ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR
El Sayed et al., 2018, 2 (3), 142-161

Journal of Advanced Pharmacy Research

Parkinson's Disease: A Review about Pathogenesis, Treatment and Experimental Models

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Submitted on: 04-03-2018; Revised on: 03-06-2018; Accepted on: 12-06-2018

ABSTRACT

Parkinson disease (PD) is the second most common age-related neurodegenerative disease after Alzheimer disease, characterized by loss of dopaminergic neurons in substantia nigra pars compacta, accompanied by motor and non-motor symptoms. Idiopathic PD is the most common cause of Parkinsonism (primary Parkinsonism) while, certain medication and different groups of neurological disorder may be causes of secondary Parkinsonism. The presence of intraneuronal proteinaceous cytoplasmic inclusions "Lewy Bodies" and the loss of the nigrostriatal dopaminergic neurons are the main neuropathological hallmarks of PD. However, the etiology of the disease is still undefined; several studies assume that oxidative stress, mitochondrial defects, neuroinflammation, apoptosis and excitotoxicity play vital roles in the pathogenesis and progress of the disease. Experimental models of PD can be induced by several neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, 6-hydroxydopamine, rotenone and paraquat which produce neuropathological and neurochemical changes that are identical to those seen in PD. The primary drug for PD treatment is L-dopa; however, drug-induced dyskinesia and motor complications restricted its use as long term treatment. Dopamine agonists are alternative options for initial treatment of PD and have been reported to retard the onset of motor complications. Combination of L-dopa with other medications, such as catechol-*O*-methyltransferase inhibitors and monoamine oxidase B inhibitors has the ability to alleviate L-dopa-induced motor complications. Anticholinergic drugs can be used to control the symptoms of PD but their cognitive and autonomic side effects make them unsuitable for the elderly.

Keywords: *Experimental models; L-dopa; Neuroinflammation; Oxidative stress; Parkinson's disease*

INTRODUCTION

Parkinson's disease (PD) is considered as a chronically progressive age-related neurodegenerative disease which affects 1% of the worldwide population over the age of 60 wherein, the percentage increases to 5 % in individuals after the age of 85 years.[1,2] PD is considered as a multisystem neurodegenerative disease in which there is a gradual loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), which is one of the basal ganglia nuclei, with resulting striatal dopamine (DA) deafferentation, leads to distinctive motor dysfunctions including, bradykinesia, resting tremor and muscular rigidity.[3,4] These symptoms of motor disturbances are usually considered as clinical diagnostic criteria for PD.[5,6]

For about 150 years, knowledge about pathogenesis of PD was little since the first clinical description of the disease in 1817 by James Parkinson.[7] In 1960; the landmark observation was that DA levels in the striatum were obviously decreased in PD patients that extremely support to understand pathophysiology of PD.[8] DA precursor (L-dopa) was found to be qualified in alleviating the symptoms of PD and till

now, the main PD management is the chronic oral administration of L-dopa.[9,10] With the discovery of a toxin-induced PD in humans in the early1980, the second advance in PD research came. An illicitly manufactured opiate contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) whose users rapidly produced progressive, L-dopa-responsive parkinsonism like to what reported in sporadic PD.[11] Parkinsonism induced by MPTP in human was resemble to pathological and clinical features of sporadic PD, which characterized by severe loss of midbrain dopaminergic neurons and consequently reduction of DA levels in the striatum.[11,12]

1. Classification of Parkinsonism

1.1. Idiopathic PD (Primary Parkinsonism)

Idiopathic PD usually presents in patients over age 60, and age is considered the most common risk factor for developing idiopathic PD; however, approximately 5% of patients begin before age 40 years. Genetic mutations are likely to be the cause of idiopathic PD for these young-onset patients.[13] The widely recognized cardinal motor features of idiopathic PD include rigidity, asymmetric resting tremor, postural instability and bradykinesia.[5] Of the essential motor features; asymmetric tremors are most often reported by patients as the first symptom. In fact, lack of asymmetry suggests a differential diagnosis.[14, 15]

1.2. Secondary Parkinsonism

1.2.1. Drug-induced Parkinsonism (DIP)

DIP is the second most widespread etiology of Parkinsonism after idiopathic PD in the elderly. Because of the clinical features of DIP and PD are indistinguishable, many cases with DIP may be misdiagnosed with PD.[16] Typical antipsychotics (neuroleptics) including, haloperidol, chlorpromazine and fluphenazine are the most common DIP due to blockage of DA receptors in the striatal region leading to alterations in the basal ganglia motor circuit.[17] Parkinsonism most often appears days to weeks after treatment with antipsychotics, however in some cases the onset may be take several months.[16] Aging is the most evident risk factor for DIP, supposedly explained by low number of striatal DA receptor. However, some studies reported the occurrence of DIP in younger patients.[18] The female gender, cognitive dysfunction and possibly a genetic predisposition are considered as individual risk factors for DIP.[19] Other drugs such as dopamine depleting drugs (reserpine), anti-emetic (metoclopramide), calcium channel blockers (flunarizine, cinnarizine, diltiazem and verapamil), amiodarone, lithium and alpha-methyldopa are considered as DIP.[16,20]

1.2.2. Vascular Parkinsonism

Ischemic cerebrovascular disease is the main cause of vascular Parkinsonism; therefore, it is categorized as secondary Parkinsonism, and it is known as arteriosclerotic Parkinsonism.[21] Vascular Parkinsonism is typically bilaterally symmetrical Parkinsonism, affecting the lower limbs greater than the upper limbs and termed as lower-body Parkinsonism, with the lack of resting tremors. There are usually additional features, such as early dementia, speech disturbance and pseudobulbar palsy.[21, 22]

1.2.3. Other causes for secondary Parkinsonism

Hypoxia, hydrocephalus, trauma and infection such as encephalitis may also produce secondary parkinsonism.[1]

1.3. Parkinsonism plus syndrome

Parkinsonism plus syndrome is a group of heterogeneous degenerative neurological disorders, which differ from the classical idiopathic PD in certain associated clinical features and poor response to L-dopa. Progressive supranuclear palsy, dementia with lewy body disease and Shy-Drager syndrome are commoner disorders.[23]

2. Pathological features of Parkinson's disease

Degeneration of the dopaminergic neurons in the SNc as well as the presence proteinaceous cytoplasmic inclusions, named “Lewy Bodies” (LBs) inside neurons are the fundamental pathological markers of PD (**Figure 1a**).[15, 24]

2.1. Degeneration of nigrostriatal dopaminergic neurons

The nigrostriatal dopaminergic neurons extend from the SNc to the putamen nucleus in the striatum. Progressive degeneration of these neurons, which contain dark pigments termed neuromelanin, [1,25] leads to depigmentation of SNc which is considered as pathological features of PD (**Figure 1b**). At the onset of symptoms, nearly 60 % of SNc dopaminergic neurons are lost and DA level in the putamen nucleus is depleted by approximately 80 %.[26] Dopaminergic neurons of the mesolimbic pathway which arise from the ventral tegmental area (VTA) to the caudate nucleus, are much less damaged, therefore, there is less reduction of DA in the caudate.[1]

