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REVIEW ARTICLE

Understanding multifactorial architecture of Parkinson's disease: pathophysiology to management

Ramandeep Kaur[1] · Sidharth Mehan[1] · Shamsher Singh[1]

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Abstract

Parkinson's disease (PD) is the second most common multifactorial neurodegenerative disorder affecting 3% of population during elder age. The loss of substantia nigra, pars compacta (SNpc) neurons and deficiency of striatal dopaminergic neurons produces stables motor deficient. Further, increase alpha-synuclein accumulation, mitochondrial dysfunction, oxidative stress, excitotoxicity, and neuroinflammation plays a crucial role in the pathogenesis of PD. Alpha-synuclein protein encodes for SNCA gene and disturbs the normal physiological neuronal signaling via altering mitochondrial homeostasis. The level of α-synuclein is increased in both normal aging and PD brain to a greater extent and secondly reduced clearance results in accumulation of Lewy bodies (LB). Emerging evidences indicate that mitochondrial dysfunction might be a common cause but pathological insult through protein misfolding, aggregation, and accumulation leads to neuronal apoptosis. The observation supporting that expression of DJ-1, LLRK2, PARKIN, PINK1, and excessive excitotoxicity mediated by dysbalance between GABA and glutamate reduced mitochondrial functioning and increased neurotoxicity. Therefore, the present review summarizes the various pathological mechanisms and also explores the therapeutic strategies which could be useful to ameliorate movement disorder like Parkinsonism.

Keywords Parkinson disease · Substantia nigra pars compacta · Dopaminergic neurons · Neurotransmitters

Introduction

Parkinson's disease (PD) is the world's most common multifactorial neurodegenerative disorder, characterized by motor deficits associated with loss of dopaminergic neurons, neuroinflammation, and neurotransmitter alterations in substantia nigra pars compacta (SNpc) [1, 2]. The deficiency of dopamine and alteration in neurotransmitter levels further recognized to cause motor and non-motor deficits [2]. More than 10 million people agonized with PD worldwide and out of it approximately 60,000 Americans are diagnosed with PD each year with thousands of cases remain undetected [3]. Approximately, 4% of people are diagnosed with PD before the age of 50 and its prevalence increases with age [4]. PD primarily affects the median spiny neurons of the midbrain but further loss of dopaminergic neurons as well as aggregation of Lewy bodies' in SNpc altered normal physiological neuronal functioning. However, exact pathological mechanism blind dopaminergic neuronal death is still not completely understood. However, mitochondrial dysfunction, neuroinflammation, excitotoxicity, and abnormal protein aggregation are believed to be prevalent factors involved in the progression of PD.

Moreover, in PD, excitability of GABAergic neurons at dopaminergic D_2 receptor is enhanced, but reduced on D_1 receptor indicating dysbalance of direct and indirect pathways [5]. Further, loss of nigrostriatal neurons leads to difficulty in initiating movement or motor functions. As the disease progresses, the pathological components such as the Lewy bodies are more widespread in neocortex. Current therapy only provides symptomatic relief but fails to halt dopaminergic neuronal death. Advancing disease and extensive striatal dopamine loss result in increased motor complications as well as wearing-off phenomenon and off periods. During this period, bradykinesia and rigidity reappear that is an absence of on periods and the development of involuntary dyskinesia.

Alpha-synuclein gene upregulation initiates the formation of abnormal mutant alpha-synuclein protein, which

✉ Shamsher Singh
shamshersinghbajwa@gmail.com

[1] Neuroscience Division, Department of Pharmacology, Indo-Soviet Friendship College of Pharmacy, Moga, Punjab, India

aggregated in the form of Lewy bodies and neuritis, responsible for neurodegeneration and produces PD-like symptoms. On the other hand, mitochondrial dysfunction and oxidative stress leads to cellular dysfunction and death. Reduced mitochondrial activity due to high level of hydrogen peroxide, superoxide, and complex-I inhibitors dramatically increase the level of ROS that enhances oxidative stress and disturbs neuronal functioning. In PD, activation of microglia (due to toxin or injury) elevates neuroinflammation which leads to loss of neurons and altered neurotransmitter level. So, excessive glutamate discharge also potentiate neuronal excitability due to reduced GABAergic transmission. The present review cites various pathological mechanisms like alpha-synuclein accumulation, mitochondrial dysfunction, neuroinflammation, neurotransmission, and oxidative stress involved in PD pathogenesis.

Alpha (α)-synuclein mutation, their phosphorylation, and Parkinson's disease

The accumulation of α-synuclein and their pathological roles in PD is strongly highlighted from the previous years [6]. Normally, α-synuclein is a neuronal protein known to play several physiological roles in the human brain, heart, muscles, and other tissues, but extensive accumulation leads to neurotoxic insult. Alpha-synuclein is encoded by SNCA gene located in chromosome 4q22. and consisted of α, β, and γ synuclein with 127 to 140 amino acid in their structure.

The number of available evidences indicates the physiological role of α-synuclein, but excessive generation causes neurodegeneration, synaptic dysfunction, neurogenesis, and neuronal differentiation. Various genes known to be involved in the pathogenesis of PD includes autosomal dominant gene α-synuclein, 1rrk2, or vps35 and autosomal recessive gene PINK1, PARKIN, and DJ-1 [7]. The point mutation in the SNCA gene relatively gives birth to a neurological disorder like PD. Several mutations in SNCA at A53T, A30P, and E46K position are directly linked to the familial form of PD and α-synucleinopathies. SNCA duplication or triplication increases the overexpression of α-synuclein and causes autosomal dominant PD [8].

