Molecular mechanisms of melatonin-induced alleviation of synaptic dysfunction and neuroinflammation in Parkinson's disease: a review

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Abstract. – This review focuses on melatonin's role in advancing Parkinson's disease (PD) pathogenesis by inhibiting synaptic dysfunction and neuroinflammation. The early pathological changes in PD, caused by *SNCA/PARK1* and *LRRK2/PARK8*-mediated synaptic vesicle endocytosis during the early pathogenesis of PD, are briefly reviewed. The pathological changes related to synaptic plasticity and dendrites caused by synaptic dysfunction in neurotoxin 6-hydroxydopamine (6-OHDA) and 1-methl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP)-induced PD models are also discussed. The molecular mechanisms of pathological changes in PD, caused by the activation of microglia, astrocytes, and inflammatory vesicles, are discussed. The effectiveness of melatonin (MLT) in the restoration of dopaminergic neurons in the substantia nigra (SNc) has been established. MLT can upregulate dendritic numbers and restore synaptic plasticity by inhibiting alpha-synuclein aggregation and neurotoxicity. These functions of MLT improve sleep patterns in PD patients and suppresses synaptic dysfunction by inhibiting the overactivation of the PKA/CREB/BDNF signaling pathway and reactive oxygen species (ROS) production. MLT can maintain the typical transport and release of neurotransmitters. MLT also reduces neuroinflammation by promoting microglia 2 (M2) polarization, which reduces the expression of inflammatory cytokines. Additionally, MLT stimulates the activation of the retinoic acid receptor-related orphan receptor α (RORα) ligand and inhibits the activation of the Recombinant Sirtuin 1 (SIRT1)-dependent pathway, the NLR family pyridine structure domain 3 (NLRP3) inflammasome. By integrating the latest advances in synaptic dysfunction and neuroinflammation-related PD, researchers can develop clinical interventions for treating PD and further explore the pathological hallmarks of prodromal PD.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder impacting more than 10 million people worldwide[1]. It is the second most prevalent neurodegenerative condition after Alzheimer's disease (AD). According to projections, the number of people living with PD will double by 2050[2]. PD is a neurological disorder characterized by a gradual decline in dopaminergic neurons (DA). As one of the pathological manifestations of PD, the depletion of dopaminergic neurons in the substantia nigra pars compacta (SNpc) results in the gradual deterioration of the nigrostriatal dopaminergic pathway. It can produce various symptoms in PD patients, including motor and non-motor symptoms (NMS). The most predominant motor symptoms of PD are resting tremors, myotonia, and bradykinesia. The symptoms of NMS are associated with depression, anxiety, sleep disorders, fatigue, pain, cognitive and autonomic dysfunction, emotional apathy, and anxiety. The NMS typically precedes motor symptoms and can remain quiescent for over 20 years before becoming manifest as the disease advances[3,4]. Recent studies[5-7] found several factors involved in the pathophysiology of DA neuronal loss in PD, including synaptic dysfunction, neuroinflammation, mitochondrial dysfunction, an imbalance in the protein volume regulatory system, and alpha-synuclein (α-syn) accumulation. Although treatments such as dopamine replacement therapy and deep brain stimulation

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can improve motor symptoms in PD patients, the disease cannot progress due to the loss of dopamine neurons[8]. As the population ages and demographics shift, PD therapy focuses on symptom management rather than addressing underlying causes. Although the number of people suffering from PD is relatively small compared to other diseases, research on interventions for its onset is underdeveloped. Most studies[9-11] are focused on the pathogenesis of DA neuronal death and alleviating the corresponding motor symptoms of PD. Few reports have addressed interventions for the PD's latent phase or early pathological markers. As a result, the early detection of pathology indications of PD is a massive medical concern that must be addressed.

Monoamine-oxidase type B-inhibitors (MAOB-I), dopamine receptor agonists (DR), Levodopa (L-dopa), and catechol-O-methyltransferase (COMT) inhibitors are the most widely applied medicines for the treatment of PD. These medications can provide PD patients with limited relief from symptoms during different stages of the disease but cannot cure the disease. Given the intricate pathophysiology and etiology of PD, a "single-target" approach is inadequate in addressing its multifactorial nature. All the different treatment methods for neurodegenerative diseases have their benefits and drawbacks. However, none of these treatments can stop the disease from progressing without causing adverse effects, such as low blood pressure and liver damage[12-15]. Finding a medication with low levels of adverse effects and high levels of efficacy is a critical goal in treating PD, as it can help reduce the disease's incidence and improve its early pathological features.

