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Review Article

A Review on Parkinson's Disease: Its Pathophysiology, Treatment and Surgery

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ABSTRACT

Parkinsonism disease (PD) is a progressive neurological disorder. Degeneration of dopamine producing cells in the substantia nigra (part of the basal ganglia) leads to a decreased dopamine production. The cause of the damage is unknown. The main known risk factor is age. 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. This review briefly focuses on deep brain stimulation neurosurgical treatment. Levodopa was the first drug approved specifically for Parkinson's disease. Levodopa is converted by enzymes in the brain to produce dopamine, thereby supplementing function that has been lost as dopamine-producing neurons die. Topics covered in the review includes pathogenesis, mechanism of action, side effects of medicines and neurological surgery.

Keywords: Parkinson's Disease, neurological condition, Dopamine

INTRODUCTION

Parkinsonism disease (PD) is a clinical syndrome involving slowed mobility (bradykinesia), at least one of the following three features: tremor, rigidity and postural instability [1]. Parkinson's disease (PD) is thought to affect more than 1 million people in the United States alone, 1 of every 100 individuals above the age of 55. [2] The treatment of PD would be symptomatic (control or reduction of symptoms), neuroprotective (halting of disease progression) and neuroregenerative (reversal of disease process). A PD diagnosis is based on evidence of at least two out of three specific signs and symptoms: tremor, slowed mobility (bradykinesia) and stiffness (rigidity).

Parkinson's disease is disorder of motor and non- motor symptoms. Motor symptoms such as Bradykinesia (slowness of movement), Rigidity (stiffness of movement), Tremor (involuntary shaking of the hands, feet, arms, legs, jaw or tongue), Postural instability (tendency to fall, usually when pivoting) (Figure 1). Non-motor symptoms include changes in mood, memory, blood pressure, bowel and bladder function, sleep, fatigue, weight and sensation. Some symptoms have both features (motor and non-motor symptoms) [3].

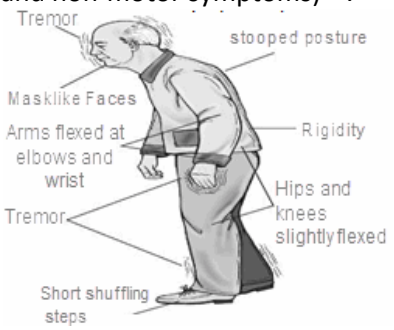

Figure 1: Parkinson's disease symptoms[4]

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Normal movement depends on the appropriate production of a chemical messenger or 'neurotransmitter' called dopamine by cells in the area of the brain called the substantia nigra (Figure 2). Parkinson's disease is a progressive neurological condition, resulting from the degeneration of dopamine producing neurones in the substantia nigra, which is located within the basal ganglia, deep in the lower region of the brain, on either side of the brain stem. Clinical signs of Parkinson's are evident when about 80% of the dopamine-producing neurons are lost. Dopamine is a major neurochemical messenger that promotes the functions of the basal ganglia, which is also where the dopamine is produced [5].

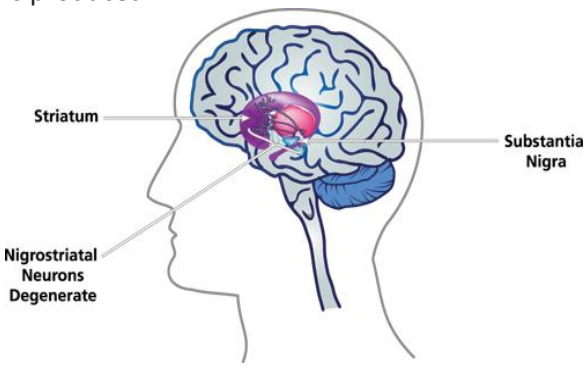

Figure 2: In Parkinson's disease, dopamine-producing cells in the brain degenerate[6]

ETIOLOGY OF PARKINSON'S DISEASE

Environmental Factors

The possible role of environmental factors has been addressed by a number of epidemiologic studies that have been well reviewed by others. Many of these studies have shown associations between rural residence, well-water drinking, herbicide exposure and the risk of developing PD[7]. A role for environmental factors in the cause of PD was given major impetus with the discover in 1983 that exposure to Mitochondrial complex I inhibitor (MPTP) is capable of inducing parkinsonism in humans [8].