Normally, there is a balance between the level of DA and acetylcholine, this balance is very critical to control the motor activity.[27] DA suppresses the release of acetylcholine in the striatum region.[28] In patients with PD; the loss of DA augments acetylcholine release which contributes to motor symptoms.[29]

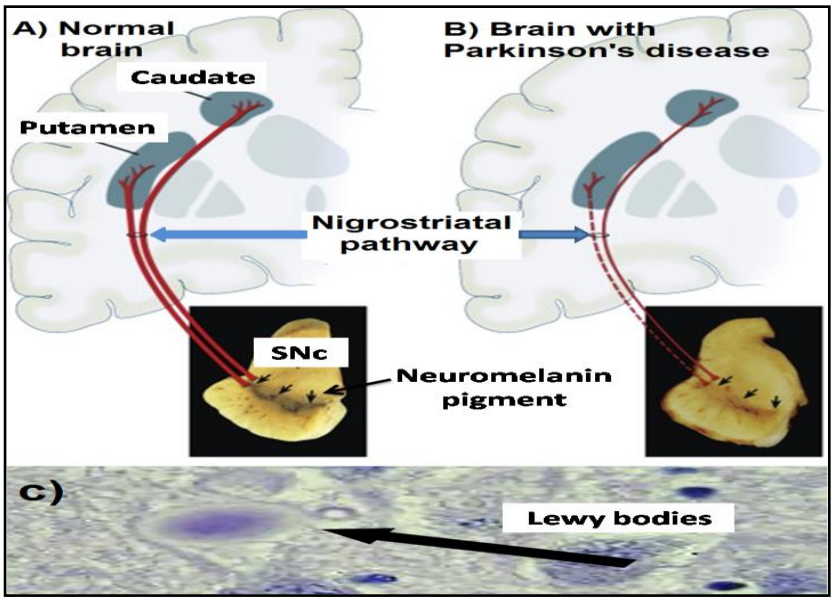

Figure 1. Pathology of PD (A) Diagram of the nigrostriatal pathway in normal condition (thick solid red lines). (B) Diagram of the nigrostriatal pathway in PD (thin dotted red line). (C) Immunohistochemical staining of lewy bodies in the SNc neurons.[1]

2.2. Intraneuronal proteinaceous cytoplasmic inclusions "LBs"

LBs are cytoplasmic protein inclusions composed of many proteins such as α-synuclein, ubiquitin and parkin (**Figure 1c**); the major component of the proteinaceous filaments of LBs is α-synuclein.[30, 31] The presence of LBs is not limited to PD; they are also reported in Alzheimer's disease, in dementia and as a pathologic finding in elderly at a higher rate than the prevalence of PD.[30]

3. Pathogenesis of Parkinson's disease

Several studies suggest two main theories concerning the pathogenesis of PD. One theory proposes that misfolding and protein inclusions are fundamental in the demise of SNc neurons, while the other posits that mitochondrial dysfunction and the consequent oxidative stress, including toxic oxidized DA species is the major culprit.[1, 32] In addition to that, other hypotheses such as neur-oinflammation,[33] apoptosis,[34] and excitotoxicity [35] are implicated in the pathogenesis of PD.

The pathogenic factors reported above are now not mutually exclusive, and the main aim of researches is to clarify the sequence in which these factors act as well as which one of these factors are essential keys to the death of SNc neurons. **Figure 2** illustrates likely points of interaction which shows that oxidative damage to α-synuclein encourages its ability to misfold.[36] Moreover; misfolded proteins accumulation can stimulate cellular stress responses that protect neurons against the toxic misfolded proteins.[37]

3.1. Misfolding and aggregation of proteins

Many age-related neurodegenerative diseases, such as PD are characterized by abnormal accumulation of aggregated protein in the central nervous system.[38,39]. Despite the fact that the location (i.e., intracellular or extracellular) and composition of protein aggregate varying among diseases, this common feature proposes that the deposition of protein in itself, or some associated event, is harmful to dopaminergic neurons.[32]

There are many different mechanisms by which protein inclusions produce a neurotoxic effect. One of these mechanisms may be through a direct damage effect, possibly by distorting the neuron or disruption of intracellular trafficking.[40] Protein aggregates may also hide proteins that are essential for cell survival.[41] Therefore, there is a direct correlation between and neurodegeneration and protein inclusion.[38] It was found that mutation in SCNA gene which encodes α-synuclein is correlated with increased risk of sporadic PD, in addition to some familial cases are linked with the *SCNA* gene mutation.[42]

3.2. Mitochondrial dysfunction and oxidative stress

Inhibition of complex I activity in the mitochondrial electron transport chain by MPTP, was the first evidence support the role of oxidative stress in the pathogenesis of PD.[43] Subsequent researches recognized complex I defects in PD, suggested that abnormalities in complex I activity leads to oxidative stress and consequently energy failure.[44,45] Complex I activity was found to be inhibited in

mitochondria isolated from SNc and frontal cortex as well as platelets of PD patients.[45]

The mitochondrial respiration inside cells consumes nearly 100% of molecular oxygen and consequently produces powerful oxidants byproducts such as hydrogen peroxide (H_2O_2) and superoxide anion radicals (O_2^-).[32,46] Inhibition complex I activity stimulate the production of superoxide anion, which may form hydroxyl radicals ($^{\bullet}OH$) or react with nitric oxide (NO) to produce peroxynitrite ($ONOO^-$). These reactive oxygen species (ROS) react with proteins, lipids and nucleic acids leading to cellular destruction.[32,47,48] The electron transport chain itself, is a target of these reactive species leading to more mitochondrial defects and further ROS generation.[49] Oxidative stress markers are found to be increased in the SNc of PD brains and also, the amount of the reduced glutathione is decreased.[50] The elevated levels of ROS in PD would augment the misfolded proteins content, increasing the ubiquitin-proteasome system demand to clear them.[1]

Dopaminergic neurons in the SNc may be an especially fertile environment for the production of ROS because of: First, DA oxidative deamination by monoamine oxidases (MAO) A and B is the main degradative pathway, resulting in H_2O_2 production.[51] Second, the SNc is an iron-rich environment,[52] H_2O_2 can react with iron through the Fenton reaction and produce hydroxyl radicals, which are very reactive and destructive, causing lipid peroxidation, amino acids modification and DNA mutations.[51] Third, non-enzymatically reaction of DA with oxygen produces quiones and semiquinones, with the formation of superoxide radicals.[53] Quinones are also classified as extremely reactive electron deficient species that easily bind to nucleophilic compounds in cells, such as antioxidant glutathione, sulfhydryl groups of protein cysteinyl residues and DNA.[54] In conclusion, there is a strong mechanistically relationship between DA oxidation, mitochondrial impairment and oligomerization of α-synuclein in pathogenesis of PD.[54,55]