Thus, altered function of SNCA leads to intracellular inclusion of Lewy bodies, which is associated with the dysfunction of the olfactory system and produces non-motor symptoms. Therefore, α-synuclein gene seems to be important for the initiation and progression of PD. Normally, α-synuclein protein helps to regulate vesicle fusion and neurotransmitter release via its interaction with presynaptic SNARE (soluble NSF attachment protein receptor) complex. Transformation of α-synuclein to fibrillary and oligomeric forms is associated with neuronal toxicity. Recent studies have highlighted that mutation in α-synuclein inhibits lysosomal degradation by binding to LAMP2A (lysosome-associated membrane glycoprotein 2A) and blocking protein uptake [8].

Not only this, α-synuclein also reduced histone acetylation, altered gene expression and negative regulation of transcription of RNA polymerase II associated promoters [9, 10]. Some controversial reports show that α-synuclein prevents unsaturated lipid oxidation, but their moderate overexpression produces defect in synaptic vesicle without apparent toxicity. Further, the improper release of dopamine from the synapses is associated with accumulation of α-synuclein in PD. So, this decreased release of dopamine could be due to disruption of glycoprotein 2C in synaptic vesicles and SNARE complex mediating synaptic vesicle exocytosis [11]. HNE-α synuclein appears to be most toxic species for dopaminergic neurons that triggers the production of reactive oxygen species (ROS) leading to neuronal death [12]. Dopaminergic neurons of the ventral tier substantia nigra express L-type of Ca^{2+} channels and appeared to be more vulnerable toward excitotoxic insult [13].

Further, α-synuclein oligomers disturbed the Ca^{2+} homeostasis increase excitotoxicity in ventral tegmental area (VTA), and enhance their oligomerization (Fig. 4). Few evidences indicate that excessive release of endonucleases-G from mitochondrial permeability transition pore (MTP) increases nuclear translation of truncated α-synuclein and raises cytosolic Ca^{2+} level [8]. Recent advancement in molecular approaches pointed out the role of ubiquitin-proteasome system and autophagy pathway in α-synuclein aggregation.

Mitochondrial dysfunction and Parkinson's disease

Mitochondrion is the cellular powerhouse that supplies energy for regulating apoptosis and exerts a wide variety of cellular functions. Electron transport chain (ETC) is a vital component of energy production in mitochondria as ATP (adenosine 5′ triphosphate) initiates oxidative phosphorylation of many proteins and cellular compounds [14]. Mitochondria contain their own genome and replicate through binary fission by the process of continuous cycles of fusion and fission. Several studies reported that mitochondrial dysfunction plays a crucial role in both sporadic and familial forms of Parkinson's disease (PD). Likely, the mutation in mitochondrial gene bioenergetics altered their structural integrity and could be the causative function. Not only this, both fusion and fission reaction alter the size and morphology and impair the transcription and the mitochondrial respiration [15].

Neuronal cells are greatly dependent on optimal mitochondrial function like for synapse assembly and transmission of action potential. So, mitochondrial dysfunction contributes significantly to neuronal injury followed by neurodegenerative disorders, like Parkinson's disease (PD), Alzheimer's

disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [16, 17]. Mitochondrial respiratory complexes are redox protein consisted of multiple subunits that generate and maintain proton gradient across the inner mitochondrial membrane through coupling of electron transfer. These transfer of electrons during mitochondrial chain acts as a source of free radical like superoxide [18]. In normal physiology, free radicals are catabolized by enzymes or antioxidant scavenges like superoxide dismutase (SOD) and glutathione, but over production leads to neuronal damage.

Toxins and Parkinson's disease

The role of various toxins like MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydrodropyridine), rotenone, paraquat, pyridaben, trichloroethylene, and fenpyroximate is already well acknowledged from previous years [19]. These toxins by inhibiting mitochondrial complexes damage the dopaminergic neurons in rodents, results in PD-like symptoms (Fig. 3). Dopaminergic neurons are more sensitive to neurotoxic insult due to their structural similarity with dopamine [20]. Recent studies also confirmed the correlation of genetic mutations and increase prevalence of familial forms of PD such as Parkin, DJ-1, UCHL-1, LRRK2, PINK1 (PTEN-induced kinase1), NURR1, VPS35 (vacuolar protein sorting 35), and HtrA2 directly or indirectly implicated in familial Parkinson's disease (PD) [21].

An autosomal recessive form of PD known as juvenile Parkinsonism is caused by Parkin PINK1 (PARK6), whereas SNCA and DJ-1 are linked to autosomal dominant forms of PD. Parkin encodes to ubiquitin protease ligase called E, which regulates the substrate RTP801 and mediates neuronal necrosis in PD. Romani-Audeles et al. 2014, has proposed that one way to prevent neurodegeneration is by averting the accumulation of RTP801 protein levels. A small increase in RTP801 was found in parkin-knockout mice, but its minor accumulation contributed to motor and behavioral impairments. Mutations in PARK8-encoding LRRK2 and loss-of-function mutations in the PARKIN gene have been shown to cause accumulation of RTP801, which is responsible for neurodegeneration [22].