Genetic factor

The younger the age of symptom onset, the more likely genetic factors play a dominant role. This concept was based largely on twin studies conducted in the early 1980s that demonstrated a very low rate of concordance for the disease among identical twins [9]. Familial cases are relatively rare (5-10%). The PD genes that have been identified and studied in some details α-synuclein, parkin, and ubiquitin C-terminal hydrolase L1 (UCHL1) appear to participate in the ubiquitin-proteasome pathway, a particularly compelling finding considering the Lewy Body (LB) protein aggregates that characterize PD neuropathology (Figure 3) [10].

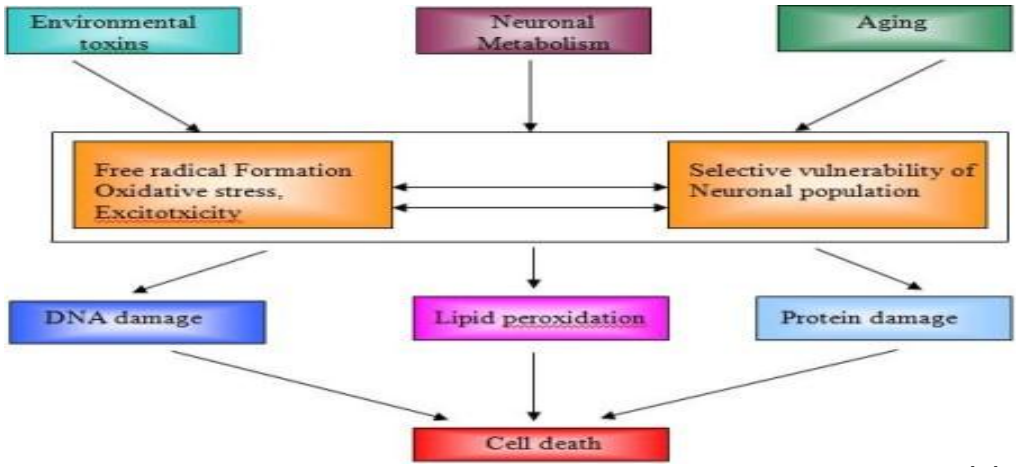

Figure 3: Mechanisms of Selective neuronal vulnerability in Parkinson's disease [11]

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PATHOGENESIS OF PARKINSON'S DISEASE

The primary deficit in PD is a loss of the neurons in the substantia nigra pars compacta that provide dopaminergic innervations to the striatum. Dopamine (DA) is synthesized within neuronal terminal from the precursor tyrosine by the sequential actions of the enzymes tyrosine hydroylase, producing the intermediary L-dihydroxyphenylalanine (DOPA) and aromatic L-amino acid decarboxylase. In the terminal, dopamine is transported into storage vesicles by a transporter protein associated with the vesicular membrane. The actions of dopamine are terminated by the sequential actions of the enzymes catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO) or by reuptake of dopamine into the terminal. A hallmark pathologic feature of PD, and essential for its pathologic diagnosis, is loss of DA neurons of the substantia nigra pars compacta (SNpc). The key feature of basal ganglia function, which accounts for the symptoms observed in PD as a result of loss of dopaminergic neurons, is the differential effect of dopamine on the direct and indirect pathways. The dopaminergic neurons of the substantia nigra pars compacta (SNpc) innervate all parts of the striatum; however, the target striatal neurons express distinct types of dopamine receptors. The striatal neurons giving rise to the direct pathway express primarily the excitatory D_1 dopamine receptor protein, while the striatal neurons forming the indirect pathway express primarily the inhibitory D_2 type (Figure 4).