3.3. Neuroinflammation

It has been suggested that neuroinflammation have a fundamental role in onset and progression of PD through activation of microglia cells.[56, 57] Microglia are phagocytic cells and considered as a key immune cells in the brain, generally show a resting state, and only turn out to be activated upon immune challenge or brain injury.[33] Microglia can be either neuroprotective by clearing cellular debris or boost neurodegenerative process through releasing inflammatory mediators.[33,58] Activated microglia is one of the important sources of nitric oxide and superoxide radicals, which increase the risk to nitrative and oxidative stress inside the dopaminergic neurons. Glutamate produced by microglia and toxic inflammatory mediators such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) are also implicated in the neurodegeneration of dopaminergic neurons.[59] Notably, activated microglia were reported in the SNc of PD patients concomitant with an increase of the brain pro-inflammatory mediators.[57,60] Several postmortem investigations reported the presence of activated microglia producing inducible nitric oxide synthase (iNOS) in the dopaminergic neurons of PD.[60] Furthermore, activated microglia cells were noticed in both *in vivo* and *in vitro* models of PD like 6-hydroxydopamine, MPTP as well as rotenone.[61,62,63,64]

Dopaminergic neuronal death leads to liberation of oxidized lipids, proteins and DNA causing further activation of microglia cells.[61,62,] Therefore, dopaminergic neuronal death triggered by microglia further increases inflammatory mechanisms, producing a neurotoxic ferocious cycle of inflammation and neuronal death (**Figure 3**).[33,56] Because of the midbrain region contains a massive number of microglia cells, the SNc dopaminergic neurons are especially susceptible to microglia mediated neurotoxicity.[65]

TNF-α and IL-1β from the overactive microglia cells can enhance the activation of neighboring astrocytes, which increase the expression of several pro-inflammatory proteins, including iNOS, resulting in elevated levels of NO magnifying the neuronal damage.[67,68] Several studies suggested that astrocyte-mediated iNOS production is involved in the loss of SNc dopaminergic neurons.[69] Astrogliosis, an abnormal increase in the number of reactive astrocytes characterized by high expression of glial fibrillary acidic protein (GFAP), has been reported in different models of PD. Interestingly, astrogliosis also exists in the affected brain regions of PD patients, providing a possible indication for the implication of astrocytes in the immune processes in PD.[70]

3.4. Apoptosis

Apoptosis is a physiologic condition occurs normally during development and aging and plays a crucial role in tissue homeostasis to keep cell populations in tissues.[71] However; exaggerated apoptosis in adulthood can cause needless cell death, which might lead to diseases such as cancer and neurodegenerative disorders.[72, 73] Apoptosis is characterized by membrane blabbing, cell body shrinkage, nuclear condensation and DNA fragmentation.[74] Several studies demonstrated that the mitochondrial-mediated apoptosis pathway is a cause of neurodegeneration of the SNc in PD and many neurodegenerative disorders.[75,76]

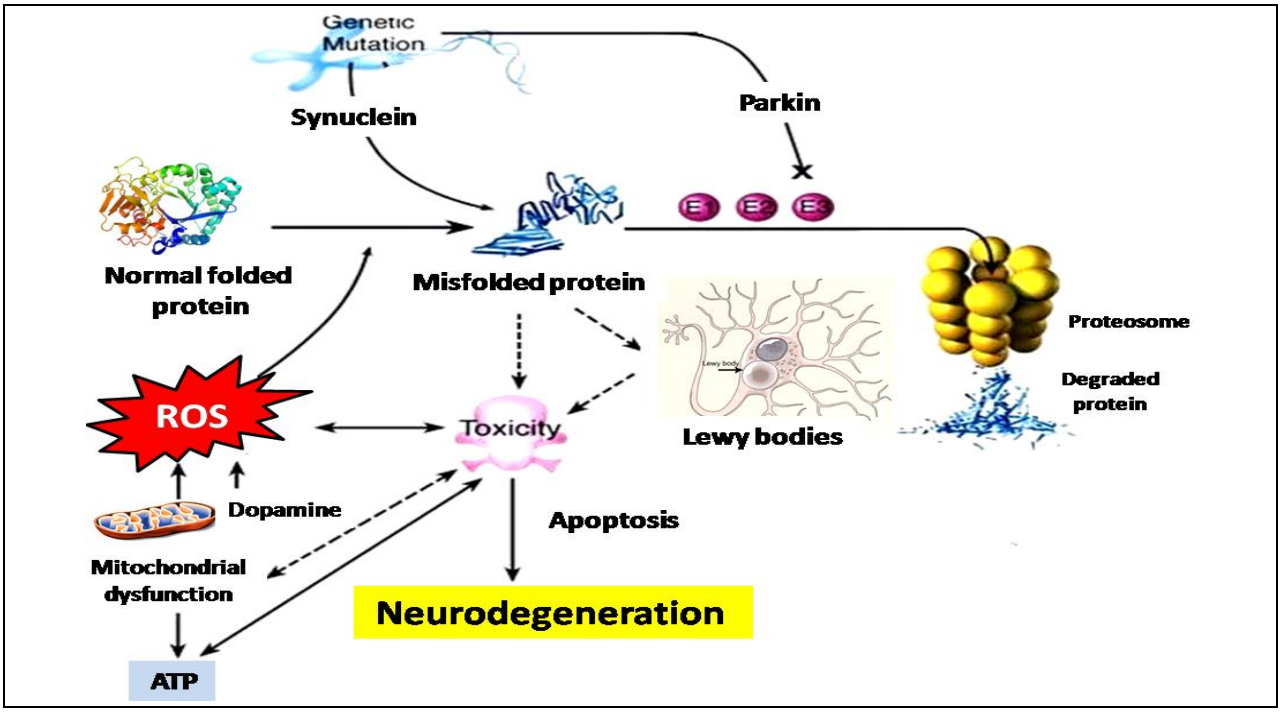

Figure 2. Mechanisms of Neurodegeneration[32]. A growing body of evidence proposes that the accumulation of misfolded proteins is likely to be a key event in PD neurodegeneration. Pathogenic mutations may directly induce abnormal protein conformations (as believed to be the case with α-synuclein) or damage the ability of the cellular machinery to detect and degrade misfolded proteins (Parkin). Oxidative damage, linked to mitochondrial dysfunction and abnormal dopamine metabolism, may also promote misfolded protein conformations. Oxidative stress, energy crisis (i.e., ATP depletion) and the activation of the programmed cell death machinery are also believed to be factors that trigger the death of dopaminergic neurons in Parkinson's disease. ROS: Reactive oxygen species.