PARKIN

Parkin was firstly identified as a recessive gene thought to be associated with autosomal recessive juvenile Parkinsonism in a Japanese family, just 1 year after the discovery of SNCA (α-syn) [23]. Parkin transcribed ubiquitously and is present in the mitochondria, synaptic vesicles, endoplasmic reticulum, and Golgi apparatus. Parkin is the parkin gene product, a ring finger structure containing E3 ubiquitin ligase involved in ubiquitin proteasomal pathway [24]. Due to the excitotoxicity-mediated damage, Parkin became impaired via S-nitrosylation and results in accumulation of its substrates like Pael-R leading to the dopaminergic neuronal death. *PARK2* knockout mouse models have reduced mitochondrial respiratory electron transport chain functions and decreased antioxidant proteins. Moreover, mitochondrial complex I and IV mitochondrial activities in peripheral blood are reported to decreased in individuals due to mutations in *PARK2* [18].

PINK1

PINK1 (PTEN-induced putative kinase 1) is serine/threonine, encodes for PINK1 gene. Any homozygous mutation may result in loss of gene function and origin of autosomal recessive PD. PINK1 is also involved in mitochondrial quality control through mitophagy. PINK1 is localized to mitochondria and is revealed to protect against neuronal death during acute oxidative stress [25].

Oliveras and Salvas has reported that downregulation of PINK1 resulted in aggregation of α-synuclein that promotes oxidative damage. The toxicity of α-synuclein is sufficient to cause neurodegeneration in SNpc and mitochondrial dysfunction in the absence of the PINK1. In PD, balance between mitochondrial fission and fusion was affected due to downregulation of PINK1. Rojas reported that fission is favored when PINK1 is downregulated, and the number of cells possessing fragmented mitochondria increased in PINK1-absent cells when compared to cells with PINK1. Excessive accumulation of Ca^{2+} expression of Fis (protein) which altered the mitochondrial membrane potential promotes overproduction of ROS. Furthermore, PINK1 interacts with Parkin and regulates cell death [26].

The absence of PINK1 compromised with apoptotic cycle, which ultimately leads to death of dopaminergic neurons. Thus, absence of PINK1 is crucial for neurons because it prompts fission rather than fusion due to the significant decrease in Mfn2 and an increase in Fis1. Aging and mutations in PINK1 cause dysfunction of apoptotic pathway in mitochondria. The defect in complex I due to PINK1 deficiency leads to mitochondrial depolarization and increased sensitivity to apoptotic stress [23]. Even small amount of stress contributed to inhibiting PINK1 and downregulation of autophagy proteins such as Beclin and LC3.

DJ-1

DJ-1 is a multifunctional protein involved in several cellular functions, including transcriptional regulation, mitochondrial protection, antioxidative, and chaperone activator [27]. The DJ-1 gene is present throughout the body including intermembrane space and matrix of mitochondria to work against oxidative stress-induced cell death [24]. Mutations in DJ-1 gene (PARK7) cause autosomal recessive young-onset PD. During oxidative stress, pathogenic forms of DJ-1, such as

L166P and M26I, are relocated to the outer mitochondrial membrane which sensitizes cells to oxidative stress. DJ-1 completely binds to subunits of complex I and losses with integrity. [28].

LRRK2

Mutation in *LRRK2* (leucine-rich repeat kinase 2) gene is associated with an autosomal dominant form of PD. LRRK2 (leucine-rich repeat serine/threonine-protein kinase 2) found in the outer mitochondria membrane, nucleus, cytoplasmic membrane, and nucleus. Mutation in *LRRK2* is G2019S and this mutation results in mitochondrial fragmentation and reduced mitochondrial fusion resulting in oxidative stress [29]. Mutation in LRRK2 G2019S was reported to cause 5–8% of autosomal dominant PD and even 0.4–1.6% of sporadic PD patients the decrease membrane potential and ATP level in fibroblast harboring LRRK2 G2019S mutation, further leads to mitochondrial elongation in PD patients. The increased mitochondrial fission, mitochondrial ROS production, and DRP1 mitochondrial translocation due to inhibition of LRRK2 activity suggest the involvement of LRRK2 in the regulation of oxidative stress and mitochondrial dysfunction [30].

The balance between the fusion and fission for the cell survival and synaptic function is crucial to maintain. The regulation of mitochondrial fission and fusion is also influenced by PINKI and Parkin during pathological insult of PD. The targeting of DRP1 to the nerve terminal from mitochondria is important because disruption of mitochondrial fission can lead to death of dopaminergic neurons.

PGC-1α

PGC-1α (peroxisome proliferator-activated receptor gamma coactivator1-alpha) is a transcriptional co-regulator involved in mitochondrial biogenesis in the brain, liver, heart, adipose cell, and kidney. It regulates ETC-mediated oxidative phosphorylation, glucose and pyruvate metabolism, and Krebs cycles in cells. Recently, in neurodegenerative diseases, PGC-1α has emerged as a link between mitochondrial dysfunction and transcriptional dysregulation [31].In PD, PGC-1α appears to be exacerbated in substantia nigra as compared to normal aging due to reduced expression of transcription factor for mitochondrial biogenesis. PGC-1α gene is under-expressed in PD not only in dopaminergic neurons but also in non-neural tissue. In an adult mouse knockout model of PD, PGC-1α is essential for the survival of nigral dopamine neuronal [32]. Similarly, disruption in the pathway of energy metabolism in PD is apparent in PI3K/Akt signaling, and the mTOR regulatory network provides additional nutrient-responsive targets.

