drugs used in Parkinson's Disease.**

**Dopaminergic Agents**

**Levodopa**

Levodopa is converted in the brain into dopamine, the same chemical created by substantial nigra cells and used to control movement. Levodopa was introduced as a PD therapy in the 1960s, and remains the most effective therapy for motor symptoms. It lessens and helps to control all the major motor symptoms of PD, including bradykinesia, which is generally the most disabling feature of the disease. Carbidopa is included in the standard oral formulation to increase the effectiveness of a dose of levodopa and minimize side effects such as nausea and vomiting.

**Modes of action**: Levodopa is a type of amino acid. These building blocks are transported into the blood stream through the wall of the intestines. In similar fashion, Levodopa must be absorbed into the blood stream through the wall of the intestines. This requires the action of a specific "transporter" or amino acid vehicle in the intestinal lining. Because this transporter can only work so fast, an excessive amount of dietary protein can slow the transport of Levodopa into the blood stream.

**Adverse effects**

- ✓ Nausea and vomiting are the most common side effects, and are due to accumulation of dopamine in the bloodstream.
- ✓ Orthostatic hypotension (low blood pressure upon standing) also occurs.
- ✓ Drowsiness

- ✓ The long-term Levodopa use is dyskinesia. Dyskinesia is uncontrolled movements, including writhing, twitching, and shaking. It results from the combination of long-term Levodopa use and continued neurodegeneration. They begin to develop in milder forms after 3 to 5 years of treatment, but are more severe after 5 to 10 years of treatment.

**Dopamine Agonists**

Dopamine agonists are drugs that imitate or mimic the action of Levodopa in the brain by directly stimulating dopamine receptors, the same receptors that dopamine itself stimulates. While they are not quite as effective as Levodopa, they provide excellent relief of symptoms and delay the onset of motor complications. A variety of dopamine agonists are available that differ in their duration of action, chemical makeup, method of delivery, and adverse effect profile.

**Apomorphine**

Apomorphine (Apokyn®) is the dopamine agonist whose symptomatic effect is most like that of dopamine. However, it cannot be taken in pill form, and must be delivered by injection in subcutaneous region. It's a short duration effect than Levodopa. Subcutaneously injected apomorphine is used as a "rescue" therapy for patients with "off" episodes. Its onset of effect is approximately 10 minutes, and lasts approximately 90 minutes. It can be used up to 10 times per day. Nausea and vomiting are the principal adverse effects.

**COMT Inhibitors**

COMT inhibitors prolong the effectiveness of a dose of levodopa by preventing its breakdown. Two agents are approved in the United States, entacapone (Comtan®) and tolcapone (Tasmar®). Both have been shown to decrease the duration of "off" time (the period of time when PD symptoms are present) in patients with significant off time. Tolcapone is more effective than entacapone, reducing off time in clinical trials by 2-3 hours, versus 1 to 2 hours for entacapone. Both treatments usually allow reduction of levodopa dose, in the range of 20% to 25%.

A combination of levodopa, carbidopa, and entacapone in a single tablet (Stalevo®) is also available, with a similar side effect profile to the agents used alone.

**MAO-B Inhibitors**

It is selective and irreversible MAO-B inhibitor. Two isoenzyme forms of MAO, termed MAO-A and MAO-B are recognized both are present in the peripheral adrenergic structure and intestinal mucosa. While the letter predominates in the brain and blood platelets. MAO-B slows the breakdown of dopamine in the brain. There are two MAO-B inhibitors, in three formulations, approved for use in PD in the United States.

Side effects of MAO-B inhibitor therapy include insomnia, hallucinations, and orthostatic hypotension. Patients who are also taking certain types of antidepressants may not be eligible to take MAO-B inhibitors, since these drugs may interact to dangerously raise blood pressure (called the serotonin syndrome).

**Anticholinergics**

Anticholinergics have a limited role in PD. They are primarily effective against tremor and rigidity, and their side effects may be significant, especially in elderly patients. Common side effects are memory loss, dry mouth, urinary retention, constipation, sedation, delirium, and hallucinations.

**Amantadine**

Amantadine (Symmetrel®) has a mild symptomatic effect on the motor symptoms of PD, but a more significant effect on the reduction of dyskinesias. The usual dose is 100 mg 2 to 4 times each day. Side effects include hallucinations, difficulty falling asleep or staying asleep (insomnia), agitation, and difficulty concentrating; dry mouth, ankle swelling, and skin mottling (uneven colour tones) may also be present.[49]

**The future of Neuroprotection[12]**

In 2003, the NIH-appointed Committee to Identify Neuroprotective Agents in Parkinson's (CINAPS) published an assessment of potential neuroprotective compounds and prioritized 12 compounds to be studied further in clinical trials. Since then, the list of potential therapies has grown longer, but a convincing success in human trials is still awaited. Common factors among them are results of human genetic, pathological, and epidemiological studies. The wealth of information regarding PD pathogenesis from genetic studies is leading to novel approaches to neuroprotection based on the biology of α-syn, LRRK2, and Others. While much more research is needed before translating such theoretical therapies into clinical trials,

these approaches may lead to therapies that protect not only against dopaminergic cell loss but also against the loss of other neuronal populations at risk in PD and related disorders.[12]

**1. Adenosine receptor antagonists**

Epidemiological studies proved that caffeine reduces the incidence of PD, at least in men. As caffeine mediates its action by antagonizing adenosine receptors, this finding suggest the evaluating adenosine receptor antagonists as potential neuroprotective agents. In the striatum, the A2A receptor can heterodimerize with the D2 receptor to inhibit dopamine signaling, while inhibition of the A2A receptor can promote dopamine function. Two small clinical trials of the A2a Antagonist istradefylline (KW-6002) has demonstrated potential symptomatic effects in advanced PD. A2A antagonists not only improve symptomatic function in PD but may also be neuroprotective. Caffeine and istradefylline are both neuroprotective in the MPTP model, and caffeine (and related A2a antagonists) is a priority agent to be evaluated for neuroprotection in clinical trials.