Melatonin (MLT), a naturally occurring hormone, is released by the pineal gland. MLT hormone quickly penetrates the blood-brain barrier and is generated mainly in the mitochondria. In addition, MLT has significant redox signaling effects. MLT levels decrease significantly with age, accompanied by a deterioration of several circadian rhythms, including changes in sleep/wake cycles, temperature, and hormone production[16]. The primary activities of MLT include regulating the sleep-wake cycle, scavenging free radicals, and inhibiting tumor growth. It also has various physiological effects, such as improving cognitive function, supporting brain regeneration, and protecting cells from death. MLT and its synthetic counterparts exhibit various antioxidant properties, which can protect against several re-active oxygen species (ROS) and RNS-mediated oxidative damages to cellular macromolecules, such as lipids, proteins, and DNA[17-21].

MLT-mediated redox regulation can scavenge ROS directly through the electron-rich indole ring or achieve antioxidant effects by mediating enzymatic and non-enzymatic antioxidant systems[22]. MLT can promote the production of ROS through interactions with calmodulin and mitochondrial complex III or the mitochondrial transition pore. MLT thus has both antioxidant and prooxidant properties, making it a complex chemical. MLT can scavenge free radicals and boost the levels of vitamins in the body[23,24].

MLT is involved in cellular glutathione (GSH) depletion, which would otherwise protect macromolecules from oxidative damage. This pro-oxidative mechanism is associated with the toxic profile of indoleamine. Meanwhile, MLT is oxidized by free radicals, thereby generating MLT radicals that can then interact with reduced GSH cyclically[25]. Peroxisome proliferator-activated receptor coactivator1 (PGC-1) is a key regulator of mitochondrial function and protects cells from oxidative stress. MLT administration leads to an increase in mitochondrial oxidative phosphorylation rate *via* PGC-1-dependent mechanisms. In addition, MLT promotes the expression of PGC-1 and Recombinant Sirtuin 1 (SIRT1), which contribute to mitochondrial fusion and inhibit mitochondrial division. As a result, MLT effectively prevents mitochondrial dysfunction[26]. The administration of MLT has been found to confer neuroprotection against oxidative stress-induced apoptosis in a rat model of PD induced by homocysteine. This counteracting of oxidative stress is involved in a collaborative effort, such as enhancing mitochondrial complex I activity, eliminating hydroxyl radicals, replenishing GSH levels, and elevating the activity of antioxidant enzymes. MLT inhibited the cycle of oxidative stress and mitochondrial fragmentation in the 1-methyl-4-phenylpyridinium ion (MPP+)-induced PD model and also played a role in reducing the symptoms of PD[17]. An inadequate supply of MLT can predispose to the development of cardiovascular disease and raise the risk of metabolic syndrome by generating dyslipidemia[27]. MLT administration leads to a reduction in erythrocyte membrane oxidation deformities. Furthermore, MLT inhibits hemoglobin degradation and reduces bilirubin production. MLT induces heme oxygenase-1 (HO-1) activity through oxidative fission of hemoglo-

bin, releasing biliverdin, carbon monoxide, and ferrous iron[28-30]. MLT has been shown to reduce levels of cyclooxygenase- 2 (COX-2) activity, nitric oxide metabolites, and lipid peroxidation in patients with PD[31]. Mitochondria takes up MLT *via* the transport proteins peptide transporter-1 (PEPT1) and peptide transporter-2 (PEPT2) and repair damage to complexes I and IV caused by oxidative stress, eventually reducing the likelihood of caspase-mediated apoptosis[32]. MLT has been shown to decrease the effects of oxidative stress and boost anti-apoptotic and antioxidant capability in dopamine neurons by upregulating molecular expression of the heat shock protein 70 (HSF1/HSP70) pathway in protein quality control systems[17].

A decade of research[33-35] has revealed that people with PD have lower MLT levels linked to the severity of the disease. Given the role of MLT-associated antioxidant activity in neurological illnesses, MLT can sustain synaptic function and act against neuroinflammation early in the etiology of PD. In this article, we review the mechanisms by which MLT modulates synaptic dysfunction and neuroinflammation in the early pathogenesis of PD. This review provides insight into the potential of MLT as a safe and effective treatment for the early prevention of PD and its essential role in movement or NMS improvement.

