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Recent Advances on the Management of Parkinson's Disease: A Review

[1,2]Franklyn Nonso Iheagwam and [1]Sifon Ita Etefia

[1]Department of Biochemistry, Covenant University, PMB 1023, Ota, Ogun State, Nigeria
[2]Covenant University Public Health and Wellness Research Cluster, PMB 1023, Ota, Ogun State, Nigeria

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Corresponding Author:
Franklyn Nonso Iheagwam,
Department of Biochemistry,
Covenant University, PMB 1023,
Ota, Ogun State, Nigeria

ABSTRACT

Parkinson's Disease (PD) is a progressive neurodegenerative disease associated with loss of dopamine-producing cells and characterized by tremors, stiffness and bradykinesia. The cause of PD is unknown, however, both genetic and environmental factors play a role in the pathophysiology. In this review, Ghrelin mediated neuroprotection, the use of exenatide and bee venom as recent developments in the management of Parkinson's disease was discussed. The presence of Lewy bodies and α-synuclein in Lewy bodies has also been contraindicated in the progression of this disease. Parkinsonism is considered to arise primarily from abnormalities of basal ganglia function. Although Parkinson's disease cannot be treated, its progressive symptoms could be delayed by several methods which include the use of anticholinergic agents, amantadine levodopa, monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors and deep brain simulation. Despite numerous research on PD, more recent and less evasive mechanisms have been researched upon to understand the root cause of this disease. In this study, the possible cellular and molecular mechanisms fundamental to the action and possible role of ghrelin, exenatide and bee venom in slowing or preventing Parkinson's disease progression was considered.

Key words: Parkinsons disease, Lewy bodies, α-synuclein, levodopa, bee venom, exenatide

INTRODUCTION

Parkinson's Disease (PD) is a dynamic neurodegenerative malady found in 1917 by a British specialist, Dr. James Parkinson's. It is caused by the loss of dopamine-producing cells, characterized by tremors, stiffness and bradykinesia. Researchers theorize that PD is considered as a non-motor disorder on the grounds that as the disease advances, side effects, for example, depression, dementia and falls are perceived[1]. This disease affects 1% of the population over 60 years old, while it affects 2% of the population above 80 years of age with an increasing occurrence. In reported cases, there was large variability's of incidence rate because of difference in standard or criteria for diagnosis and case ascertainment. Although it varies, the occurrence was usually 1.5 times much more in males than females across different studies. Patients with Parkinson's disease have a lower life expectancy in comparison with the general population[1]. However, the rate of people with Parkinson's disease has declined in the past decades. When its symptoms and drugs were included in the diagnosis, the annual rate of decline was 1% but when only the diagnosis was considered, the rate of decline was 6%. Between 1990 and 2010, there was an assessment in the rate of incidence whereby there was a

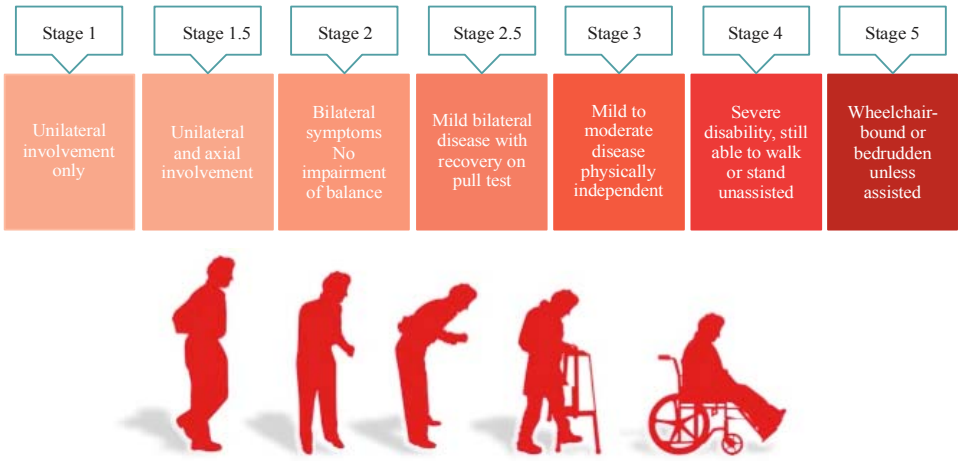

Fig. 1: The Hoehn and Yahr scale[5]

reduction down to 55% in 2000. By 2010, the incidence of PD was discovered to be 39% of what it was during the year 1990. Therefore, the rate of PD has been continuously reducing. Nevertheless, there has been a gradual increase in the rate of incidence but only in men[2]. In the world, there were more than 10 million people diagnosed with PD and there may be more, but due to inconsistent unfinished studies and an imprecise definition of Parkinson's disease, the actual number of people with this disease is yet to be known. There is a scale which helps to universally examine the progression of Parkinson's disease, compare the groups and sort patients into the stages known as the Hoehn and Yahr scale as shown in Fig. 1[3,4]. The aim of this review was to discuss Ghrelin mediated neuroprotection, the use of exenatide and bee venom as recent developments in the management of Parkinson's disease.