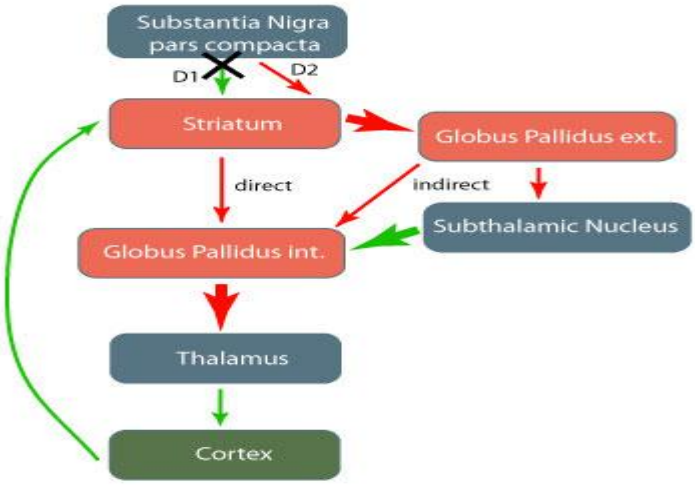

Figure 4: Pathophysiology of Parkinson's disease. Parkinson's is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta [12].

Thus, dopamine released in the stratium tends to increase the activity of the direct pathway and reduce the activity of indirect pathway, whereas the depletion that occurs in PD has the opposite effect. The net effect of the reduced dopaminergic input in PD is to increase markedly the inhibitory outflow from the inhibitory outflow from the SNpc. This degeneration leads to increased inhibition of the globus pallidus externa, which in turn causes increased inhibitory output of the globus pallidus interna. This is in part due to increased excitation by the subthalamic nucleus. The increased inhibition of the thalamus is central to PD's effects. Reduced input to the motor cortex leads to rigidity, bradykinesia and other symptoms. At the time of death, even mildly affected PD patients have lost about 60% of their DA neurons, and it is this loss, in addition to possible dysfunction of the remaining neurons, that accounts for the approximately 80% loss of DA in the corpus striatum. The

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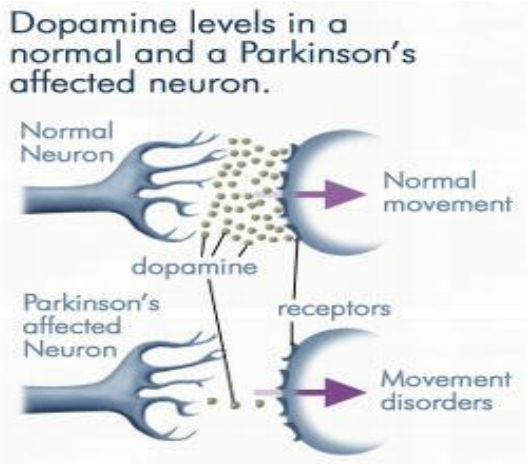
terminals of DA neurons degenerate, there is a reduction in high affinity DA uptake (Figure 5) [2, 13].

Figure 5: Parkinson's patients show a decrease in dopamine levels in the brain [14]



Parkinson's disease is still an incurable progressive disease, but treatment substantially improves quality of life and functional capacity[15]. In clinical practice, dopamine replacement with levodopa provides the most effective symptomatic treatment for PD [16]. Other medications used to treat PD include dopamine agonists, anticholinergics, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, and carbidopa/levodopa, the gold standard of symptomatic PD therapy (Figure 6, 7) [17, 18]. The central objective of using any of the below medications is to control or manage motor symptoms. A summary of the medications used to treat the primary motor symptoms of PD including typical forms, mechanism of action and side effects (Table 1) [13, 19, 20, 21, 22, 23].