MLT Regulates Synaptic Dysfunction in PD

Synaptic dysfunction occurs before the loss of dopamine neurons during PD etiology[36]. The elucidation of the molecular mechanisms underlying synaptic dysfunction in PD is meaningful for developing early diagnostic and therapeutic strategies for PD. Synapses are classified according to their function as either presynaptic or postsynaptic. The mechanisms that underlie presynaptic function include synaptic vesicle endocytosis (SVE) and synaptic transmitter release. Synaptic vesicles (SV) travel locally *via* SVE to maintain neurotransmission and synaptic structural integrity, both necessary for dopamine restoration in the nigrostriatal pathway[37]. The role of presynaptic dysfunction in the pathological process of PD has been given more attention in studies[38,39] on synaptic dysfunction and PD etiology. Synaptic vesicle transport pathway disruptions may lead to synaptic dysfunction and injury to SVEs, which could interfere with dopaminergic neuron function and increase neuronal degeneration[36,38,40,41]. Synaptic dysfunction has been implicated in other neurological disorders, such as depression and AD, but its role in PD has been less extensively studied[42,43].

Mutations of Autosomal Dominant Genes in PD

The most common autosomal dominant mutations in familial PD are mutations in the *SNCA/PARK1* (encoding alpha-synuclein) and *LRRK2/PARK8* [encoding leucine-rich repeat kinase 2 (LRRK2)][44]. The *SNCA/PARK1* gene encodes a short protein of 140 amino acids that is diffusely expressed in the brain and mainly localized at the cellular level in the presynaptic terminal. Alpha-synuclein is a protein found in Lewy bodies (LB), a hallmark of PD pathogenesis. The early pathology of PD does not appear to include cytopathological changes, based on the finding that the number of axonal Lewy neurons initially exceeds that of LBS[45,46].

The most common dominant genetic mutations at the *SNCA/PARK1* gene locus are A53T, A30P, and E46K. The extent of α-syn overexpression is connected to the seriousness of PD. Individuals who have three mutations in *SNCA* will develop early-onset, severe PD[47]. The study on the striatum of A53T-α-syn mutant mice revealed that while young transgenic mice exhibited normal striatal DA levels, aged mutant animals had aberrant striatal DA signaling and reduced long-term depression (LTD). Even though DA supplementation or L-dopa therapy may be successful, they cannot restore impaired synaptic plasticity[48]. In the alpha-synuclein-overexpressing mouse model, the impairment of long-term potentiation (LTP) is restricted to striatal cholinergic interneurons (ChIs), not medium spiny neurons (MSIs). The direct interaction of alpha-synuclein with the GluN2D subunit, which expresses the N-Methyl D-Aspartate (NMDA) receptor in ChIs, causes loss of LTP in these cells. The interaction between the two leads to striatal cholinergic dysfunction and decreased striatal DA levels[49].

α-syn influences synaptic plasticity and regulates synaptic function by influencing synaptic vesicle cell fusion. The overexpression of α-synuclein with A53T or E46K mutations inhibits cell membrane fusion in hippocampus cells, reducing

cell membrane function. Genetic variations in regulatory elements that affect *SNCA* expression may contribute to an individual's susceptibility to PD[50,51]. Recent studies[44,52,53] have found that neurons can release small amounts of α-synuclein protein into the extracellular space. α-syn can be released under normal physiological conditions and in response to various stressors, such as mitochondrial dysfunction, protein misfolding, and lysosomal dysfunction. The effects of α-syn on neurotransmission and vesicle organization have been demonstrated in transgenic mouse models. These models show that increased α-syn causes significant damage to dopaminergic neurons due to reduced DA release and degradation of striatal physiology. These changes in the nigrostriatal pathway lead to changes in dopaminergic neurotransmission[54,55]. Therefore, the early stages of PD are associated with neurophysiological changes that impact synaptic neurotransmission. The *SNCA/PARK1* gene mutations disrupt the presynaptic membrane, SV transport, and endocytic recycling, leading to neuronal dysfunction before cell death. Thus, identifying pathogenic synaptic modifications before the onset of motor symptoms and intervening in such changes may provide a new theoretical basis for preventing and treating PD.

LRRK2 gene mutations have been demonstrated to be common causes of familial and sporadic forms of PD. The Guanosine triphosphate (GTP) kinase activity of *LRRK2* affects various cellular functions, including neurotransmission, endocytosis, autophagy pathways, and inflammatory responses[56]. More than 20 mutations have been reported to be connected with *LRRK2*. However, only six altered genes have been recognized as pathogenic. The most frequently associated mutation is glycine substitution for serine at position 2019 (G2019S)[57]. Pathological alterations in PD patients with *LRRK2* mutations include nigrostriatal degeneration, α-syn aggregation, general ubiquitin or tau body loss, and other synucleinopathies. These findings indicate that LRRK2 may function upstream of the protein aggregation pathway[49-51,58-60]. Furthermore, LRRK2 expression is moderate to high in dopaminergic neurons of the striatum and substantia nigra pars compacta, as well as in cortical areas associated with PD-related cognitive impairment in the cerebral cortex and pyramidal neurons of the hippocampus[61]. LRRK2 is primarily linked with mitochondria, the endoplasmic reticulum, and various vesicular structures, including SVs[62].