RISK FACTORS AND DIAGNOSIS

No known cause has been attributed to PD, factors such as family history, environmental factors, lifestyle (illegal drugs, medications, smoking), stroke, head trauma, brain inflammation and sports have been associated with the disease. The presence of specialized proteins (Lewy bodies) in the brain cells[6], genetics[7] and presence of a-synuclein proteins in the Lewy bodies[7] are other factors associated with the progression of PD. In diagnosing PD, physical examination has to be employed. It concentrates on the common characteristics of the disease which include tremors, bradykinesia and rigidity in limbs, postural instability which makes it difficult to walk or move. Also, the patient's medical history was usually looked into. Imaging tests like magnetic resonance imaging (MRI), positron emission tomography (PET) and dopamine transporter imaging (DAT) scans may be performed to rule out other diseases that have similar symptoms to PD[5]. Assessment of persistent kinetic tremor manifestation such as classic rest tremor, predominantly unilateral tremor, leg tremor, concomitant rigidity, which often affects the limbs were done intensely to favour the diagnosis of Parkinsonism[8].

SYMPTOMS OF PARKINSON'S DISEASE

PD is characterized by motor and non-motor symptoms. For motor symptoms, bradykinesia, rigidity and tremors are the three major characteristics. Others include postural deformities, postural instability and freezing[5]. Bradykinesia could be diagnosed in other illnesses or disorders, its nonetheless, the most distinct clinical feature of PD. It is characterized by slowness of movement which results in manifestations such as impaired swallowing leading to drooling, monotonic and hypophonic dysarthria, loss of impulsive movement, hypomimia (which is a loss of facial expression). Rigidity is a distinct feature of this symptom, leading to increased resistance which makes it hard to move body parts causing pains in the process. It may happen distally (ankles, wrist) or it may happen proximally (neck, hips, shoulder) and often misdiagnosed as rotator cuff injury or arthritis. Although not everyone gets tremors, this uncontrolled shaking usually begins in the hand and arms and then gradually moves to other parts of the body. It could also occur in the legs especially when the victim feels stressed or when resting the hand. It was without problems recognized as the most common symptom of PD. For the non-motor features of PD, autonomic dysfunction such as orthostatic

hypotension, sweating, erectile and sphincter dysfunction, cognitive and neurobehavioral abnormalities such as apathy, depression, hallucination and anxiety; sleep abnormalities such as insomnia, sleepiness during daytime, having violent dream content; sensory abnormalities such as paresthesia, olfactory dysfunction, akathisia, oral and genital pain; constipation, loss of smell and low blood pressure when you stand up are usually present.

THE ROLE OF LEWY BODIES AND α-SYNUCLEIN IN PARKINSON'S DISEASE

α-Synuclein is a neuronal and glial cell protein that aggregate into insoluble fibrils to produce Lewy bodies which is a pathological trait of PD. It is an eosinophilic inclusion identified in neurons, with a surrounding pale halo and an eosinophilic core as depicted in Fig. 2[9]. They often are circular or pleiomorphic. They can be detected in the brain displaying the most loss of neuron in PD and also other parts of the body like the spinal cord, peripheral autonomic ganglia, neocortex etc. Although Lewy bodies have been known for many years now, their formation or mechanism has been unknown. But from various experiments and studies, there have been many hypotheses on the formation of Lewy bodies which was mainly from protein handling dysfunction. Molecular composition of Lewy bodies has been interpreted using conventional histological and immunohistochemical methods by researchers as described in Fig. 3[10]. These molecules include ubiquitin, torsinA, α-synuclein and the α-synuclein-binding protein synphilin-1[11].

They are formed by disrupting the equilibrium between generation and breakdown of intracellular proteins. Over expression of normal or mutant proteins (e.g., synuclein), or other biochemical deformities that can cause protein harm and build up is associated with PD. In these proteins, phosphorylation, heat-shock proteins and ubiquitination mechanisms are unsuccessful, making them undegradable and aggregating with other normal and abnormal proteins. These aggregates impair the ubiquitin-proteasome system and hence further advance accumulation of protein. Under these conditions, ubiquitinated proteins are actively transported along microtubules to at least one centrosomes situated in the perinuclear area. The centrosomal structure extends to be an aggresome then enclosed by a system of filaments like neurofilaments, synuclein etc. Aggresome expands proteolysis such that abnormal proteins break down and compartmentalize to ensure the protection of intracellular

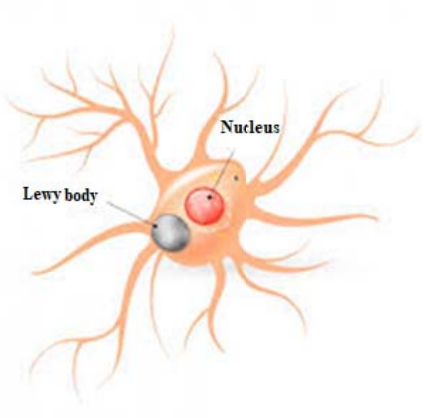

Fig. 2: Lewy body in a neuron[9]

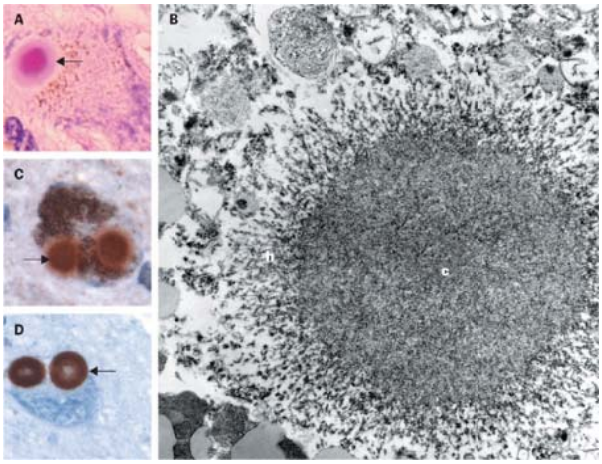

Fig. 3: (a) Conventional haematoxylin (blue) and eosin (pink) histological staining reveals a spherical Lewy body (arrow) in SNc dopamine neurons with a distinct central core and a peripheral halo, (b) Electron microscopic view of Lewy bodies reveals presence of outer halo composed of radiating filaments and granular material in the core. Immunohistochemical protocol shows (c) two Lewy bodies (arrow) with ubiquitin concentrated in the core (C) and (d) two Lewy bodies (arrow) with α synuclein concentrated in the halo[10]