PGC-1α and Parkinson's disease

A physiological transcriptional repressor of PGC-1α is PARIS (parkin-interacting substrate) that normally undergoes ubiquitination in dopaminergic neurons [33]. Accumulation of PARIS is due to inactivation of Parkin which is found in striatum and hippocampus. In PD, reduction of PGC-1α mRNA expression and PGC-1α responsive genes (e.g., NRF-1 and ATP5B, a subunit of mitochondrial ATP synthase), in striatum and substantia nigra (SN) marked by increased PARIS protein and NRF-1 protein. These findings suggest that inactivation of Parkin in PD may be due to accumulation of PARIS and inhibition of PGC-1α expression. Phosphorylation of PARIS at S322 and 613 allowing Parkin to ubiquitinate PARIS prior to its clearance because PINK1 acts as a priming kinase [33]. The progressive and selective loss of dopamine neurons due to deletion of Parkin or overexpression of PARIS gene that can be reversed by PGC-1α or Parkin overexpression, and rescue dopaminergic neurons evidenced by experimental animal models.

Neuroinflammatory markers and Parkinson's disease

Neuroinflammation is a reactive response of CNS toward toxic substances which alter the neuronal homeostasis and give birth to various neurological disorders [34]. Neuroinflammation in PD occur alongside the loss of dopaminergic neurons and associated with altered microglia activity in of CNS and other parts. However, microglia and astrocytes particularly play key roles in the regulation of inflammatory responses. Genetic background, age or past experiences, and environmental factors are some keywords which collectively activate neuronal immunomodulatory cell and thus initiate complex neuroinflammatory pathways.

Recent studies reported the presence of activated microglia either inside substantia nigra (SN) and putamen of patients with a PD prognosis. Tumor necrosis factor (TNF-α) after microglia activation releases a variety of free radicals and activate various genes and proteins including iNOS and pro-inflammatory cytokines (IL-1β, IL-6, and α) [35]. The inflammatory response in the CNS is also linked with numerous processes such as aging, systemic infection, metabolic syndrome, and intrinsic CNS disease. Overexpression of the central immune system may compromise the generation of neurotrophic factors and cytotoxic factors from the microglia cell. IL-1β family of cytokines that is a pro-inflammatory molecule also stimulates toll-like receptors (TLRs), which may impair the clearance microglia. There are few findings that shows that disrupting *IRAK-4* (interleukin-1 receptor-associated kinase 4), an essential downstream kinase of TLRs and receptors

for IL-1β, moves microglia cells from a pro-inflammatory phenotype toward an anti-inflammatory phenotype [36].

Some endotoxin-like LPS (lipopolysaccharide) also induces systemic inflammatory response syndrome through TLR and its signal transduction membrane proteins which activate inflammatory cascades. TLR-mediated LPS binding initiates inflammatory process by activating the several signal transduction pathways including MAPK, PI3K/AKT, and mTOR, lead to NF-κB activation and promotes microglial phagocytosis and increases of cytokine release [37]. NF-κB protein is part of an inflammatory cascade that is activated outside the cell but after interacting with pro-inflammatory cytokines these mediators move to different tissue sites and cause tissue injury [38].

Microglia

Microglia are the CNS immune cells that cover 5–20% of the total glial cell population in the brain and are the foremost important cellular component contributing to neuroinflammation. Microglia are mostly activated in the presence of pathogens, abnormal stimulation, tissue damage, infection, neurotoxins, or injury [35]. Even in this case, they also attack healthy neurons either physically as by phagocytosis or by secreting apoptosis factor.

Activated phenotype of microglia cell includes $M_1$and M_2. The activation of M_1 phenotype stimulates PAMPS (pathogen-associated molecular patterns), DAMPS (damage-associated molecular patterns), LPS (bacterial lipopolysaccharide), amyloid-beta aggregation, and intermediately promote dopaminergic neuron damage. In PD models, M_1 phenotype microglia is activated by exogenous as well as endogenous stimuli. Similarly, M_2 phenotype microglia produces several anti-inflammatory cytokines including interleukins (IL-4, IL-13, and IL-10), glucocorticoids, and TGF-β (transforming growth factor) by antagonizing the M_1 phenotype [39].

Neuronal cells also produced several immunomodulators such as CX3CL1, CD200, CD47, CD22, CD95, and neural cell adhesion molecule (NCAM) which maintain the quiescent state of microglia under physiological conditions. Microglial activation and protection of DAnergic neuronal degeneration induced by neurotoxins is negatively regulated by CX3CL1-CX3CR1 signaling [40].

In animal model of PD, CX3CL1, or CX3CR1 deficiency results in increased neurotoxicity and cell death of dopaminergic neurons in SNpc as evidenced by lipopolysaccharide (LPS)-induced cell death [41]. Microglia activation toward M1 phenotype is due to misfolded proteins and environmental toxins in PD animal model [42] likewise, in rat model of PD activation of microglia exacerbates the degeneration of DA neurons by dysfunction of CD200-CD200R signaling [42].

In various neurological disorders, production of cytokines and other inflammatory mediators leads to microglial activation and thus promotse apoptotic cell death [43]. Microglia cells are characterized by the expression of distinct cell surface receptors like upregulated CD16 Fc receptors, CD32, CD86, CD64, IL-1β, IL-6, IL-12, IL-23, TNF-α, iNOS, and chemokines. However, microglia cells with anti-inflammatory phenotype display the upregulation of arginase-1 (Arg-1), mannose receptor (CD206), and chitinase 3-like 3 (Ym-1).