The mechanisms of SV transport include regulating SV migration, activating SVs associated with Ca^{2+}-induced cytokinesis, breaking down the N soluble-ethylmaleimide-sensitive fusion (NSF) protein attachment protein receptor complex, and endocytosis/recycling SVs[63]. The proteins that are responsible for inducing the key components for proper SV transport are the NSF, the articulation complex (Adaptor protein 2, AP-2), a synaptic vesicle protein 2A (SV2A), the synaptic fusion protein 1, kinesin 1, reticulo plasmin and Rab5b, and actin[40]. Given our current understanding of its structure and function, LRRK2 may be involved in synaptic dysfunction through its effects on proteins and SV transport.

SV mobility is regulated by the LRRK2 kinase, which affects actin stability and phosphorylation/dephosphorylation of synapsin 1A. This, in turn, modulates SV attachment to actin filaments. LRRK2 has been shown to regulate SV mobility, connection with actin filaments, and blockage of SV flow in cortical neurons[40]. LRRK2 has been shown to promote Ca^{2+} exocytosis and interaction with the protein SV2A, essential for cellular exocytosis and cytokinesis. The binding of SV2A to synaptic proteins is inhibited by Ca^{2+} and facilitated by the phosphorylation of SV2A by LRRK2. This phosphorylation increases the affinity of SV2A for synaptic binding proteins, which leads to increased fusion of the presynaptic membrane with SV[64]. During the process of soluble NSF attachment protein receptors (SNARE) complex disintegration, LRRK2 interacts with NSF, a key protein molecule responsible for SNARE complex disassembly. The phosphorylation of NSF can inhibit its ability to associate with SNAP (soluble NSF attachment protein), a protein required to disassemble SNARE complexes. LRRK2 can therefore control the catabolism and polymerization of SNARE complexes by altering the NSF phosphorylation state[65]. LRRK2 interacts with dynamin-1, AP-2, lacticin, and Rab5 to control endocytosis/recycling of SVs, accomplished by phosphorylation/ dephosphorylation[66] (Figure 1).

Sleep disorders are a common symptom of PD-related NMS. Sleep plays an important role in restoring energy metabolism in the brain. Sleep disorders can increase energy consumption and worsen metabolic problems in PD patients, making secondary damage more likely[67]. Although the manifestations of sleep problems vary, sleep fragmentation is a prominent feature in PD patients, and transgenic Drosophila expressing hLRRK2 recapitulates the sleep symptoms associat-
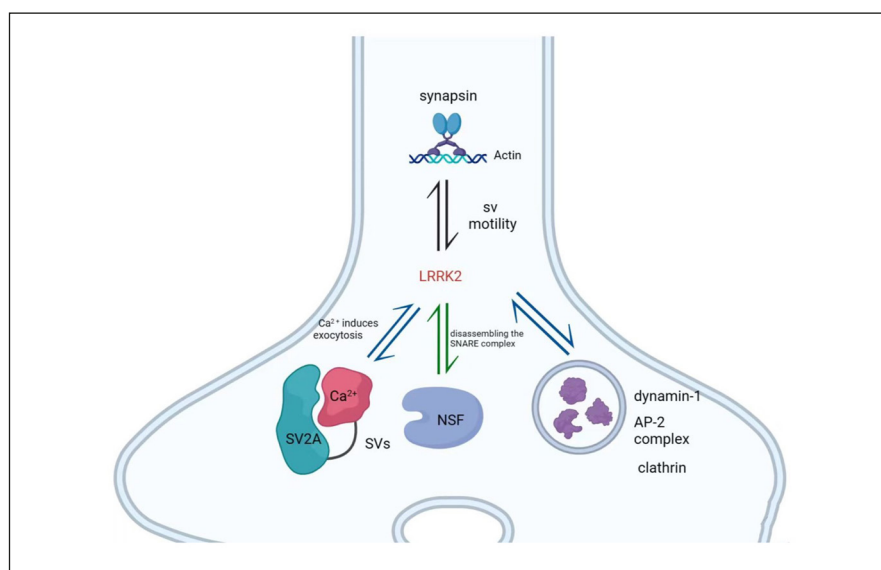
Figure 1. Effects of LRRK2 on vesicle trafficking at the presynaptic location. The Figure illustrates four steps of SV trafficking where LRRK2 may play a role: (1) SV motility; (2) priming of SVs to be competent for Ca^{2+}-evoked exocytosis; (3) disassembling the SNARE complex; and (4) endocytosis/recycling of SV. (1) Actin and synapsin are two proteins involved in the motility of SVs; in particular, synapsin tethers SVs to actin filaments, and this function is finely regulated by synapsin phosphorylation/dephosphorylation. LRRK2 kinase activity might modulate the motility of SV acting on these two proteins. (2) LRRK2 interacts with SV2A, which renders SVs competent to Ca^{2+}-triggered release. Since phosphorylation of SV2A increases its binding to synaptotagmin, an SV integral protein that acts as a Ca^{2+} sensor, LRRK2 kinase activity may modulate SV Ca-evoked release. (3) NSF is the protein implicated in disassembling the SNARE complex, and it has been characterized as an LRRK2 interactor. Hypothetically, LRRK2 could affect the disassembling of the complex by phosphorylating NSF. (4) LRRK2 is implicated in SV recycling, as indicated by defects in several LRRK2 models. LRRK2 has been reported to interact with dynamin-1, AP-2 complex, clathrin, and Rab5. t-snare, target SNARE; v-snare, vesicle SNARE.