organelles and molecules. If this process occurs, protein aggregates will be cleared and if not (due to lack of ubiquitin-proteasome system function or over-production of abnormal proteins), continuous aggresome growth and Lewy body formation are hypothesized (Fig. 4)[11]. The fate of Lewy bodies may fluctuate with some seen in surviving neurons and others discovered free in the extracellular space. These consistencies with their conservation after the destruction of the host neuron were observed[12].

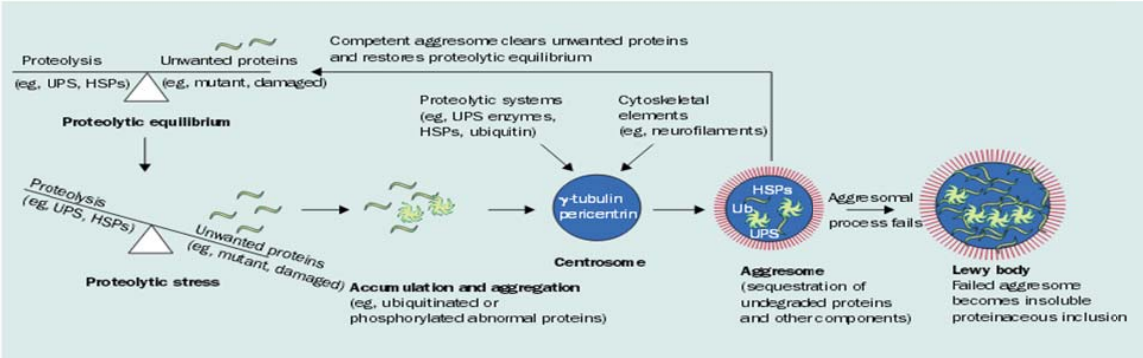

Fig. 4: Formation of Lewy bodies[11]

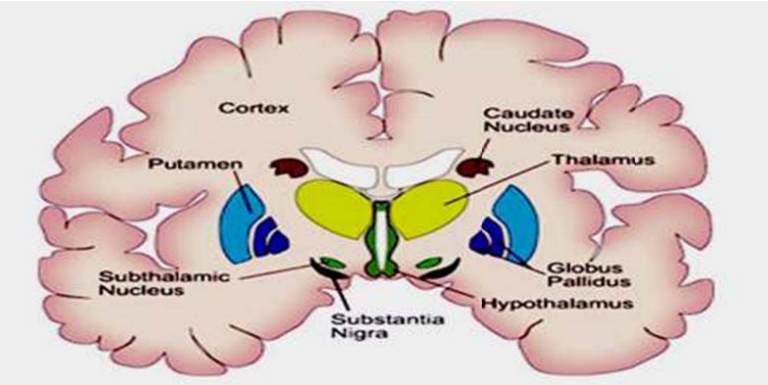

Fig. 5: Anatomy of basal ganglia[14]

In different situations, Lewy bodies may have been destroyed by the autophagic system as has been reported for aggresomes or engulfed with the host neuron by activated microglia, which were spotted at pathological points in PD.

THE BASAL GANGLIA

The basal ganglia is situated at the base of the forebrain (cerebrum) and has been considered as a therapeutic target for dysfunctions caused by sicknesses or injury. Different automatic developments, including chorea, ballism, athetosis, dystonia and trouble in the execution of deliberate or common movement in Parkinsonism have been portrayed clinically and their relationship with pathological changes in the basal ganglia were set up at the beginning of the 20th century[13].

The basal ganglia frame a complex system of parallel circles which coordinate cerebral regions (cooperative, oculomotor, limbic and motor). The thalamus, caudate nucleus, putamen, subthalamic nucleus, substantia nigra and globus pallidus located in the base of the forebrain make up the anatomy of the basal ganglia (Fig. 5). The motor circuit can be specifically identified with the pathophysiology of movement disorders. Cortical motor areas project in a somatotopic fashion to the postero-lateral putamen where they set up excitatory, glutamatergic synaptic connections with medium spiny neurons containing GABA. These neurons offer ascent to two pathways that interface the striatum to the output cores of the basal ganglia, to be specific the Globus pallidus pars internal (GPi) and the substantia nigra pars reticulata (SNr). Neurons in the 'direct pathway' project directly from the putamen to GPi/SNr. They bear dopamine D1 receptors, coexpress the peptides substance P and dynorphin and give a direct inhibitory impact on GPi/SNr neurons. Striatal neurons in the 'indirect pathway' associate the putamen with the GPi/SNr by means of synaptic associations in the globus pallidus pars externa (GPe) and subthalamic core (STN). They contain D2 receptors and the peptide enkephalin (ENK). Projections from putamen to GPe and from GPe to STN are GABAergic and inhibitory. Neurons beginning in the STN