Treatment

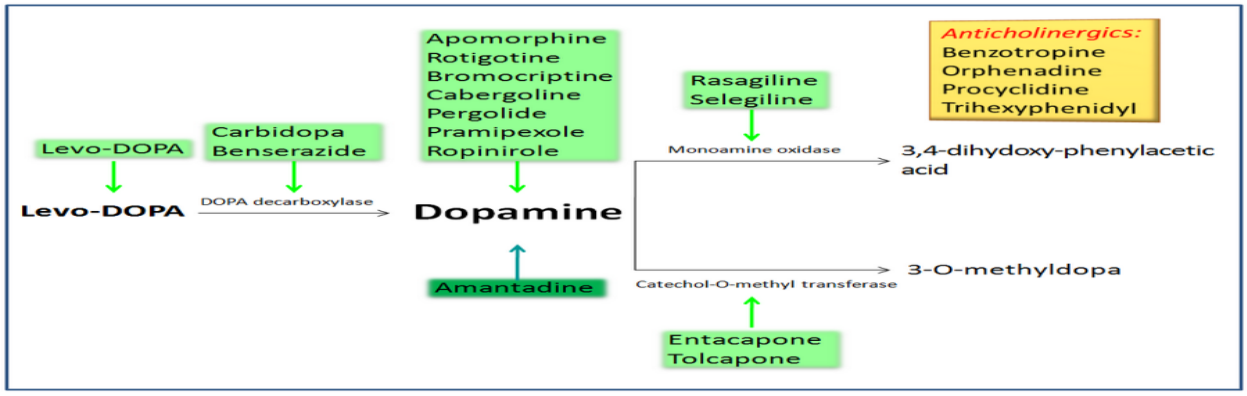


Figure 6: Treatment options for Parkinson's disease and the mechanism of action [24]

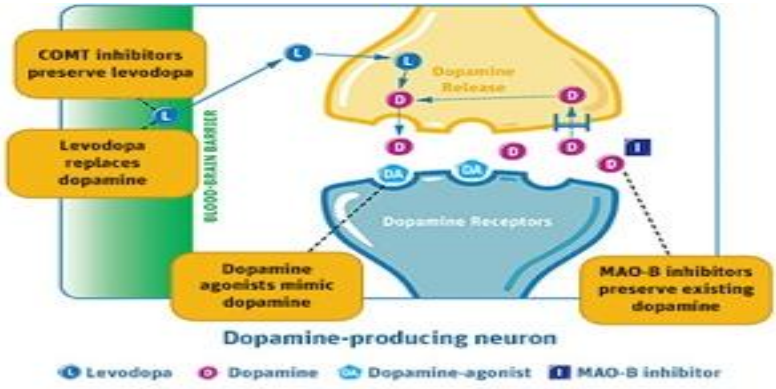


Figure 7: Medication work in Parkinson's disease[25]

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Table: 1 Summary of the medications used to treat the Parkinson's disease

Drug	Branded name	Forms available	Mechanism of action	Side effects
Levodopa				
Levodopa combined with Carbidopa	Sinemet	Tablets	Levodopa is converted to dopamine by decarboxylation, primarily within the presynaptic terminals of dopaminergic neurons in the striatum. Levodopa is most frequently combined with Carbidopa/ Benserzaide to slow enzyme (aromatic L-amino acid decarboxylase) breakdown of Levodopa before it reaches the brain.	Nausea Vomiting Loss of appetite Lightheadedness Lowered blood pressure Confusion
	Sinemet CR	Controlled release tablets		
	Caramet CR	Controlled release tablets		
	Lecado	Prolonged release tablets		
	Parcopa	Oral Disintegrating		
Levodopa combined with benserzaide	Madopar	Capsules, dispersible tablets		
	Madopar CR	Controlled release capsules		
Carbidopa combined with Levodopa and Entacapone	Stalevo	Tablets		
Dopamine Agonists				
Bromocriptine	Parlodal	Tablets, capsules	Bromocriptine is a strong agonist of the D_2 class of dopamine receptors and a partial antoganist of the D_1 receptors, while pergolide is an agonist of both classes. Ropinirole and pramipexole have selective activity at D_2 class sites (especially at the D_2 and D_3 receptor proteins) and little or no activity at D_1 class sites.	Daytime sleepiness, sudden unanticipated sleep ("sleep attacks"), hallucinations or confusion.
Pergolide	Permax	Tablets		
Ropinirole	Requip	Tablets		
	Adartrel	Tablets		
	Ralnea XL	Prolonged release tablets		
	Spiroco XL	Prolonged release tablets		
Pramipexole	Mirapex	Tablets		
	Mirapexin prolonged release	Prolonged release tablets		
MAO-B Inhibitors				
Selegiline	Eldepryl	Tablets, liquid	Selegiline and rasagiline inhibit the action of monoamine Oxidase isoenzyme type B (MAO-B). MAO-B prevents	Dry mouth, anxiety, sleeps disturbances, confusion, nausea, dizziness
	Zelapar	Tablets that dissolve on the tongue		