Astrocytes

Around 50% of glial cells are covered by astrocytes which are the most abundant and heterogeneous type [44]. Astrocytes contribute to synaptogenesis and dynamically modulate signal transmission and regulate neural and synaptic plasticity. They also provide trophic and metabolic support and are involved in controlling the cellular environment by regulating pH and modulating oxidative stress, blood flow, and ion homeostasis [45]. The neuronal cell components microglial astrocytes are supportive for neuronal cell because they respond to reactive astrogliosis and this process is a reliable mechanism of tissue damage.

In PD, astrocytes are majorly involved in regulating neuroinflammatory process that are well demonstrated in several studies. Astrocytes rapidly act in response to pathological condition and undergo morphological and functioning changes, after detecting a harmful signal during injury. In vitro and in vivo, studies showed that astrocytes mediate pro-inflammatory cytokines in response to inflammatory stimuli LPS [46].Various animal models of PD, show that reactive astrogliosis characterized by increased expression of GFAP (glial fibrillary acidic protein) hypertrophy of neuronal cell body and neuronal cell body extensions. Responses of activated astrocytes are recognized by astrocytes reactivity marker such as change in their morphology and increased expression of glial fibrillary acidic protein (GFAP). NF-κB is activated due to activation of astrocytes which control the secretions of chemokines, adhesion molecules, and thus supports peripheral lymphocyte infiltration that ultimately leads to neurodegeneration [43].

Toll-like receptors

Initial detection of microbes emerges innate immune system via PRRs (germline-encoded pattern-recognition receptors) and referred as PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecules patterns) [47]. Innate immune responses is initiated by type I interferon (IFN), inflammatory cytokines, and other mediators through downstream signaling of PRRs. It has several distinct classes including toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), AIM2-like receptors (ALRs), and intracellular DNA sensors such as cGAS [37]. Among these, TLRs

were the first to be identified, and consisted of 10 family members (TLR1–TLR10) in humans and 12 (TLR1–TLR9, TLR11–TLR13) in animals.

Toll-like receptors (TLRs) are localized in peripheral blood leukocytes, in glial cells, and in neurons where they mediate inflammation particularly in the case of PD. The expression of TLR2 in postmortem brain tissue of PD patients is high as compared to controls normal individual [48]. During the disease progression, the expression of α-synuclein-positive Lewy bodies and neuronal TLR2 is significantly increased [49]. For initiating the inflammatory response in PD, several receptors are responsible where toll-like receptors are one to be prominently expressed. TLR1–9 is located in CNS neurons out of ten TLRs (TLR1–10) which are currently identified in humans. In PD, upregulation of TLRs expression (especially TLR2 and TLR4) and their related signaling proteins play a key role in neuroinflammation. Similarly, TLR-2 receptors are responsible for microglia activation and release toxic factors which progress neuronal insult [39] Fig. 1.

Various clinical evidences indicated the increases in PD; clinically, expression of TLR2 has been elevated, indeed MPTP administration in mice also augments expression of TLR-4. Activation of NF-kB and other pro-inflammatory pathways including induction of inflammatory genes and iNOS cytokines are associated to stimulate of TLR-4 receptors [50]. The number of reports has shown that neuroinflammation in the SNPc and striatum region is due to stimulation TIR domain contain adapter-inducing interferon-β (TRIF)-dependent pathway that activates type I IFNs by TLR-4 in PD patients. On the other hand, involvement of TLR-4 and TLR2 in PD might be bi-dimensional increase microglial associated neurotoxic ex. α-synuclein clearances or neuroprotected.

Pro-inflammatory cytokines and Parkinson's disease

Cytokines are the large proteins (15–25 kDa) that act as signaling molecules during inflammation, infection, and cellular activities such as growth and repair of damaged tissues. In the brain, cytokines play an important role through regulation of leukocyte trafficking and recruitment of other inflammatory proteins [51].

Cytokines act as signal molecule between the immune cells and are divided into pro-inflammatory mediator such as IL-1β, IL-6, and TNF-α and anti-inflammatory mediators like IL-4 and IL-10 [52]. In PD, elevation of pro-inflammatory cytokines levels, adhesion molecules, and expression of their receptors has been reported [53]. Pro-inflammatory cytokines damage to blood–brain barrier (BBB), upregulate adhesion molecule expression, and stimulate diffusion of toxic substances [54]. In the progression of neurodegenerative diseases such as PD and AD, IL-1β plays a crucial role in neuroinflammation [55].

Role of GABA, glutamate, and Parkinson's disease

Neurotransmitters are the endogenous chemical messengers that permit signal transmission across a chemical synapse-like neuromuscular junction from one nerve cell to another