ed with clinical PD. A study of PD sleep disorders and synaptic dysfunction found that hLRRK2 disrupts normal sleep patterns in Drosophila by increasing arousal during sleep and decreasing total sleep time. Electrophysiological recordings of Kenyon cells (KCs) suggest that hLRRK may reduce excitatory postsynaptic potentials (EPSPs) and microexcitatory postsynaptic currents (mE-PSCs). Nevertheless, the amplitude of mEPSCs does not appear to be impacted by the reduction in frequency. The amplitude of mEPSCs indicates the postsynaptic function, while the frequency of mEPSCs indicates the presynaptic function. The mEPSC is the current produced at the cell surface when a single vesicle worth of neurotransmitters is released from the presynaptic terminal. EPSPs are excitatory postsynaptic potentials generated when excitatory neurotransmitters bind to receptors on the postsynaptic membrane. Thus, hLR-RK2 expression leads to impaired synaptic function and decreased membrane excitability in KC cells[68]. Belluzzi et al[40] discovered that LRRK2 impedes the transit and distribution of synaptic vesicles, inhibiting neurotransmitter release from synaptic junction vesicles and reducing synaptic effectiveness. Simultaneously, an increased density of synaptic nodules requires more energy because synaptic nodules occupy more space. Hence, reduced synaptic effectiveness and stress may further impair synaptic homeostasis and contribute to greater hLRRK2-induced sleep disorders[69]. In conclusion, we believe that LRRK2 plays a role in regulating synaptic vesicle SV recycling/endocytosis in the pathogenic characteristics of PD and is also a crucial molecule in the pathological features of early PD.

Synaptic Disruption in 6-OHDA- and MPTP-Induced PD Models

The 6-hydroxydopamine (6-OHDA)-induced PD model can exhibit multiple stages of dopaminergic neuronal degeneration. Although a slight decrease in neuronal death may be present, synaptic transmission can still be affected[44]. In the 6-OHDA model, presynaptic changes in cortical terminals severely reduce nigrostriatal dopami-

nergic transmission, in turn hindering synaptic plasticity. For this type of plasticity to occur, dopamine (DA) levels must be kept low. Although small amounts of dopamine are critical for the development and upkeep of LTP, as PD progresses, long-term potential (LTP) is further diminished, and thus there is no considerable change in LTP[70]. Research[71,72] on 6-OHDA and 1-methl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP)-induced PD models and human postmortem PD brains has shown that the death of striatal dopaminergic neurons causes a significant decrease in dendritic spines on dorsal striatal medium spiny neurons. DA has been shown to promote dendritic remodeling by regulating intracellular Ca^{2+}, which in turn alters dendritic spines. The synaptic transmission function varies due to different structural foundations[73,74]. The degree of striatal dopaminergic loss in MPTP-treated non-human primates and humans is correlated with the degree of spine loss. Spine loss within the striatum is a hallmark of pathological alterations that indicate early synaptic dysfunction in PD[75-77]. At the same time, studies[78,79] on the electrical activity and structure of PD models show that reducing the level of DA in the striatum causes structural abnormalities in the spines. This, in turn, leads to an increase in glutamate release and further impairs synaptic plasticity. The loss of LTD in the striatal MSNs is hypothesized to disturb homeostasis and cause excessive motor inhibition, which may initiate the onset of dyskinesia in PD[80,81]. Collectively, the nigrostriatal pathway demonstrates a complex balance rearrangement in response to progressive striatal DA depletion in PD, resulting in different effects on synaptic transmission during the early and late stages of the disease.