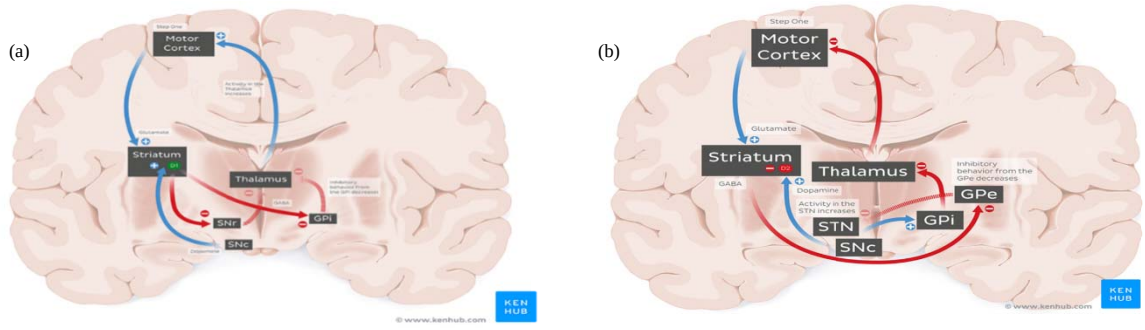

Fig. 6: (a) Direct and (b) Indirect pathway of the basal ganglia[17], GPe: Globus Pallidus externus, GPi: Globus Pallidus internus, SNc: Substantia Nigra pars compacta, SNr: Substantia Nigra pars reticulata and STN: Subthalamic nucleus

utilize glutamate as a neurotransmitter and enact neurons in the GPi/SNr. Incitement of neurons in the indirect pathway prompts restraint of the GPe, disinhibition of the STN and excitation of the GPi/SNr. In this way, the contradicting impacts of inhibitory inputs from the direct pathway and excitatory inputs from the indirect pathway affects the output movement of the basal ganglia. This gives an inhibitory impact on brainstem and thalamocortical neurons engaged with motor exercises. The occurrence of movement was related to delays in the neuronal movement of GPi/SNr neurons. The initiation of neurons from the direct and indirect pathways encourages and smothers motor action, separately. In this way, the direct and indirect pathways affect the capacity of the basal ganglia as presented in Fig. 6[15,16].

In the parkinsonian state, the fundamental pathophysiologic feature increases the neuronal movement in GPi/SNr output nuclei of the basal ganglia, which leads to too much inhibition of thalamocortical and brainstem motor frameworks. The model predicts that lessened activation of dopamine receptors, caused by lack of dopamine, results in diminished inhibition of neurons of the indirect pathway and diminished excitation of neurons of the direct pathway. Lessened inhibition from the indirect pathway prompts over-inhibition of the GPe, disinhibition of the STN and increased excitation of GPi/SNr neurons, while diminished activation from the direct pathway causes a decrease in its inhibitory impact on the GPi/SNr. Excessive activation of basal ganglia output neurons joined by unnecessary restraint of motor frameworks, prompting parkinsonian motor characteristics becomes the net outcome (Fig. 7)[18,19].

MANAGEMENT OF PARKINSON'S DISEASE

Symptomatic treatment: The conventional method in handling the treatment of patients with PD involves dispensation of drugs to ease its symptoms.

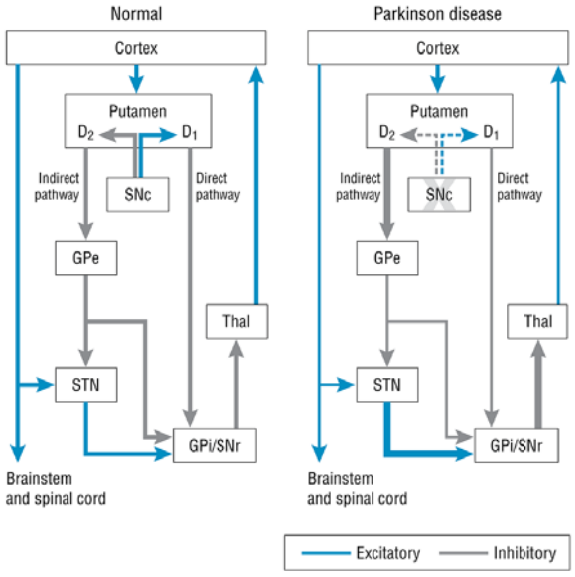

Fig. 7: Mechanism of basal ganglia[15,20], The thickness of the arrows indicates the strength of the connections. Loss of substantia nigra neurons leads to increased thalamic inhibition. D1 and D2 indicate postsynaptic dopamine receptor type, GPe: Globus pallidus externus, GPi: Globus pallidus internus, SNc: Substantia nigra pars compacta, SNr: Substantia nigra pars reticulata, STN: Subthalamic nucleus and Thal, thalamus

Anticholinergic agents: Anticholinergic drugs such as trihexyphenidyl and benztropine, faintly affect the clinical signs of Parkinson's disease by correcting balance between dopamine and acetylcholine winding up towards cholinergic predominance in the striatum of patients with PD[21]. They are used to control tremor, however, in cases of rigidity or bradykinesia, they are sparingly used. They elicit adverse effects on both the central and peripheral nervous