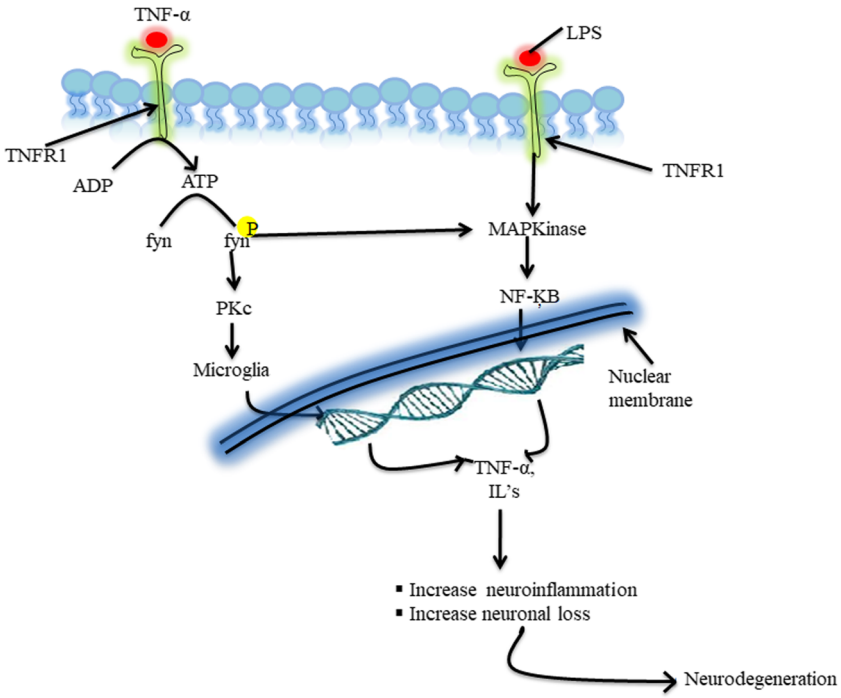

Fig. 1 Inflammatory cascade and neurodegeneration

on muscle cell and gland cells. GABAergic and glutaminergic neurons help in neural network signaling in basal ganglia, dopaminergic neurons, and muscarinic cholinergic neurons. The excitatory neurotransmitter glutamate also regulates memory, synaptic plasticity, and neuronal development. However, excessive release of glutamate excitotoxicity leads to neuronal loss [56].

The imbalance between glutaminergic and GABAergic neurons cause motor dysfunction in PD (Fig. 2).Glutamate in the central nervous system (CNS) regulates neuronal development, memory, and synaptic plasticity. Glutamate reuptake takes place via EAATs (excitatory amino acid transporters) in synaptic cleft [57]. In PD, death of dopaminergic neurons occurs to enhance glutamate-dependent excitotoxicity which leads to cognitive and motor impairment disorders. Glutamate prompts intracellular Ca^{2+} overload, reactive oxygen species, mitochondrial dysfunction, and osmotic swelling of nerve cells. GABA is an inhibitory neurotransmitter that comprises about 95% of striatum and 99% entire basal ganglia [23].

Role of dopamine and toxic metabolites

Dopamine is a neurotransmitter known to play various biological functions like motor coordination, cognition, emotions, and memory. Dopamine is produced and released by SNpc neurons which potentiate dopaminergic neurons and control motor movements. Therefore, patients with PD who have deficiency of dopamine show severe motor symptoms, leading to difficulties in performing voluntary movements.

"Dopamine deficiency syndrome" is a common name for PD which arises in dorsal striatum due to loss of dopaminergic neurons in SNpc. Inhibition of mitochondrial respiratory system increases dopamine oxidization reported in both in vivo and in vitro analysis [58]. Several studies suggested that metabolite of dopamine-like DOPAL to be more toxic to dopaminergic neurons could be one of the key factor for PD pathogenesis. Studies have demonstrated that proteasome activity is directly inhibited by DA and its oxidative metabolites such as H_2O_2, DA quinones, and aminochrome (AM). The ability of DA to get auto-oxidized to an orthoquinone and generate superoxide anion has been implicated as an endogenous neurotoxicant.

Oxidative stress, ca^{2+} dysregulation, and Parkinson's disease

Oxidative stress is one of the chief contributing factor for neurodegenerative diseases that occurs due to imbalance of redox potential of cell [59]. Oxidative stress and Ca^{2+} deregulation cooperatively promote synuclein aggregation and mutate α-synuclein which cause neuronal cell death [60].

Oxidation of dopamine is increased due to early compensatory changes in dopamine turnover in Parkinson's disease (PD). In addition to dopamine oxidation, the dopaminergic neurons in SNpc are known to experience increased oxidative stress from their autonomous pacemaker mechanism, which utilizes L-type Ca^{2+} channels resulting in intracellular Ca^{2+} oscillations [61]. These L-type Ca^{2+} channels control the repeated and persistent entry of Ca^{2+} into dopaminergic cells and ATP-dependent pumps are required to restore the Ca^{2+} concentrations. These channels are also seen in the other regions of the brain which are selectively involved in PD such as the dorsal motor nucleus of the vagus, the serotonergic neurons of the raphe nucleic, and the neurons of the locus coeruleus.

In the mitochondria, high level of oxidative stress is due to overstimulation of these L-type channels. Calcium