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Rasagiline	Azilect	Tablets	the breakdown of dopamine, leading to greater dopamine availability.	and Hallucinations.
COMT-Inhibitors				
Tolcapone	Tasmar	Tablets	Catechol O-methyltransferase (COMT) inhibitors allow a larger amount of Levodopa to reach the brain, thus raising dopamine levels there. They help provide a more stable, constant supply of Levodopa, which makes its beneficial effects last longer and manage off times better.	Nausea, orthostatic hypotension, confusion and hallucination. An important adverse effect associated with tolcapone is hepatotoxicity.
Entacapone	Comtan	Tablets		
Glutamate Antagonist				
Amantadine	Symmetrel	Capsules, syrup	Amantadine's mechanism of action is not clear. A blockade of N-methyl-D aspartate (NMDA) glutamate receptors and an anticholinergic effect are proposed, Whereas other evidence suggests it might alter dopamine release or re-uptake.	Dizziness, dry mouth, lithargy , insomnia, confusion and hallucinations
Anticholinergics				
Trihexyphenidyl	Artane	Tablets, Elixir	The actual mechanism of action is not clear. In Parkinson's disease causes a relative imbalance between the dopaminergic and cholinergic neurological pathways. It has long been believed that anticholinergics can correct this imbalance in less advanced forms of Parkinson's by reducing the	Sedation, Mental confusion, Constipation, Urinary retention and Blurred vision
Benztropine mesylate	Cogentin	Tablets		

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			degree of neurotransmission mediated by neostriatal acetylcholine.	

Surgery

Deep brain stimulation (DBS) should only be considered for patients with PD who have displayed a very clear and dramatic response to L-dopa. When motor fluctuations and dyskinesia cannot be managed by medications, surgical treatments for PD are often considered, DBS may provide an alternative. Patients with medication resistant tremor may also benefit from surgical therapy. The current surgery approved by the Food and Drug Administration (FDA) for the treatment of PD includes deep brain stimulation (DBS). In 1997, the FDA approved the use of the Active Tremor Control Therapy which uses a DBS electrode, extension wire and an implantable pulse generator (IPG) for thalamic stimulation to control parkinsonian and essential tremor. DBS is carried out as a staged procedure in which cerebral electrode implantation is performed under local or no anesthesia. The electrode can be placed in different parts of the brain. Thalamic stimulation in which the electrode tip is placed in the ventrointermediate (VIM) nucleus of the thalamus primarily to control tremor. The electrode tip can be placed in the Globus pallidus interna (GPi) to control the primary symptoms of PD (tremor, rigidity, slowness) and dyskinesia. In the stimulation of Subthalamic nucleus the electrode tip is placed in the STN to control the primary symptoms of PD (tremor, rigidity, and slowness) and dyskinesia. During postoperative management, stimulation is increased while L-dopa dosage is reduced. DBS treat the underlying symptoms of the disease, not the cure of PD. Adverse behavioral effects are mania, laughing episodes, impulsive behaviors, depression and anxiety have occurred during the first few months after surgery [26, 27].

CONCLUSION

The pathogenesis, medication and surgery of PD are presented in this review; briefly highlight the more important aspects of these topics. Although Parkinson's disease was first described almost two centuries ago, it is only recently that we have begun to understand the complex nature of the functional deficits that it entails or its neurobiological causes. In this review, briefly discussed about medications which currently available for symptomatic treatment and future developments in the treatment of PD. PD treatment plan consist of appropriate medications, regular exercise, a healthy diet, social engagement and cognitive activities, counseling and other therapies. Deep brain stimulation (DBS) surgery may be a reasonable therapeutic option for some individuals.

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