In experimental models of PD, the neuronal loss of the SNc appears to occur via activation of mitochondria- mediated apoptosis.[74, 75] Complex I inhibition in animals causes neurodegeneration of dopaminergic neurons of the SNc, like that seen in PD through stimulating apoptotic pathways.[77] Complex I inhibition and the consequently mitochondrial defect encourage the activation of the mitochondrial-dependent apoptotic pathway by increasing the liberation of the apoptogenic molecule cytochrome *c* from the impaired mitochondria in to cystosol to initiate a caspase-dependent mechanism leading to cytoskeletal alterations, DNA fragmentation, and subsequent cell death.[78]

3.5. Excitotoxicity

Excitotoxicity is a well settled mechanism of neurodegeneration that had been involved in the pathogenesis of PD as well as other neurodegenerative diseases.[35, 79] It was reported that striatal excitotoxic neuronal injury was correlated with induced apoptotic cell death in the SNc neurons.[80] Excitotoxicity is provoked by the excessive liberation of glutamate from presynaptic nerve terminals as well as astrocytes into the extracellular space, with resultant over-activation of glutamate receptors, especially NMDA (N-methyl-D-aspartate) receptors.[81] Excessive glutamate can simulate the neurodegenerative of the SNc dopaminergic neurons. Many studies reported that synergistic interactions between oxidative stress, mitochondrial impairment and glutamatergic activation occur at the level of SNc.[82]

4. Clinical symptoms in Parkinson's disease

Since the initial description of the disease in the 19th century by James Parkinson's, the classical motor signs of PD have been recognized as prominent components of the disease.[83] These parkinsonian symptoms include resting tremor, muscle rigidity, bradykinesia (slowness and decreased amplitude of movement), flexed posture and the freezing phenomenon.[84] The neurodegeneration of dopaminergic neurons in PD progresses over a period of years before the appearance of classical motor features.[85] Motor symptoms of PD usually appear when about 70-80% of striatal nerve terminals and 50-60% of SNc neurons have been lost.[86,87]

All types of tremor such as rest, kinetic and postural tremor may present in PD. The classical resting

tremor is the most common type, which refers to a 4 to 6 Hertz pill-rolling tremor in the resting limb, which is inhibited during the beginning of movement.[88] Often, resting tremor is more noticeable unilaterally, and the upper limbs are commonly more affected than the lower limbs. Resting tremor may also occur in lip and chin, in the tongue, but the head is seldom involved.[89] Clinically, suppression of resting tremor during movement onset is one of the most essential diagnostic features of PD.[90]

While the cardinal motor signs and symptoms of PD are in command of the clinical picture and even give an explanation of parkinsonian syndrome, other complaints that have been categorized as non-motor symptoms may be present. Non-motor symptoms include sleep disturbances, fatigue, anxiety, depression, constipation, urinary incontinence, gastrointestinal and sexual dysfunctions, apathy and decreased motivation, slowness in thinking (bradyphrenia), and cognitive impairment that can advance to dementia.[84, 91, 92]

5. Experimental models for induction of Parkinson's disease

5.1. Chemically induced Parkinson's disease model

MPTP, rotenone, 6-hydroxydopamine (6-OHDA) and paraquat are the most important neurotoxins have received an attention to induce dopaminergic neurodegeneration. Presumably, all of these neurotoxins stimulate the ROS formation.[93]

5.1.1. MPTP

MPTP is one of the most important tools used to investigate the molecular mechanisms concerned with the death of dopaminergic neurons in the SNc. MPTP has been known to be neurotoxic in a wide variety of species; primates as well as mice are the most common species. However, other species such as rats were resistant to this neurotoxin.[94, 95]

MPTP is an extremely lipophilic compound that easily passes the blood-brain barrier. Therefore, MPTP can be injected systemically to produce an experimental model of PD.[96] MPTP is considered to be non toxic by itself, but its metabolite 1- methyl-4-phenylpyridinium (MPP+) produced via neuronal MAO-B in glial cells, is the actual toxic product.[97] Inside the dopaminergic neurons, MPP+ accumulates in the cytoplasm and crosses the mitochondrial membrane where it inhibits complex I activity leading to oxidative stress.[98] In addition to its direct effect on mitochondrial complex I activity, it was reported that the toxicity of MPTP also includes an apoptotic process stimulated by the damaged mitochondria, involving the up-regulation of proapoptotic Bax and consequently the release of cytochrome c as well as the activation of caspase-3 and 9. Additionally, MPTP mediated excitotoxicity process through activation of NMDA receptor.[99]

MPTP administration showed neuro-pathological and neurochemical changes that are identically to those reported in PD include damage of the nigrostriatal dopaminergic pathway (nearly 50% to 90% cell loss in the SNc) with a severe reduction in the striatal DA levels (> 90%) (Table 1).[11, 95] Similar to PD, MPTP causes lower loss of dopaminergic neurons in VTA than in SNc.[100,101] Monkeys injected with small doses of MPTP, showed a high rate of neurodegeneration of dopaminergic nerve terminals in the putamen nucleus than in the caudate.[102]

The point of weakness with MPTP model is the absence of LBs inside dopaminergic neurons.[103] Although the lack of LBs has been reported in this model, a few studies have recognized the expression of α-synuclein following the exposure to MPTP.[104] Behavior is also an issue, features of PD are lacking in mice while, monkeys exhibited typical PD features including rigidity and bradykinesia upon treated with MPTP. However, severe dopaminergic degeneration in mice indicated some motor alterations.[105] MPTP model of PD has some limitations. Most protocols for MPTP use acute drug treatment but unable to produce progressive PD. chronic treatment with MPTP may overcome this situation; but, long treatment with low doses resulted in recovery of motor dysfunctions once the treatment is stopped.[106]

5.1.2. 6-OHDA

6-OHDA is a selective neurotoxin used to induce lesions in dopaminergic neurons of the nigrostriatal pathway in rats.[107] Systemic administration of 6-OHDA fails to produce Parkinsonism because; it is hydrophilic molecule and so, it is unable to cross the blood brain barrier. Therefore, 6-OHDA is required to be injected directly into the striatum or SNc via stereotaxic procedures.[108] The effects of 6-OHDA resemble those seen in MPTP model, causing dopaminergic neuronal death. 6-OHDA injection produces progressive neurodegeneration in the SNc and VTA.[109] Direct injection of 6-OHDA in the SNc leads to a huge (> 90%) and fast (12 hrs to 2–3 days) neurodegeneration of dopaminergic neurons.[98]

The extent of lesion is depended on many factors including, the site of the injection, the amount of 6-OHDA injected and the inherent sensitivity between different animal species. Extensive loss of DA in the striatum (80-90%) is achieved in the majority studies and corresponds to specific behavioral changes. Injection of 6-OHDA into the striatum results in a slow retrograde neurodegeneration of the nigrostriatal dopaminergic system over a period of weeks.[106, 109]

Similar to the MPTP model, LBs inclusions not reported with 6-OHDA model.[93] Partial lesions using 6-OHDA, are considered as models for an early stage of PD while, bilateral lesions are used to evaluate