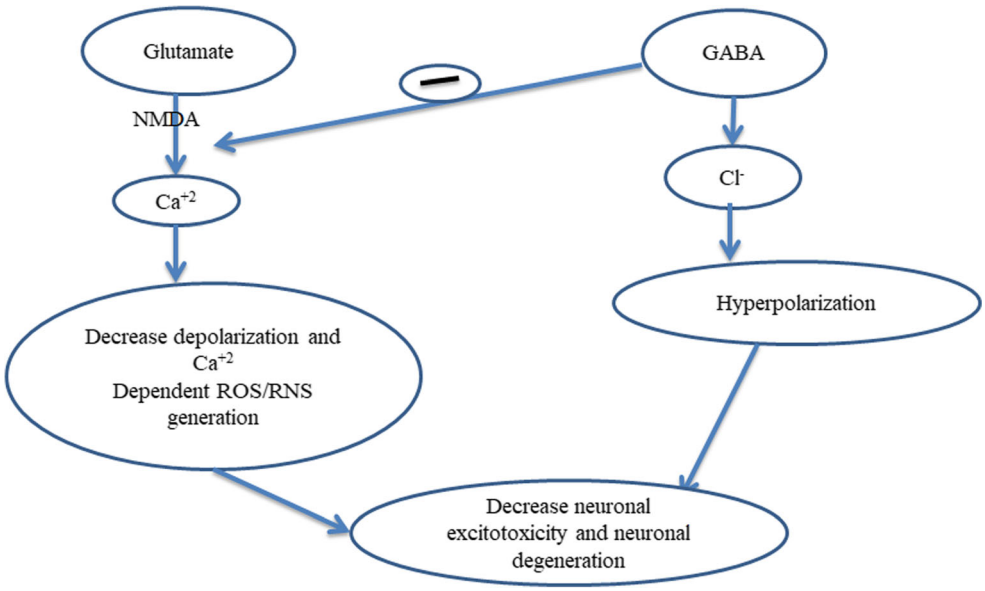

Fig. 2 Neurotransmitters dysbalance and neurodegeneration

homeostasis is regulated by several calcium channels. In brain disease, neurotoxic effects of Ca^{2+} that have been extensively reported in clinical and experimental studies reveal the diversive role of Ca^{2+}homeostasis in the PD pathogenesis [62].SNpc neurons might be subjected to excessive glutamate signaling by projections from overactive neurons in PD patients. Glutamate receptor blockers facilitated attenuation of MPTP toxicity which has suggested the Ca^{2+} dysregulation as a key driver of SNpc vulnerability in pathology of PD (Fig. 3).

Future perspectives and treatment strategies

Nowadays, the management of Parkinson's disease is a current challenge and current therapies are not capable to slow down or prevent the disease progression [63]. In proteins degradation, both ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathways (ALP) are the most important pathways. Wenbo et al. have reported that treatment with both ginkgolide K (GK) and ginkgolide B (GB) reduced cell death and enhanced cell proliferation results in overexpression of A53T mutant α-syn. Moreover, clearance of A53T α-syn was promoted by GK but not by GB, and eliminated by 3-methyladenine autophagy inhibitor [64].

Secondly, treatment with GK inhibits the p-NF-kB/p65 and induces phosphoinositide 3-kinase (PI3K), brain-derived neurotrophic factor (BDNF), postsynaptic density protein 95 (PSD-95), and did not affect the neural precursor cell expressed developmentally downregulated protein 4 (NEDD4). GK promotes the clearance of α-syn, reduced neuronal cell death, and triggered complex crosstalk between different signaling pathways along with GB administration [64].

In PNAS, Perni et al. reported that squalamine has a specific effect against α-synuclein aggregation and reveals that squalamine reduced α-synuclein–mediated aggregation by acting on α-synuclein oligomers and their uptake into neurons by blocking their binding to neuronal membranes (Fig. 4). An important strategy in disease intervention is modulation of α-synuclein membrane binding, but while conserving its physiological functions there is a need to inhibit α-synuclein pathological activities [65].

Triptolide (T10) is isolated from a traditional Chinese herb which possesses potent neuroprotective properties in PD models. Guanzheng et al. have reported that T10 in neuronal cells is a potent autophagy inducer, which promotes clearance of various forms of α-synuclein in neuronal cells. According to his study, the level of pathogenic proteins in neurons is reduced, promising that T10 is to treat PD and other neurodegenerative disorders [66].

The production and release of cytotoxic molecules such as pro-inflammatory cytokines and NO can be reduced by cannabinoids. Cannabinoids also modify microglial cell