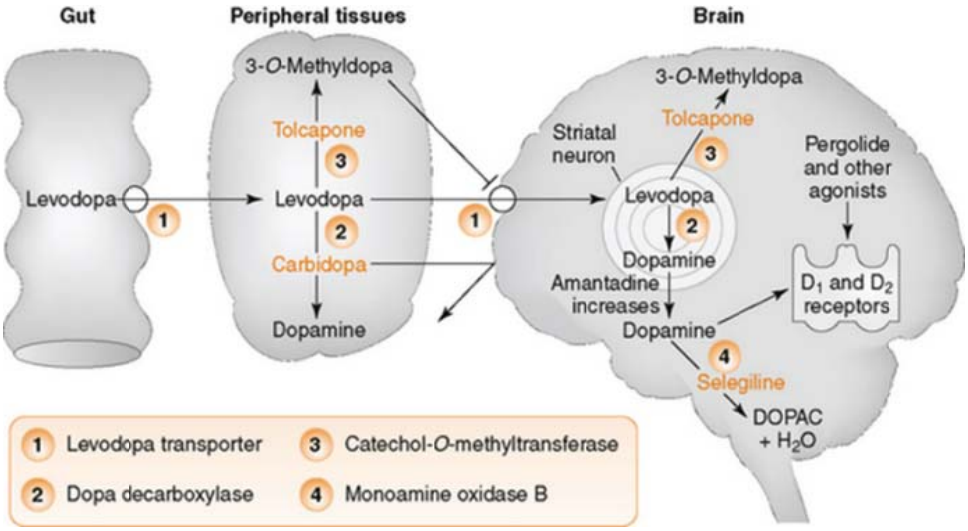

Fig. 8: Mechanism of levodopa[24]

system. These effects include impairment of memory and hallucinations, impaired ocular accommodation, dryness of the mouth, constipation, urinary retention and vasodilatation[21].

Amantadine: Amantadine looks like the anticholinergic drugs in numerous ways, however, it frequently leads to some change in rigidity. Despite its unestablished therapeutic mechanism, its adequacy was found by chance. Its side effects are like that of anticholinergic drugs due to structure similarity, yet also, livedo reticularis of the legs and ankle oedema are other side effects that occur[21].

Levodopa: Levodopa is a dopamine precursor which is the foundation of symptomatic treatment[22]. It is decarboxylated to dopamine and consequently acts on the dopamine receptors (Fig. 8)[23]. Unfortunately, the abnormal state of levodopa viability was defaced by obvious undesirable activities that turn out to be prominent with the disease. It has been contended that levodopa deleteriously affects neuronal survival in the substantia nigra, yet proof of this impact was restricted and uncertain. Levodopa is typically regulated with a peripheral decarboxylase inhibitor; carbidopa or benserazide, to lessen symptoms, for example, nausea due to the decarboxylation of levodopa to dopamine outside the blood-brain barrier. A few combinations of levodopa and a peripheral decarboxylase inhibitor were accessible[21,24]. Despite the insufficient evidence to support the toxicity of levodopa in humans, patients treated with levodopa showed a decrease in dopamine transporters after neuroimaging. This may suggest the possibility of some toxic effect as well as pharmacologic down-regulation of the transporters[25].

Monoamine oxidase inhibitors: They hinder the oxidative breakdown of dopamine by inhibiting monoamine oxidase. Selegiline hydrochloride (deprenyl; Eldepryl, Somerset) inhibits this enzyme[26]. It is utilized in this way to increase the impact of dopamine by impeding its breakdown and treat patients in whom administered levodopa is either losing its effects or prompting fluctuations[27]. Increased monoamine oxidase B activity, reduced glutathione levels and diminished activity of antioxidant enzymes are synonymous with the substantia nigra of patients with Parkinson's disease contains. This leads to the oxidative deamination of dopamine[28]. Type B monoamine oxidase inhibitors protect against oxidative damage and thereby slow the progression of the disease[29,30]. The limitation was the non-selective effect of these inhibitors[25].

Catechol-O-methyltransferase inhibitors: The inhibition of dopa decarboxylase (by the carbidopa component of Sinemet) prompts a compensatory action of different pathways for the metabolism of levodopa, particularly catechol-O-methyltransferase (COMT) which prompts expanded circulating levels of 3-O-methyldopa[31]. The 3-O-methyldopa competes with levodopa for an active carrier mechanism associated with its transport over the intestinal mucosa and the blood-brain barrier (Fig. 8). Particular COMT inhibitors may in this manner enhance the advantages of levodopa therapy