MLT Alleviates Synaptic Dysfunction

There is limited research on the efficacy of MLT in treating synaptic dysfunction caused by mutations in the *SNCA/PARK1* gene. Although it is unclear whether MLT is the most effective method, it has been demonstrated[4,82] to suppress α-syn aggregation and reduce neurotoxicity effectively. MLT effectively reverses the damage caused by MPTP and restores dopaminergic neuronal Tyrosine hydroxylase (TH) in the substantia nigra (SNc). Additionally, MLT treatment increased dendrite number, while MPTP caused a drastic decrease in total dendrite length and dendritic complexity in cultured primary cortical neurons. MLT has been shown to ameliorate the hLRRK2-driven increase in the frequency of light and dark phase sleep, as well as the mean sleep duration and quantity of light phase sleep, in a study on Drosophila synaptic dysfunction associated with NMS sleep disorder. The electrophysiological analysis showed that MLT recovered its EPSP and mEPSC frequencies to the levels seen in healthy controls[83]. MLT has been shown in various studies[84,85] to improve cognitive dysfunction in aged rats caused by propofol. MLT does this by inhibiting the over-activation of the PKA/CREB/BDNF signaling pathway, reducing ROS production, and restoring syntaxin and presynaptic synapsin levels.

Effects of MLT in Neuroinflammation-Induced PD

Acute inflammatory responses in the central nervous system can promote tissue repair, but chronic inflammatory responses can cause permanent brain damage. During neuroinflammation, glial cell activation leads to neuronal damage and neurodegeneration by releasing proinflammatory and neurotoxic factors[86]. Also, active microglia and astrocytes can generate many inflammatory mediators, including cytokines, chemokines, proteoglycans, complement cascade proteins, and ROS. Various factors that compromise the blood-brain barrier allow cytokines from the adaptive immune system to enter the central nervous system (CNS), exacerbating brain damage[87]. The SNpc is more vulnerable to neuroinflammation because it has fewer astrocytes to protect against microglial activation. Increased microglia density is associated with enhanced inflammatory responses. Neuroinflammation in the SNpc may be more potent in the presence of increased microglia density. Furthermore, the activation of microglia by neurons in the SNpc is one mechanism by which neuroinflammation can be caused[88].

Microglia Induce Neuroinflammation in PD

Neuroinflammation is a fundamental process of PD that is caused by activated microglia. Microglia are macrophages that settle in the brain and monitor changes in the brain's local environment. They are responsible for phagocy-

tosing metabolic waste and dead cells and can be activated as a barrier to innate immunity or a major mediator of inflammatory responses. These cells play a vital role in the central nervous system by secreting various proinflammatory factors[89,90]. Microglia are classified into two subtypes: M1 and M2. M1 macrophages secrete proinflammatory mediators that can induce neuronal inflammation and cell death, whereas M2 macrophages have anti-inflammatory, A clearance, and memory enhancement activities[81]. Microglia react to inflammation by assuming a proinflammatory M1-like phenotype and secreting tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β. Large amounts of inflammatory substances activate the local inflammatory response, which increases inflammation and neurodegeneration. On the other hand, anti-inflammatory (M2-like) polarization is associated with the production of anti-inflammatory molecules such as IL-4 and IL-10, which may operate as neuroprotective agents[91]. Triggering receptor expressed on myeloid cells 2 (TREM2), belonging to the TREM family, is a type I transmembrane innate immune receptor primarily expressed in brain microglia. In addition to the conventional proinflammatory M1-like and anti-inflammatory M2-like phenotypes, disease-associated microglia (DAM) have been shown to play both immunosuppressive and proinflammatory roles in neurodegenerative disorders. TREM2 expression has been implicated in this progression[92]. Toll-like receptors (TLRs) are a kind of transmembrane protein. This protein family helps stimulate the body's innate immune response to various pathogens. Toll-like receptor-4 (TLR4) plays a role in innate immunity by activating transcription factors that lead to the activation of nuclear factor-kappa B (NF-κB) pathway genes. The primary components of NF-B, p50, and p65 collectively form a complex that enters the nucleus and attaches to the I B region. This leads to the development of TNF-, IL-1, IL-6, and inducible nitric oxide synthase (iNOS) as inflammatory regulatory proteins[93,94].