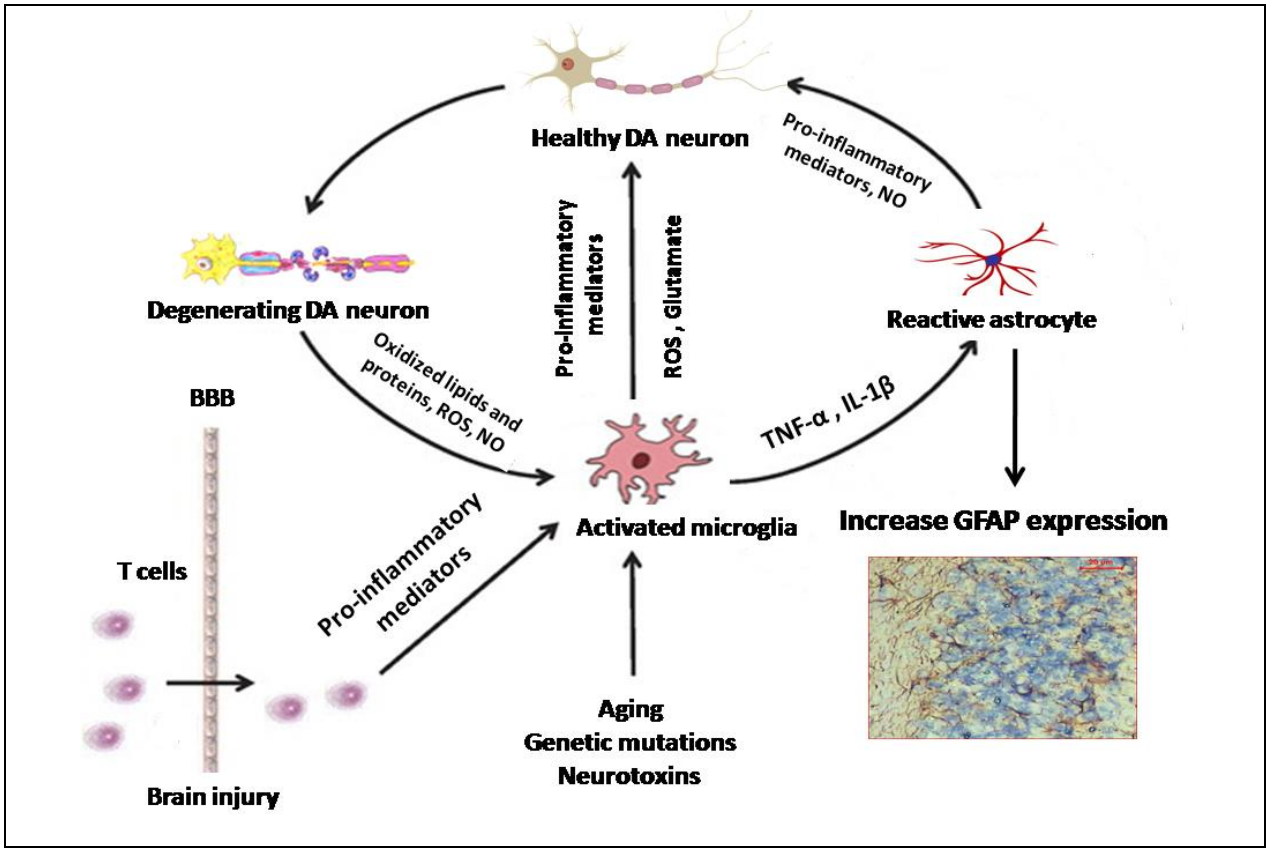

Figure 3. Diagram of inflammatory mechanisms participated in the pathogenesis of PD. Under pathological conditions of PD such as gene mutations, neurotoxins and cytokines liberated from infiltrated T cells, the microglia become activated and release the pro-inflammatory mediators which stimulate astrocytes leading to high levels of nitric oxide and proinflammatory mediators, contributing in the degeneration of dopaminergic neurons. The molecules released from damaged dopaminergic neurons can further cause activation of microglia and enhanced inflammatory response.[65] IL-1β: Interleukin-1β; TNF-α: Tumor necrosis factor-alpha; NO: nitric oxide; ROS: Reactive oxygen species; GFAP: glial fibrillary acidic protein; DA: Dopamine

more complex neurobehavioral changes, induce non-motor symptoms such as depression, anxiety and olfactory impairment.[98]

There are vast evidences for the participation of oxidative stress in 6-OHDA-induced dopaminergic neurodegeneration. Many studies reported the generation of hydrogen peroxide and superoxide radical following 6-OHDA injection. This effect can be explained by the ability of 6-OHDA to inhibit complex I activity.[106] At the cellular level, 6-OHDA model provides some molecular events. For example, it was reported that glutamatergic neurotransmission in the basal ganglia was markedly elevated in rats injected with 6-OHDA and alteration in corticostriatal synaptic plasticity was also documented.[110, 111] Therefore, the 6-OHDA model acts a beneficial model to study the mechanism of action of classical drugs used in treatment of PD as well as novel agents targeting glutamate receptors.[112]

5.1.3. Rotenone

Rotenone is one of the most potent cytotoxic compounds of rotenoids; it is widely used as a pesticide, insecticide as well as fish poison. In contrast to 6-OHDA, rotenone is highly lipophilic compound, therefore it is easily pass the blood brain barrier. Rotenone produces dopaminergic neurodegeneration in a way similar to MPTP through binding and inhibiting complex I activity.[113, 114]

Chronic systemic injection of rotenone in rats produces many features of PD, including neurodegeneration of dopaminergic neurons in the nigrostriatal pathway.[115] Importantly; intracellular LBs inclusions were reported in the degenerating neurons. These inclusions showed immunoreactivity for ubiquitin and α-synuclein as did the original LBs.[93] Rotenone-injected rat model also produces all of the behavioral features similar to those seen in PD where the rats were found to be hypokinetic with a flexed posture like the stopped posture in PD.[106,116]

Commonly, rotenone administration may be through intraperitoneal injection,[93] subcutaneously or intravenously.[117] Recently, chronic intragastric administration of rotenone has been examined in mice[118] or as a stereotaxic injection (direct infusion in the brain).[119] Intragastric administration of rotenone showed an expression to α-synuclein in the dorsal vagal nucleus, the enteric nervous system, the SN and the spinal cord,[118] theses finding support the theory assumed that the guts is the main origin for synucleopathy in PD.[98]

In conclusion, the rotenone model causes a specific, progressive and chronic neurodegeneration of the nigrostriatal pathway. In addition, neuronal LBs inclusions and oxidative stress are also involved in the rotenone-induced PD model. Therefore, the rotenone model summarizes most of the mechanisms involved in the pathogenesis of PD. For these reasons, neuroprotective agent treatment trial in rotenone model may be more appropriate to PD than other acute models. The main disadvantages of rotenone model are its variability, with some animals producing lesions and other not as well as its labor-intensive nature and high mortality rate. Moreover, animals with bilateral lesions are difficult to continue as with animals injected bilaterally with MPTP or 6-OHDA.[106, 120]

5.1.4. Paraquat/Maneb

Paraquat is the most worldwide herbicide, a chemical structural analog of MPP+ which has the ability to pass the blood brain barrier and reach to the mitochondria where it inhibits the activity of complex I.[98, 121] Paraquat triggers oxidative stress and neuronal cell death where, it's reduced form able to react with the molecular oxygen to produce ROS especially superoxide anion and also interfere with the recycling of glutathione.[122] Moreover, paraquat seems to be involved in apoptosis through caspase-3 activation.[123] Maneb is the trade name for manganese ethylene bisdithiocarbamate, a fungicide lipophilic compound that easily penetrates the blood brain barrier, inhibits the transportation of glutamate and obstruct the release and uptake of DA.[124]