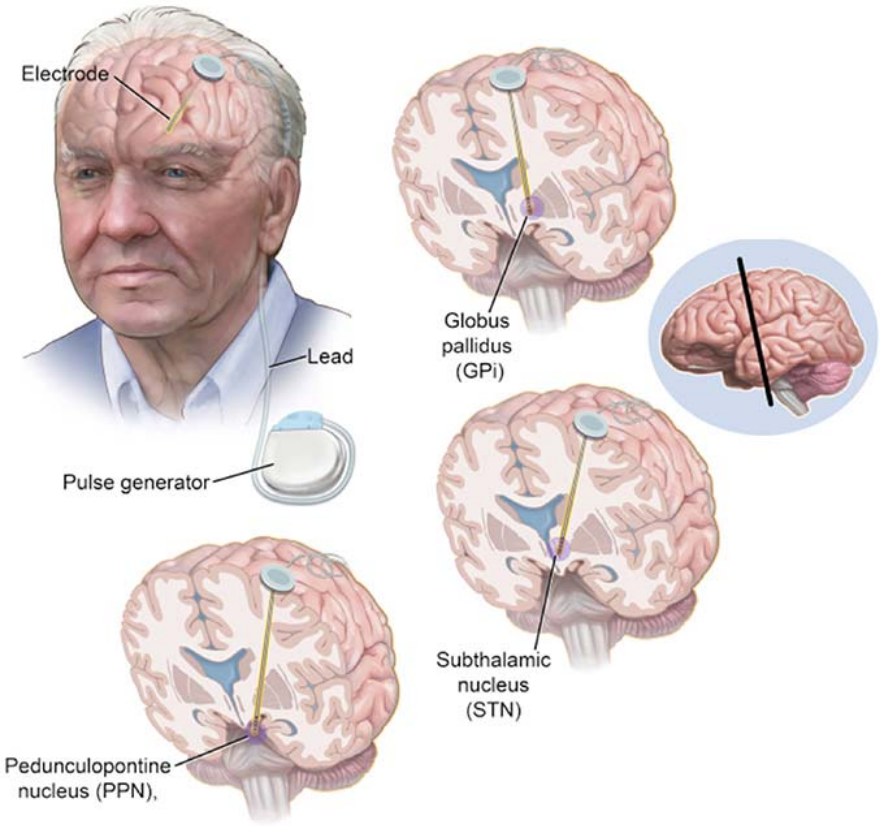

Fig. 9: Locations where electrodes can be implanted for deep brain stimulation[32]

by reducing the conversion of levodopa to 3-O-methyldopa and expanding the accessibility of levodopa in the mind itself. Clinical investigations are as of now in advancement to assess their therapeutic functions[27].

Deep brain stimulation: Thalamotomy and thalamic stimulation involve the use of electrodes connected to an impulse generator implanted into the chest. The generator sends impulses through wires to the electrodes which are implanted into the substansia nigra (Fig. 9). During the surgery, the patient would be awake and asked to perform certain tasks like wiggling their toes or clapping their hands to know exactly which point the electrode was to be placed[17,32]. In cases of advanced PD, when medications were no longer controlling motor symptoms adequately, deep brain stimulation (DBS) was used as a powerful therapeutic alternative[33]. The major side effect associated with DBS is as a result of unintended stimulation of structures adjacent to the intended target. However, the complication was reduced when used bilaterally[34].

RECENT ADVANCEMENTS IN PD TREATMENT

Ghrelin mediated neuroprotection: Calorie Restriction (CR) without malnutrition has been connected to lessening the occurrence of a few neurodegenerative diseases. While the mechanisms underlying this impact are not clear, there might be mediation by the gastrointestinal hormone, ghrelin which is secreted from the stomach during CR to alarm the brain on changes in metabolic status and to advance re-feeding. Ghrelin is a 28 amino-acid hormone that is elevated during CR, a unique reaction as other gastrointestinal hormones are increased by feeding to induce satiety. Initiation of the ghrelin gene prompts the transcription and translation of the preproghrelin peptide that was consequently cleaved into two known products-unacylated ghrelin (UAG) and obestatin. UAG can experience post-translational acylation by ghrelin O-acyltransferase (GOAT) to form acyl-ghrelin (AG). Acyl-ghrelin upregulates the calcium/calmodulin-dependent protein kinase-B (CAMK), which enacts AMP-activated protein kinase (AMPK), acyl-ghrelin regulates AMPK capacity to advance neuronal survival[33]. Also, CR increases circulating

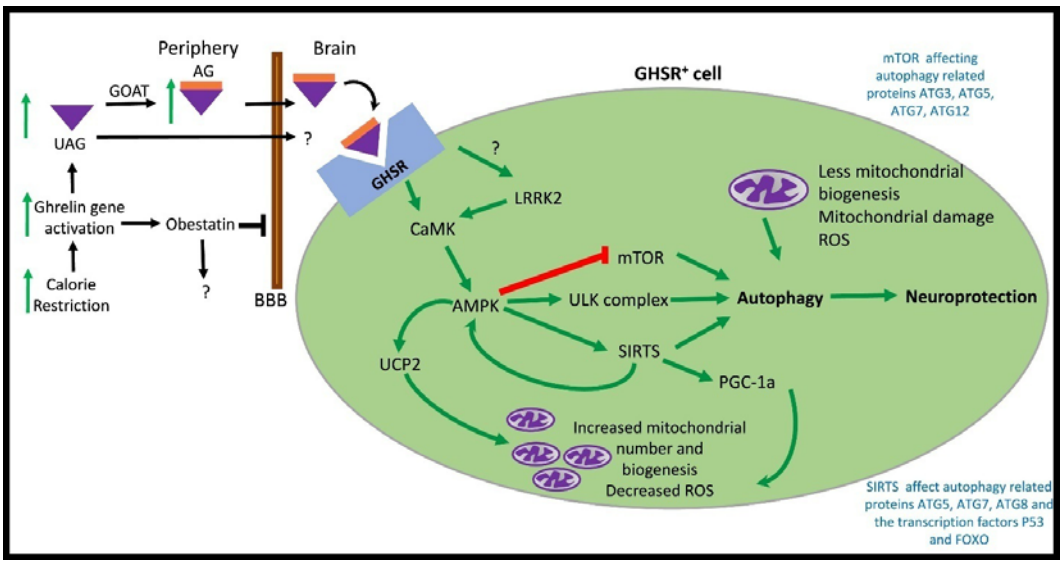

Fig. 10: Mechanism of ghrelin[35], Autophagy-related (ATG), Leucine-rich repeat kinase 2 (LRRK2), Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)

acyl-ghrelin which crosses the blood-brain barrier (BBB) and binds growth hormone secretagogue receptor (GHSR) leading to activation of Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and AMPK-mediated autophagy by up-regulating sirtuins (SIRTS) or the formation of the Unc-51 like autophagy activating kinase (ULK) complex. In addition, AMPK may inhibit mechanistic target of rapamycin (mTOR) to induce autophagy, whilst promoting uncoupling protein 2 (UCP2) dependent changes in mitochondrial biogenesis results in adaptations to mitochondria and autophagic flux, leading to neuroprotection[35], hence corroborating the putative mechanism portrayed in Fig. 10.