In microglia cells, misfolded α-syn protein promotes neurotoxicity by generating reactive oxygen species and proinflammatory cytokines. The *LRRK2* mutant PD model generates more proinflammatory cytokines than wild-type (WT) *LRRK2*-expressing cells due to the activation of microglia[95,96]. Parkin deficiency can also cause microglia activation indirectly by influencing neurons' response to inflammatory stimuli and disrupting the homeostasis between neurons and microglia[97]. DJ-1 deficiency in astrocytes can contribute to neurodegeneration by reducing the neuroinflammatory response. Microglia are activated in response to neuronal injury in cellular co-cultures, and this heightened response contributes to further neurodegeneration[98]. As such, we can surmise that PD-related stresses may disrupt the careful balance between the protective and damaging effects of glial cell responses.

MLT Reduces Neuroinflammation in PD Patients

Retinoic acid receptor–related orphan receptor α (RORα), a natural ligand for MLT, is a circadian nuclear receptor that regulates the immunological response to inflammation[99]. Previous research[100,101] suggests that the activation of the signal transducer and activator of transcription (STAT) family may be essential for regulating macrophage/microglia polarization. The anti-inflammatory effects of MLT and the promotion of microglia polarization towards an M2-like phenotype may be mediated by an elevated phosphorylation level of Signal Transducer and Activator of Transcription 3 (STAT3) (p-STAT3)[102,103]. On the other hand, the phosphorylation of STAT1 (p-STAT1) is necessary for the proinflammatory M1-like polarization[4]. STAT-related pathways contribute to cytokine signaling and macrophage/microglia polarization. Previous research[104] has found that MLT can reduce the increase in p-STAT1 expression and decrease p-STAT3 expression in BV2s that are activated by 1-methyl-4-phenylpyridinium ion (MPP+), suggesting that MLT may help to direct microglia towards an anti-inflammatory M2 phenotype. MLT-ROR alters microglial phenotype through the STATs pathway, which leads to improved motor function in DA neurons and protection against DA neuron loss. MLT can reduce the levels of proinflammatory cytokines (TNF-, IL-6, IL-1) produced in response to MPP+ treatment and increase the expression of anti-inflammatory cytokines such as IL-10 and IL-4. MLT administration was shown to decrease the expression of proinflammatory molecules such as TNF-α, CD36, IL-1, and iNOS during microglia polarization, as well as the expression of DAM phenotypic factors, including toll-like receptor (TLR4) and TREM2. Furthermore, MLT increased the expression of anti-inflammatory M2-like markers. The anti-inflammatory effects
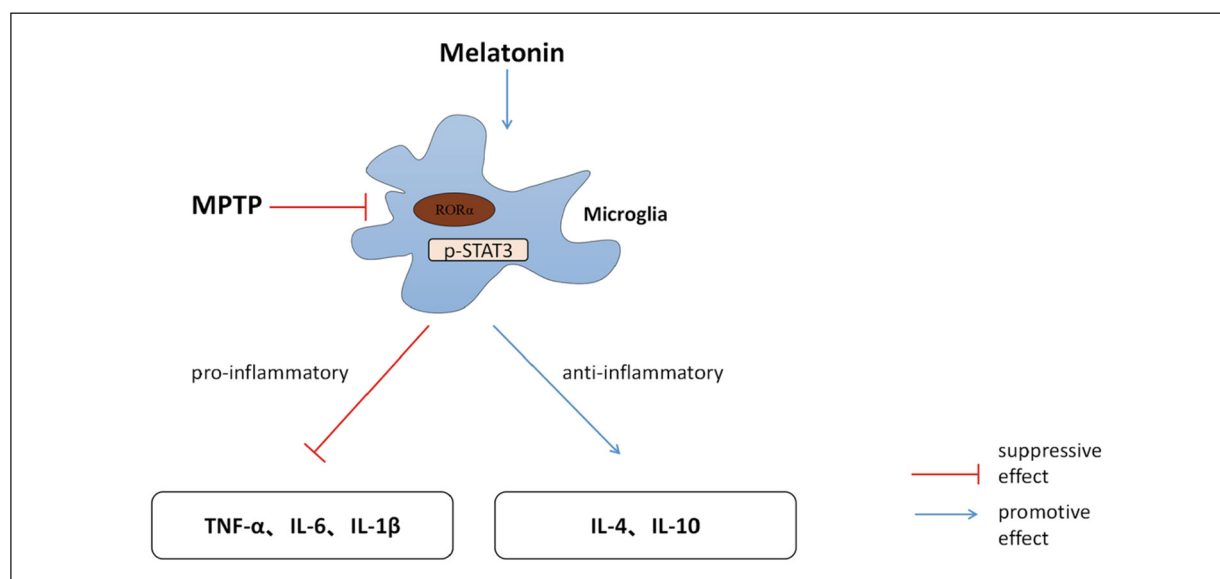
Figure 2. RORα-related anti-inflammatory effect of MLT in PD. Reprinted with permission by Springer Nature[4].

of MLT in PD animal models may be mediated by the downregulation of M1 and DAM phenotypic markers *via* RORα-STAT signaling[4]. The study suggests that MLT may act as a neuroprotective agent by promoting microglia M2 polarization and reducing proinflammatory cytokine expression. The study also found that RORα has an anti-inflammatory effect in PD through its role as a relevant ligand for MLT (Figure 2).