It has been reported that the herbicide paraquat as well as the fungicide maneb (manganese ethylene bisdithiocarbamate) may cause Parkinsonism in humans.[125] Regarding animal models, some studies report that the systemic administration of paraquat in mice causes reduction in the motor activity as well as a dose-dependent loss of striatal tyrosine hydroxylase fibers and dopaminergic neurons in SNc with relative sparing of the VTA.[121,126] Like rotenone, paraquat and maneb have the ability to induce LBs inside dopaminergic neurons.[127] Maneb has been shown to produce SNc neurons loss and decrease locomotor activity.[128] Additionally, maneb potentiates the effects of both MPTP and paraquat.[129]

5.2. Genetic models

Genetic models are preferable to stimulate the mechanisms underlying the genetic forms of PD. Mutations in α-synuclein, Parkin, PINK1, LRRK2 (*leucine rich repeat kinase 2*) and DJ-1 are considered as models for genetic PD.[120] These gene defects leads to a number of cellular and molecular dysfunctions such as fragmented and dysfunctional mitochondria,[130] dysfunction of ubiquitin-proteasome system,[131] altered the production of reactive oxygen species.[132] Some studies have also reported behavioral alteration and motor dysfunction in these mice.[133]

Over the past decades, dopaminergic drugs were classified as the main drugs used for treatment motor symptoms of PD. It is suggested that, the combination of dopaminergic drugs with other drugs, like catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors as well as anticholinergic drugs can produce a better improve of motor symptoms. In addition to, non-motor symptoms, such as neuropsychiatric, sleep, cognitive, autonomic disturbances are gaining a great attention and urgently required to be taken in consideration due to their effect on quality of life. Recently, pre-clinical studies extensively investigate many neuroprotective therapies and some therapies were subjected to clinical trials.[134]

6.1. Drug treatments for motor symptoms

6.1.1. L-dopa + Dopa decarboxylase inhibitors (DDC-I)

L-dopa (L-3,4-dihydroxyphenylalanine), the metabolic precursor of DA, is the single most efficient pharmacologic drug for PD; both the therapeutic and adverse effects of L-dopa result from its decarboxylation to DA. L-dopa is rapidly absorbed from the small intestine via aromatic amino acids transport system. After oral administration of L-dopa, peak plasma of the drug is reached between 0.5 and 2 hrs with short plasma half-life (1-3 hrs). Many factors such as gastric emptying rate, gastric juice pH and the degradative enzymes of the gastrointestinal tract determine the rate and extent of absorption of L-dopa. L-dopa administration with meals retards its absorption and decreases peak plasma concentrations. This effect is due to the competition of some dietary amino acids with its absorption sites. In the central nervous system, L-dopa is converted to DA by decarboxylation, inside the presynaptic terminals of striatal dopaminergic neurons. Therefore, the produced DA is accountable for the therapeutic effect of L-dopa in PD.[135]

Treatment with L-dopa should be recommended when patients with PD have troublesome motor symptoms impact on their quality of life and

Table 1. Animal models of Parkinson disease.[120]

	Animal model	Motor behavior	SNc neuron loss	Striatal DA loss	LBs pathology
Toxin-based	MPTP Mice	Decreased locomotion, bradykinesia	↑↑↑	↑↑↑	NO
	MPTP Monkeys	Decreased locomotion, altered behavior, tremors and rigidity	↑↑↑	↑↑↑	NO
	6-OHD rat	Decreased locomotion, altered behavior	↑↑↑	↑↑↑	NO
	Rotenone	Reduced locomotion	↑↑↑	↑↑↑	YES
	Paraquat/maneb	Reduced locomotion	↑↑	↑↑↑	YES
Genetic mutation	α-synuclein	Altered behavior, reduced or increased motor activity	Not ↑consistent	↑	(in old animals)↑
	LRKK2	Mild behavioral changes	NO	NO	NO
	PINK1	No obvious alteration or reduced locomotion	NO	NO	NO
	PARKIN	No obvious alteration or reduced locomotion	NO	↑	NO
	DJ-1	Reduced motor activity	NO	NO	NO

↑↑↑: Severe loss; ↑↑: Moderate loss; ↑: Mild loss.
MPTP: 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; 6-OHDA: 6-hydroxydopamine; SNc: Substantia nigra pars compacta; DA: Dopamine; LBs: Lewy bodies.

therefore, a potent treatment is urgently needed.[136] At the beginning of treatment, L-dopa is particularly effective to control symptoms of PD such as bradykinesia and rigidity, and it is well-tolerated, which called "honeymoon". However, there is a probability that approximately 40 % of patients develop motor complications after 4-6 years of L-dopa therapy.[137] Although the mechanisms causing motor complications are not completely understood, the pharmacokinetics of L-dopa, especially short plasma half-life,[138] the absorption regions, gastric emptying rate and pulsatile stimulation which is an intermittent delivery to DA receptors,[139] in addition to the progression of disease itself are believed to participate to the common occurrence of motor complications.

Clinically, L-dopa is usually combined with a DDC-I (carbidopa and benserazide) that does not cross well into the central nervous system. In the absence of the DDC-I, L-dopa is extensively decarboxylated in the intestine and other peripheral sites and this decreases the concentration of the drug reaches the brain (approximately less than 1%). Therefore, combinations of L-dopa and DDC-I increases cerebral L-dopa bioavailability and decreases the peripheral adverse effects of DA (e.g., hypotension and nausea). Generally, carbidopa at a dose of 75 mg/day is sufficient to prevent the development of nausea. Therefore, 3-4 daily times of carbidopa/ L-dopa (Sinemet®) which contain 25 mg carbidopa and 100 mg L-dopa is considered the most widely prescribed formulation.[135]

Treatment with L-dopa can affect all the symptoms and signs PD. In early stage of PD, the duration of the beneficial effect of L-dopa extends its plasma lifetime, indicating that nigrostriatal DA system has some ability to store and release DA. The main limitation of chronic treatment with L-dopa is the "wearing off" phenomenon. Since by time, the progression of PD increases and the nigrostriatal DA system loses its "buffering" capacity leading to fluctuated motor state with each dose of L-dopa. Therefore, increasing the dose and frequency of administration is required to ameliorate this situation; however, this can lead to dyskinesia. Dyskinesia is an abnormal involuntary movement occurs when the plasma level of L-dopa is elevated. In the later stages of PD, patients may fluctuate quickly between being "off," having no beneficial effects from the drug, and being "on" a situation called the on/off phenomenon.[135]

L-dopa methyl ester (melevodopa) is an effective pharmacological agent for improving daily motor activities and quality of life in PD patients "wearing-off".[140] Several new formulations of L-dopa such as IPX066 (extended-release formulation of L-dopa /carbidopa) have been manufactured in order to provide a more stable plasma concentration of L-dopa, reduce off-time and the frequency usage, and increase on-time without troublesome dyskinesia.[141] Novel formulation of L-dopa /carbidopa intestinal gel was found to be effective in optimizing the delivery of L-dopa and consequently decrease the risk of

dyskinesia. Therefore, intestinal gel infusions of L-dopa support the concept of continuous DA receptor stimulation needed to prevent dyskinesias induced by L-dopa.[10, 142]