Bee venom: It contains numerous active substances (e.g., peptides, catalysts and biogenic amines) with various pharmacological activities. In spite of the fact that BV can cause neurotoxic and nociceptive impacts, it likewise has anti-nociceptive, radioprotective and anti-mutagenic effects. In this way, it has been utilized as conventional therapy for a few sicknesses, for example, rheumatoid joint inflammation, asthma, growth and skin illnesses. It tends to be applied as a cream, ointment, liniment, injection, needle therapy, or specifically through a living bee. Mellitin, a 26 aminoacid peptide, is the essential part of BV (40 to 60%). At low doses, it can increase capillary permeability, exert anti-inflammatory effects and lower blood pressure. It has been demonstrated to hinder apoptosis in SH-SY5Y cells and moderate the inflammatory reaction of microglial cells. Another part of BV is apamin (2% of BV content), an 18 aminoacid peptide, that was generally perceived as an irreversible blocker of Ca^{2+} initiated K^+ channels. These channels were in charge of neuronal hyperpolarization and for the most part, found in AMPA and NMDA glutamatergic neurotransmitters. In this way, obstructing these channels can decrease hyperpolarizing impacts, improve synaptic plasticity and memory capacities. In addition, BV contains phospholipase A2 (PLA2), a compound that catalyzes the hydrolysis of layer phospholipids, plays an essential job in signal transduction and regulates inflammatory responses[36]. Attenuation of neuroinflammation and microglial activation, inhibition of apoptosis in dopaminergic neurons, protection against glutamate-induced neurotoxicity and restoration of normal brain neurochemistry were the major proposed mechanisms of bee venom therapy on PD as illustrated in Fig. 11[36].

Exenatide: Exenatide is a glucagon-likepeptide 1 (GLP-1) mimetic, based on the peptide exendin-4. Unlike GLP-1, when administered peripherally it can cross the blood-brain barrier in humans influencing cellular processes[37]. This was as a result of the inability of dipeptidylpeptidase-4 (DPP-IV) which degrades GLP-1 to degrade it. This compound has demonstrated neuroprotective- and neurotrophic- effects in different models of neurodegenerative diseases[38,39]. Various studies has reported GLP-1 receptor stimulation preserved mitochondrial function in dopaminergic neurons by increasing expression of complex I and anti-apoptotic proteins

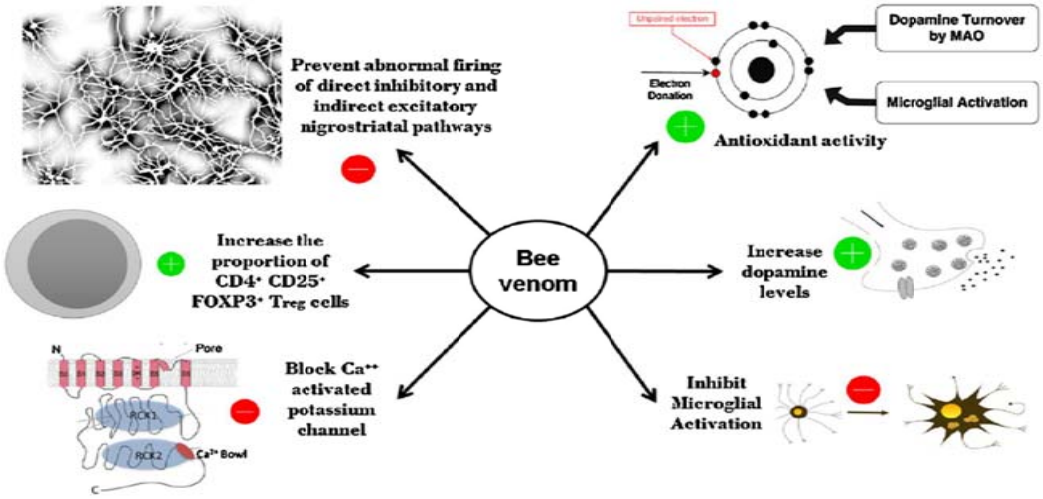

Fig. 11: Proposed mechanisms of bee venom therapy[36]