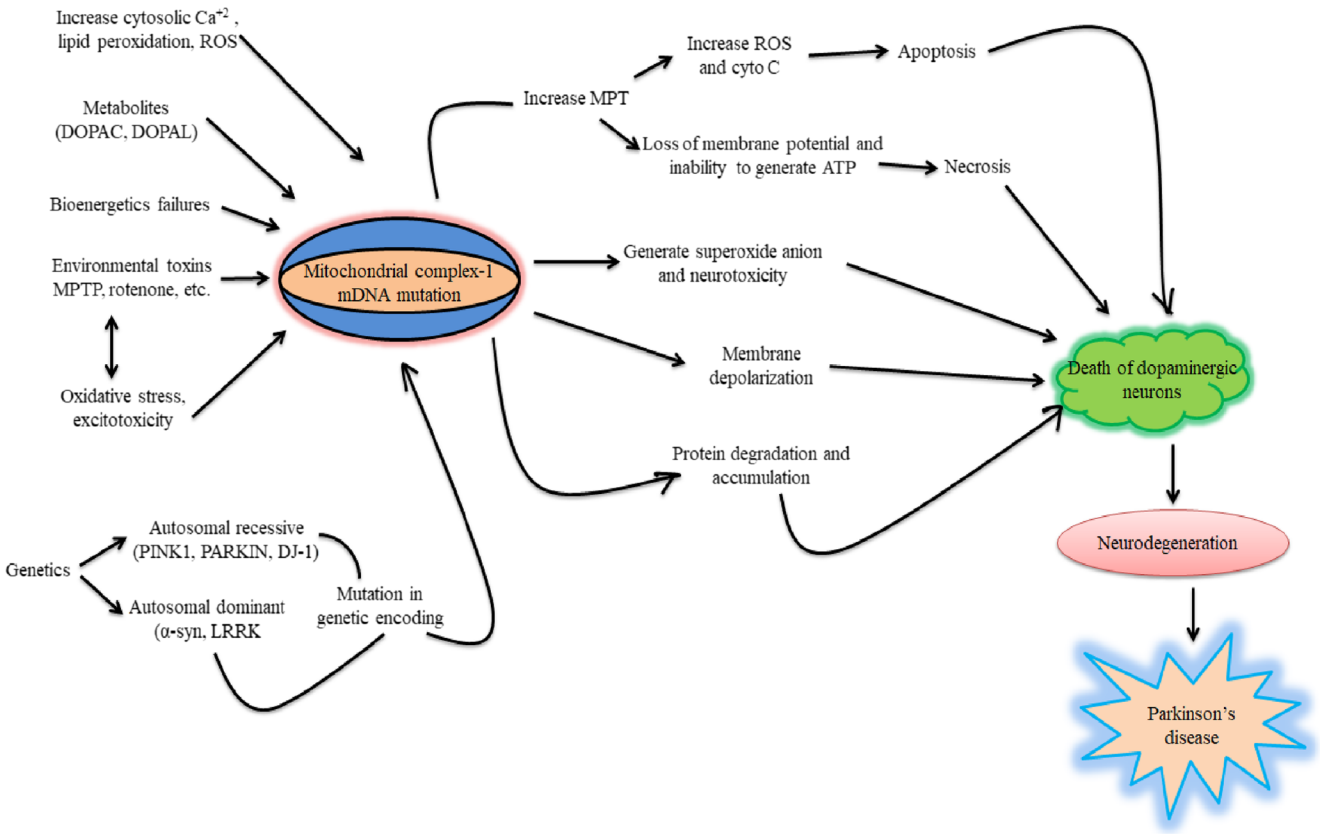

Fig. 3 Mitochondrial dysfunctioning and gene mutation associated neurodegeneration

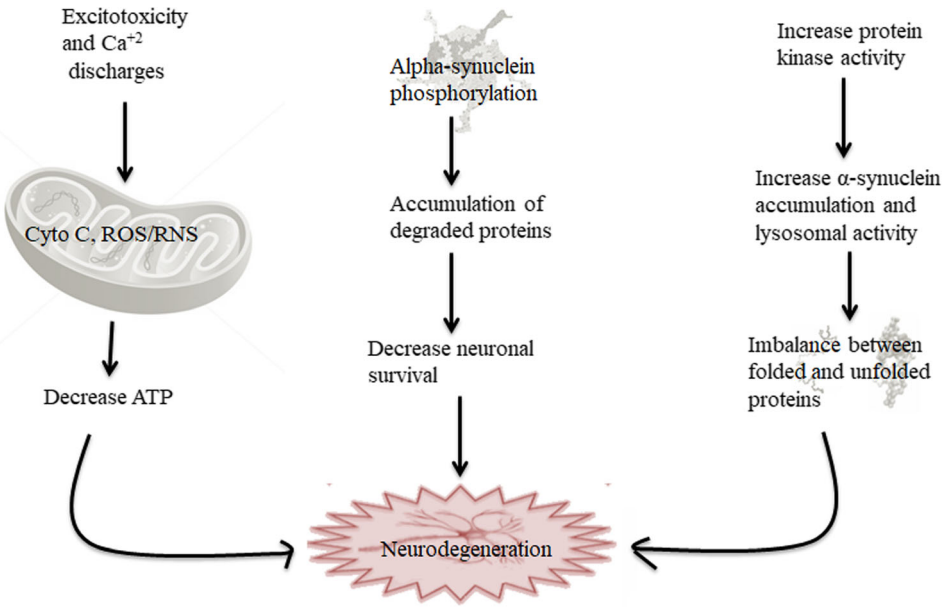

Fig. 4 Alpha synuclein aggregation and neurodegeneration

migration which results in resolving neuroinflammation and limiting neurodegeneration process. Therefore, in preclinical studies cannabinoids are actively pursued in many mental and neurodegenerative disorders with great success [67].

Mito-apocynin (Mito-Apo) is a derivative of apocynin, which is newly synthesized for targeting mitochondria, glial-mediated inflammation, protects against oxidative damage, and nigrostriatal neurodegeneration PD models. Mito-Apo have excellent brain bioavailability, and it also exhibits neuroprotective effects in both pre-clinical and cellular PD models by attenuating neuroinflammatory process and oxidative damage [68].

Quercetin and rutin flavanoids have neuroprotective effects against neurodegenerative disorders. Quercetin also enhanced CREB phosphorylation and expression of the CREB target gene BDNF. Quercetin augmented mitochondrial biogenesis by increased mitochondrial bioenergetics capacity and protected MN9D cells against 6-OHDA-induced neurotoxicity [69]. Oral administration of quercetin significantly reversed behavioral deficits, striatal dopamine depletion, and TH neuronal cell loss in MitoPark mice. Luo et al., demonstrate that quercetin activates PKD1-Akt cell survival signaling axis and suggest further exploration of quercetin as a promising neuroprotective agent for treating PD may offer clinical benefits [69].

Pramipexole is a new non-ergotamine dopamine receptor agonist, which has an ability to ease the symptoms of PD by stimulating D2 receptor and can improve the state of patient's depression, while dropping the amount of dopamine usage. During the course of PD treatment dose, of levodopa and occurrence of dyskinesia can reduce by pramipexole. It has lighter adverse drug reaction than levodopa because it has no toxic metabolites, and will not compete with other substances to absorb and transfer into the brain [70].

Selegiline and rosagiline, MAO-B inhibitors can be used as monotherapy or adjuvant therapy to levodopa in Parkinson's disease (PD). Selegiline and rosagiline had equal efficacy in PD patients for controlling motor symptoms [71].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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