In addition to motor complications and nausea, many other adverse effects may be associated with L-dopa treatment. Hallucinations and confusion are the most adverse effects e in the elderly and in those with preexisting cognitive dysfunction. Typical antipsychotic drugs, such as the phenothiazines, are efficient against psychosis induced by L-dopa but may worsen the symptoms of PD due to blocking the D2 receptor. Clozapine and quetiapine which are "atypical" antipsychotic drugs were found to be effective in the treatment of psychosis without worsen Parkinsonism. Circulatory DA produced from peripheral decarboxylation of L-dopa may stimulate DA receptors in the blood vessels and leads to orthostatic hypotension. Effects of DA at α and β receptors may produce cardiac arrhythmia, particularly in patients with preexisting conduction disturbances.[135]

6.1.2. Dopamine receptor agonists

All dopamine agonists activate DA receptors (D2); stimulation of postsynaptic D2 receptor is related to antiparkinsonian effects where, activation of presynaptic D2 supposed a neuroprotective activity for dopamine agonist.[143] Treatment with dopamine agonists provides many advantages over L-dopa: because of enzymatic conversion of DA agonist is not necessary for their activity, they do not depend on the functional capacities of the nigrostriatal dopaminergic neurons, they produce a direct stimulation to DA receptors; they have a longer half-life in comparison with L-dopa, they possess possible neuroprotective effects and the most important advantage is confirmed decreased occurrence of motor complications compared to L-dopa.[135,144] Finally, if free radical formation from metabolism of DA really participates in the death of neurons, then DA receptor agonists able to modify the course of PD by decreasing the release of endogenous DA and the need for L-dopa.[135]

In practice, four orally DA receptor agonists are accessible for management of PD: two older drugs such as bromocriptine and pergolide which are ergot derivatives and two recent, more selective drugs such as ropinirole and pramipexole which belong non-ergot derivatives. DA agonists are characterized by long duration of action (8-24 hours), while the action of L-dopa lasts for 6-8 hours, and they are mainly effective in the treatment of patients with on/off phenomena. Similar to L-dopa, DA agonists also may cause hallucinations or confusion and may worsen orthostatic hypotension particularly in elderly patients who are more susceptible.[135]

The principal difference between the recent and the older drugs is in their tolerability and speed of titration. Initial treatment with bromocriptine or pergolide may lead to sever hypotension, nausea, and fatigue; therefore, they should be started with low dose. Symptoms usually are temporary, but need a slow gradual increase of the dose over a period of weeks to months.[135] Because of severe side effects of pleuropulmonary fibrosis and valvulopathy, ergot derivatives are rarely used now and have been withdrawn from the U.S. market.[135, 145] Pramipexole and ropinirole can be started more rapidly, producing therapeutically beneficial doses in a week or less. They usually produce less GIT disturbance than do the ergot derivatives, but they can cause nausea and somnolence.[135]

The introduction of ropinirole and pramipexole has changed the clinical use of DA agonists in treatment of PD. These selective agonists are well tolerated and are used more and more as initial therapy for PD rather than as adjuncts to L-dopa. This change is due to two factors: (1) DA agonists may be less likely than L-dopa to produce dyskinesia and on/off phenomenon, this can be explained by their longer duration of action (2) the concern that L-dopa may participate in oxidative stress, consequently exacerbating the degeneration of dopaminergic neurons. Many experts favor DA agonists as initial therapy in younger patients and L-dopa as the initial treatment in elderly who may be more susceptible to the cognitive adverse effects of the DA agonists.[135]

Apomorphine is a dopaminergic receptor agonist that can be administered by subcutaneous injection. Apomorphine is used as a "rescue therapy" for the acute intermittent treatment of "off" episodes in patients with a fluctuating response to dopaminergic therapy. Apomorphine has the same side effects of the other dopamine agonists; it is highly emetogenic and requires pre- and post-treatment antiemetic therapy. Trimethobenzamide (300 mg three times daily) is started 3 days before the initial dose of apomorphine and continued at least during the first 2 months of therapy. Ondansetron, antiemetic drugs of the 5-HT_3 blocker class is contraindicated with apomorphine because of the markedly reported hypotension. Other potentially serious side effects of apomorphine including QT prolongation, hallucinations, dyskinesia, and abnormal behavior are well reported.[135]

6.1.3. COMT Inhibitors

COMT is an enzyme involved in the peripheral degradation of L-dopa. Approximately 99% of the orally administered dose of L-dopa does not reach the brain but, rather, is decarboxylated to DA, which causes nausea and hypotension. Addition of a DDC-I (carbidopa) decreases the formation of DA but increases the fraction of L-dopa that is methylated by

COMT. COMT inhibitors block the peripheral conversion of L-dopa to 3-*O*-methyl dopa, augmenting the bioavailability and the half-life of L-dopa, which is beneficial in patients with motor fluctuations.[135, 146, 147]

Tolcapone and entacapone are the two main COMT inhibitors for treatment of PD. Because of the relatively long duration of action, tolcapone is administered 2-3 times daily. Entacapone has a short duration of action, approximately 2 hrs, thus it generally is taken simultaneously with each dose of L-dopa/carbidopa.[148] Triple combination of COMT inhibitors, L-dopa and carbidopa has become a first line treatment for motor fluctuation of PD. Stalevo®, a tablet contain L-dopa / carbidopa and entacapone can produce a more stable plasma L-dopa level as well as a persistent stimulation of striatal DA receptors.[149] Recently tolcapone can significantly improve the cognitive function in PD patient.[150] Nebicapone, is a more efficient COMT inhibitor than entacapone, it decreases off-time by approximately 70-80 min as compared to entacapone.[151]

Hepatotoxicity is a common adverse effect of tolcapone therefore; tolcapone should be used with a caution in patients with liver damage and monitoring of hepatic transaminases is required. Entacapone has not been linked with hepatotoxicity and no special monitoring is required.[135]

6.1.4. MAO-B Inhibitors

MAO-B is the predominant enzyme in the striatum which is responsible for most of the oxidative metabolism of DA in the brain. By inhibiting MAO-B activity, the levels of DA increase in the SN. MAO-B Inhibitor also blocks DA re-uptake from the synaptic cleft, therefore it increases the DA concentrations in the brain. At the early stage of PD, initial treatment with MAO-B Inhibitor can delay the progression of the signs and symptoms of PD.[136]

Selegiline is the first selective inhibitor for MAO-B used in treatment of PD. It was reported that selegiline can delay the need for L-dopa by retarding the progression of PD.[136, 152, 153] Since it may delay the degradation of DA in the striatum; selegiline has been used to alleviate the symptoms of PD, although its profit is modest. A supposed action of selegiline is to delay the metabolism of DA, decrease oxidative stress and free radical formation, and thereby give neuroprotective effects.[135]