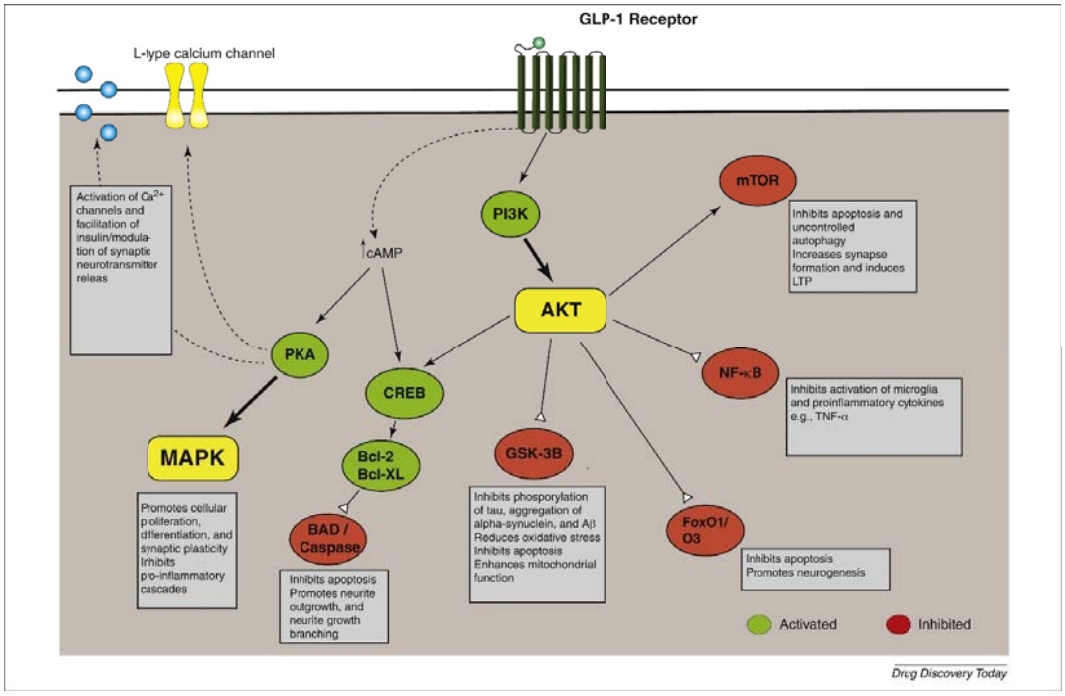

Fig. 12: Influence of neuronglucagon-like peptide 1 receptor (GLP-1R) activation on pathways in Parkinson's Disease (PD) pathogenesis[39], Bcl-2: B cell lymphoma 2, BAD (Bcl-2) antagonist of death, Bcl-XL: B cell lymphoma 2 extra-large, cAMP: cyclic AMP, CREB: cAMP response element-binding protein, FoxO1/O3: Forkhead box O1/O3, GSK-3B: Glycogen synthase 3 beta, LTP: Long-term potentiation, mTOR: mammalian target of rapamycin, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, TNF: Tumour necrosis factor

Bcl-2 while reducing caspase-3 activation, leading to attenuation of cell death (Fig. 12)[40,41].

Exenatide provides complete protection against dopaminergic cell loss by suppressing activation of microglia and attenuating the expression of pro-inflammatory molecules leading to improved performed on motor assessments[42]. Reported mechanisms of exenatide such as cellular proliferation, differentiation, inflammatory pathways,

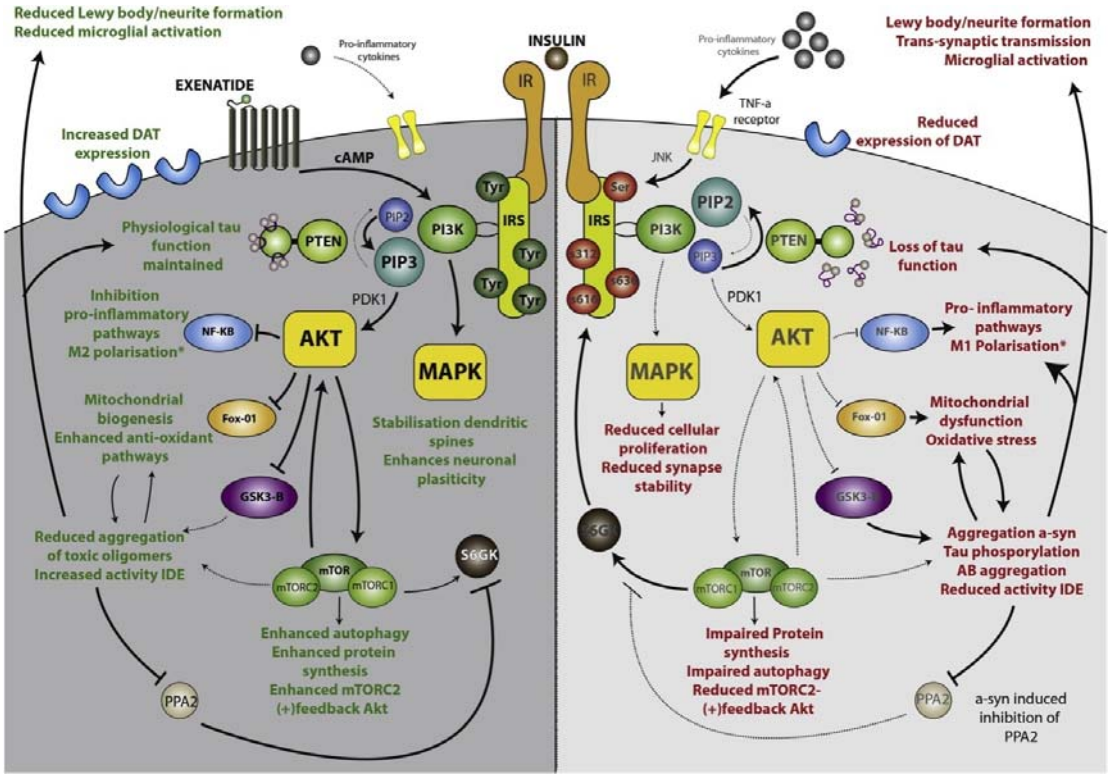

Fig. 13: Exenatide activation of glucagon-like peptide 1 receptor (GLP-1R) in neurons[42]

mitochondrial function and dopaminergic survival were associated with restoration and reversal of motor deficits in various animal models of PD (Fig. 13). These proposed mechanisms may have therapeutic benefits in the treatment and management of PD patients[42].

CONCLUSION

It was concluded that the cause of PD is usually due to loss of certain neuron in the brain and scientists are yet to find its treatment, but there have been several new methods developed that can delay the progression of the disease and help relieve patients from most of its symptoms. Nonetheless, more recent mechanisms should be further researched upon to understand the root cause of this disease thereby, improving potential drug design and delivery.

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