In addition to microglia and astroglial, the activation of inflammatory vesicles can amplify the inflammatory response. The stimuli that trigger the release of inflammatory vesicles include aggregated proteins, microbial or injury-associated stimuli, ROS, and metabolic abnormalities[105]. Inflammatory vesicles recruit the cysteinyl aspartate specific proteinase (CASPASE) family through the CARD-containing apoptosis-associated speck-like protein (ASC), which cleaves proinflammatory cytokine precursors to their mature form. ASC-enriched caspase-1 recruitment structures promote inflammatory activity during vesicle assembly. A growing body of evidence suggests that NLR family pyridine structure domain 3 (NLRP3)-containing inflammatory vesicles play a role in PD[106]. In microglia, the NLRP3 inflammasome is assembled and activated in response to the MPTP molecule as a priming signal (signal 1) and to adenosine triphosphate (ATP) or nigericin as activation signals (signal 2). The activation of the NLRP3 inflammasome leads to the proteolytic cleavage of pro-IL-1β, resulting in the mature IL-1β that can promote the production of ASC specks. However, MLT protects dopaminergic neurons against PD by negatively impacting NLRP3 inflammasome activation mediated by the SIRT1-dependent pathway[107].

It has been found that MLT can significantly restore SIRT1 downregulation and attenuate NLRP3 inflammatory vesicle activation and ASC protein assembly. MLT also prevents MPTP-induced dopaminergic neuronal death, restores TH expression, and suppresses NLRP3 inflammatory vesicle activation and IL-1β secretion in MPP+-stimulated BV2 cells. The findings together suggest that MLT may help to reduce neuroinflammation by decreasing NLRP3 inflammasome activation through a SIRT1-dependent pathway in the MPTP-induced PD model[107]. The mechanism by which MLT prevents NLRP3-mediated inflammatory vesicle activation in PD remains to be elucidated. These findings suggest that MLT may reduce inflammation in PD by affecting various inflammatory mediators.

Conclusions

PD is a chronic, progressive neurological disorder that manifests as motor and NMS symptoms. At the start of the disease, dopaminergic and non-dopaminergic treatments are employed. As

the disease progresses, it becomes increasingly difficult to treat with a single medication, and side effects from the medication may limit its effectiveness. In advanced PD characterized by motor fluctuations and dyskinesia, available pharmacotherapy only suppresses individual symptoms rather than providing optimal clinical benefit[108]. Consequently, it is vital to find a medicine that is both safe and efficient in order to avoid early NMS symptoms of PD and improve PD motor symptoms. MLT is an auto-synthetic compound produced by the body and decreases with age. MLT has been shown to inhibit the effects of oxidative stress, mitochondrial dysfunction, protein quality control system dysfunction, and inflammatory responses[109].

The present review highlights the efficacy of MLT in impeding the aggregation of alpha-synuclein and diminishing neurotoxicity, which consequently restores the functionality of dopaminergic neurons in the substantia nigra. Additionally, MLT ameliorates sleep disorders in individuals with PD and suppresses the excessive activation of the PKA/CREB/BDNF signaling pathway. Furthermore, MLT can also reduce ROS production and maintain regular neurotransmitter transport and transmission[68,83,84]. Moreover, MLT can reduce the expression of inflammatory cytokines by promoting microglia M2 polarization[43]. Simultaneously, MLT can stimulate its ligand ROR alpha to exert anti-inflammatory effects[4]. MLT also can down-regulate the activation of NLRP3 inflammasome mediated by a SIRT1-dependent pathway, thereby mitigating neuroinflammation[107].

The utilization of MLT treatment may ameliorate synaptic dysfunction, neuroinflammatory responses, and the emergence or exacerbation of PD. This novel disease-modifying therapy regulates PD. Nevertheless, well-designed, large multicenter clinical trials are urgently needed to investigate further the protective and therapeutic effects of melatonin on the clinical symptoms of PD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Y.-L. Guo: Conceptualization, Formal analysis, Methodology, Writing-Original draft. X.-J. Wei, T. Zhang: Methodology, Data Curation, Helped in writing of the manuscript. T. Sun: Writing-Reviewing and Editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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