**2. Anti-inflammatory agents**

Activation of microglia, increased cytokine production, and increased complement protein levels have been demonstrated in PD is occurring due to the neuroinflamation. As a means to slow disease progression, anti-inflammatory agents, including NSAIDs and minocycline, have been pursued as potential disease-modifying treatments for PD. Several studies in culture and in animal models have shown that certain NSAIDs, such as aspirin, have neuroprotective qualities. Epidemiological studies examining the association of Regular NSAID use with the risk of PD has provided conflicting results.

An example of an alternative approach to targeting neuroinflammation may be the use of statins (3-hydroxy-3-methylglutaryl-coenzyme, a reductase inhibitors). In addition to lowering cholesterol, these drugs have anti-inflammatory effects, including reduction of TNF-α, nitric oxide, and superoxide production by microglia. Statins may also act to scavenge free radicals. Simvastatin has been shown to reduce dopamine loss in MPTP animal models. Minocycline blocks microglial activation and may also have anti-apoptotic activity in culture. It protects against dopaminergic cell loss in both the MPTP and 6-OHDA animal models.

**Aantioxidants**

Epidemiological studies have pointed to uric acid as a potential neuroprotective agent in PD.

Uric acid acts as an antioxidant by scavenging reactive oxygen and nitrogen species. Studies have shown a decreased incidence of PD among subjects with high serum urate levels and among subjects with gout. In patients with early PD, higher plasma urate levels correlate with slower disease progression. Uric acid can reduce dopaminergic cell death in response to rotenone and homocysteine in culture. A recent study showed that subjects on diets that promote high urate levels have a reduced risk of developing PD. Such a urate-rich diet could serve as a neuroprotective therapy in PD. However, the potential benefits of a urate-rich diet have to be weighed against the risk of developing gout and cardiovascular disease. A large-scale clinical trial of the effectiveness of elevating urate in patients with PD is in the planning stages.

**Alpha-synuclein directed therapies**

Although its mechanism for inducing neurotoxicity is not well understood, α-synuclein appears to be an important mediator of toxicity in PD. Disruption of α-syncline aggregation has been the focus of research to develop novel therapies against PD. Alpha-syncline aggregation can be reduced at several levels: By reducing α-synuclein protein production; or increasing clearance; by preventing or reducing chemical modifications that can promote aggregated species.

Potential methods to reduce α-synuclein protein production include small-molecule modifiers of transcription and RNAi-based methods to knock down translation. Increased α-synuclein clearance could become enhanced by activation of proteosomal or lysosomal pathways. Augmentation of parkin or UCH-L1 activity, promotion of chaperon function, antioxidant therapies and kinase inhibitors could also promote α-syn clearance. The chaperone protein Hsp70 can reduce insoluble α-syn aggregates *in vitro* and *in vivo*, and the compound geldanamycin can reduce α-syn aggregation *in vitro* by increasing Hsp-70 levels. Activation of lysosomal degradation could also induce α-syn clearance; the lysosomal enzyme cathepsin D reduces α- syn aggregation and toxicity in culture and in animal models.

All of these strategies are at a relatively early stage of development and await further study before proceeding to human intervention trials.

**Kinase inhibitors**

The most common genetic cause of PD to date is mutation in the gene *LRRK2*, which causes about 2% of all cases of PD and up to 40% in historically isolated populations. The *LRRK2*

gene codes for a large protein, also known as dardarin, which contains a serine/threonine kinase domain and a GTPase domain. The native function of this protein is currently poorly understood. The most common pathogenic mutation of LRRK2 is associated with increased kinase activity. Evidence that pathogenic mutations increase this activity makes the kinase activity of LRRK2 an important target for neuroprotective therapy. Kinases are generally good targets for small molecule therapies, and indeed certain therapies in other diseases are based on inhibition of kinase activity. At this time, however, the Endogenous substrates for LRRK2 are unknown, making it difficult to devise the development of LRRK2 kinase inhibitors. As the function of LRRK2 is further characterized, a clearer therapeutic strategy based on LRRK2 biology should become more apparent.

**Trophic Factors**

Trophic factor approaches are one of the older strategies for neuroprotective therapy in PD. Strength of this Approach is that the biology of the factors themselves is well known, and it does not rely on a detailed understanding of the mechanisms of cell death in PD. Trophic factors may enhance Dopaminergic survival, regardless of the mechanism of cell death, they directly target the dopaminergic deficit. The studies of gene therapy delivery of neurturin are in an advanced stage, and if successful will not only provide an immediate treatment for many patients with PD, but may also open to the door to a wider range of gene therapy approaches.

## CONCLUSIONS

Neuroprotection in PD remains an important but elusive goal. A successful neuroprotective Treatment could transform PD from a relentlessly progressive and disabling disease to a problem that can be managed with only a modest effect on quality of life. Current barriers include a lack of knowledge of the basic mechanisms of PD, and deficiencies in the methodology used to study disease progression. Overall, however, the activity aimed at Understanding and treating PD has grown exponentially and should ultimately result in better Therapies for PD.

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