Unlike non-specific MAO inhibitors (e.g., phenelzine, isocarboxazid, tranylcypromine), selegiline does not affect peripheral metabolism of catecholamines and can be taken safely with L-dopa. Selegiline does not potentiate the lethal effect of indirectly acting sympathomimetic amines such as dietary tyramine.[135] Amphetamine and methamphetamine are the main metabolites of selegiline, which may cause anxiety and insomnia. A related compound, rasagiline, also acts through inhibition of MAO-B but does not form these undesirable metabolites.[135] The main obstacle for MAO-B Inhibitors is the first-pass effect since; the bioavailability of selegiline is approximately 10 %.[154] The bioavailability can be improved by the orally disintegrating tablets, which are effective and decrease dose significantly.[155] Recently, nanoparticals of rasagiline as a new delivery system through intranasal route enhance its bioavailability in brain.[156] Although both selegiline and rasagiline are irreversible MAO-B inhibitors, the most recent drug, safinamide, acts as a reversible inhibitor for MAO-B and was reported to be effective in combination with L-dopa, where it increases on time and decreases troublesome dyskinesia.[157]

6.1.5. Anticholinergic

Antagonists of muscarinic acetylcholine receptors were used widely for the treatment of PD before the discovery of L-dopa. The biological basis for the therapeutic actions of anticholinergic is not completely understood.[135] By blocking muscarinic receptors, the disequilibria between acetylcholine and DA levels will be corrected.[158] Monotherapy of anticholinergic drugs or combination with other drugs offer mild symptomatic control in patients with PD. Anticholinergic drugs like benztropine and trihexyphenidyl were registered by FDA and they are often used in tremor treatment.[158,159] Due to the explicit adverse effects of anticholinergic drugs which outweigh their therapeutic benefits, clinical treatment with anticholinergic drugs is limited to some extent. The important risk of using anticholinergics drugs includes state of immobility, urinary bladder dysfunction, digestion disorders as well as psychiatric and neurologic comorbidities, such as PD, depression and epileptic seizures.[160] There is a correlation between the use of anticholinergics and the decline of all the daily life activities, delirium, gait freezing and higher rate of falls.[161] Therefore, anticholinergics should be avoided in PD patients with comorbid dementia.[162]

6.1.6. Amantadine

Amantadine is an antiviral agent used for the prophylaxis and treatment of influenza A. By chance, it was found that amantadine has the ability to relieve early symptoms of PD as well as treatment of dyskinesia.[163] Many mechanisms of action elucidate antiparkinsonian effects of amantadine where, it increases DA release and inhibits DA reuptake, blocks NMDA glutamate receptors. In addition, it has antimuscarinic activity.[158] The fact that amantadine has the ability to block NMDA glutamate receptors proposes that amantadine can inhibit excitotoxicity

process which results from glutamatergic overstimulation. Therefore, it may be suggested that amantadine has possible neuroprotective effects when used in the early stage of PD.[158, 164] Several clinical studies reported that amantadine can decrease the duration of L-dopa-induced dyskinesia and severity of freezing as well as improve daily activities in patients of PD.[165,166] It also ameliorates parkinsonian symptoms, particularly gait and balance.[167]

6.2. Drug treatments for non motor symptoms

Low doses of antidepressants including tricyclic antidepressant (doxepin) and trazodone, eszopiclone (nonbenzodiazepine hypnotics), as well as melatonin have been reported to treat insomnia and sleep disorder in PD patients.[168, 169, 170]

Clinically, treatment of cognitive impairment and dementia associated with PD involve the use of acetylcholinesterase inhibitors. It was reported that rivastigmine, donepezil and galantamine able to improve cognition in PD.[169,171] Recently, systematic meta-analysis proposed that memantine, a glutamate NMDA receptor blocker, possibly improves cognitive deficits in PD.[172]

Selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, paroxetine and citalopram as well as serotonin-norepinephrine reuptake inhibitors such as venlafaxine and mirtazapine are the most common drugs for treatment of depression and anxiety in PD.[173]

Antimuscarinic drugs such as oxybutynin, trospium and solifenacin are used usually in clinical practice to control overactive bladder.[174] Mirabegron, β_3 adrenergic receptor agonist is considered as a new treatment option used to treat bladder dysfunction in PD. recently, urinary incontinence in PD can be treated with intravesical botulinum toxin injections.[175]

Constipation is most common gastrointestinal dysfunction in PD, therefore lifestyle modifications such as increasing water intake, fibers intake and physical activity are recommended especially in elderly. In addition to, laxative such as bisacodyl is efficient but long-term treatment is not recommended because of the potential side effects.[176]

6.3. New approaches for treatment of Parkinson's disease

Cannabis is one of medical marijuana. After 30 min of cannabis smoking in a small controlled trial, it was found that smoking of cannabis has beneficial effect on muscle rigidity, tremor and bradykinesia. This explain that cannabis may be used as an alternative therapy for treatment of PD, but it still needs more investigations through further studies with larger sample size over a longer term.[177] Recently, the development of angiotensin IV analogs which could bind to angiotensin IV receptor shows a promising effect in overcoming motor dysfunctions of PD patients in the preclinical trials.[178]

Several studies investigate the neuroprotective role of bee venom molecules in different models of PD. Subcutaneous injection of bee venom in MPTP-induced PD in mice protects dopaminergic neurons in SNc.[179] This study proposed that neuroprotective mechanisms of bee venom are explained mainly by decreasing neuroinflammation and suppressing the proinflammatory cytokines, such as TNF-α , IL-1 and iNOS expression.[180] Another study by Khalil et al reported that bee venom has a potential neuroprotective effect in rotenone model of PD by suppressing apoptotic pathways through decreasing Bax expression and caspase-3 activation.[181] Behavioral studies demonstrated that treatment with bee venom improves motor dysfunction and balance.[182]

In addition, bee venom phospholipase A2, the major compound of bee venom, is proposed to be an applicable pharmacological tool in treatment of PD, since it protects the dopaminergic neurons in MPTP-induced PD in mice.[183] Apamin, another compound of bee venom, protects cultured midbrain dopaminergic neurons.[184] According to all these experimental results, clinical studies were done to evaluate the potency of bee venom in treatment of PD. Recently; clinical studies showed that bee venom could be an effective adjuvant therapy for PD.[185]

CONCLUSION

PD is a very complex neurodegenerative disease characterized by the loss of dopaminergic neurons in the SNc and the presence cytoplasmic inclusions (Lewy bodies) leading to motor and non-motor symptoms. Several mechanisms, such as mitochondrial dysfunction, ROS, neuroinflammation, excitotoxicity and apoptosis are involved in its pathogenesis. MPTP, 6-OHDA, rotenone and paraquat are neurotoxins which able to selective damage to the nigrostriatal pathway and produce experimental models of PD. The emerging new formulations of classical drugs and novel therapeutic targets of new drugs provide better strategy for PD treatment.

Conflict of Interest

The authors declare that they don't have any conflict of interest.

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