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REVIEW

Effects of Melatonin Disorders on Parkinson's Disease: A Review of Mechanisms and Clinical Manifestations

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Abstract: Melatonin is a vital hormone that is important for antioxidant activity, neuroprotection, and biological rhythm control. Melatonin anomalies may have a high correlation with the onset and development of Parkinson's disease, according to recent studies. A common neurodegenerative illness that severely lowers a patient's quality of life, Parkinson's disease is typified by non-motor symptoms and aberrant movement. A recent study found that abnormal melatonin levels may have a detrimental effect on patients' motor function and cognitive ability, potentially exacerbating Parkinson's disease symptoms. To completely comprehend the clinical symptoms linked to Parkinson's disease and potential therapy options, further study is necessary to determine the exact role of melatonin in this condition. This article will investigate the relationship between melatonin and Parkinson's disease, how it contributes to the illness's progression, and the clinical symptoms that are linked with it in order to provide new perspectives and resources for more research and treatment strategies.

Keywords: melatonin, Parkinson's disease, mechanism, clinical manifestations, neuroprotection

Introduction

Parkinson's disease (PD), a common neurodegenerative disease that also produces a range of non-motor symptoms like anxiety, depression, and disrupted sleep, is characterized by dyskinesia, tremor, and muscle rigidity. As the world's population ages, it is anticipated that the frequency and incidence of PD would climb dramatically, potentially increasing by over 30% by 2030.[1] Therefore, comprehending its pathomechanisms and developing efficient therapies have become especially crucial.

Melatonin, or N-acetyl-5-methoxytryptamine, is a pineal gland-derived neurohormone crucial for regulating circadian rhythms, sleep, and endocrine functions since its discovery in 1958.[2] Melatonin, secreted by the pineal gland at night, is triggered by norepinephrine from sympathetic neurons, activating α and β receptors.[3] Melatonin regulates sleep-wake cycles and biological rhythms, peaking at night to aid sleep onset.[4] As the hub of the biological clock, the suprachiasmatic nucleus (SCN) can detect variations in ambient light and use neural impulses to control the pineal gland's production of melatonin.[5] Recent studies show that melatonin benefits neuroprotection, antioxidants, sleep, and circadian rhythm control.[6] Furthermore, aging and conditions like endocrine disorders and jet lag lower melatonin levels in the elderly.[7]

Melatonin is produced centrally as well as in a number of peripheral organs, including the liver, gynecological system, skin, bone marrow, and gastrointestinal tract.[8–11] Melatonin receptors (MT1 and MT2) are found in peripheral

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organs and the central nervous system (CNS), indicating their wide physiological significance. While MT2 receptors are mostly expressed in the SCN and the retina,[12] MT1 receptors are extensively distributed in areas of the SCN, pituitary, hypothalamus, and hippocampus, suggesting a function in the control of circadian rhythms and the reproductive system.[13] Melatonin acts via receptors and non-receptor methods, affecting signaling pathways and offering anti-inflammatory and antioxidant benefits.[14,15] By triggering antioxidant enzymes that shield cells from oxidative stress, such as glutathione peroxidase, catalase, and superoxide dismutase, or superoxide dismutase (SOD), melatonin lessens cellular damage.[16] Among the many biological roles of melatonin are the control of endocrine and circadian cycles, as well as its anti-inflammatory and antioxidant properties.[17] Melatonin and its metabolites act as antioxidants, enhancing mitochondrial function and reducing free radicals.[18] Furthermore, melatonin improves mitochondrial structure and function via a number of pathways, which has a significant effect on the pathophysiology of neurodegenerative illnesses like PD.[19] The pathophysiology of PD17 may be intimately linked to the considerable decline in nocturnal serum and cerebrospinal fluid melatonin levels observed in middle-aged and older persons as they age.[20]

PD patients frequently have reduced melatonin levels, which may be directly related to the onset of non-motor symptoms.[21] Melatonin's biological roles extend beyond regulating sleep; it also plays a part in neuroprotection. According to research, melatonin can shield dopaminergic neurons from oxidative stress and apoptosis, which may have therapeutic implications for the management of PD.[22] Additionally, melatonin may influence the degenerative course of PD by controlling neurotransmitter release and neuroinflammatory responses.[23]

In terms of therapeutic application, melatonin is seen to be a safe and effective therapy alternative, especially when it comes to improving the quality of sleep for those with PD. Randomized controlled trials have shown that melatonin significantly improves sleep quality and decreases non-motor symptoms in PD patients with fewer side effects.[24] Furthermore, melatonin's effectiveness at various dosages and release types has drawn a lot of interest; research indicates that ≥10 mg/day of melatonin has substantial therapeutic potential in reducing sleep disruptions and motor symptoms.[24]

Melatonin's Link with Parkinson's disease: Parkinson's Disease and Melatonin Abnormalities are Related

Changes in Melatonin Levels Seen Clinically

There has been a lot of interest in how melatonin levels change in people with PD. Research has indicated a possible correlation between melatonin levels and non-motor symptoms (such as anxiety, sadness, and sleep difficulties) in individuals with PD. A cross-sectional investigation found that PD patients had considerably greater plasma melatonin levels than healthy controls, which may indicate an anomaly in melatonin secretion.[21] Furthermore, there was a negative correlation found between the patient's melatonin levels and their pharmaceutical therapy (such as the dosage of levodopa), indicating that individuals receiving varying amounts of levodopa may have varied melatonin secretion.[25] This behavior could be a reflection of PD patients' disrupted nighttime biorhythms, which impact their quality of sleep and general well-being. Thus, keeping an eye on and controlling melatonin levels could be a key tactic to help PD patients with their non-motor symptoms.

Melatonin Disorders' Impact on Motor Symptoms

Melatonin disturbance not only impacts sleep in PD patients but may also have a major influence on their motor symptoms. Studies have indicated that melatonin has a significant role in regulating motor activity, notably in neurons involved with the dopamine system. Melatonin supplementation improves motor deficits caused by neurotoxins (such as 6-hydroxydopamine) in animal models, as demonstrated by improved neuronal survival and locomotor performance recovery.[22] Furthermore, melatonin may reduce motor symptoms in PD patients due to its anti-inflammatory and antioxidant qualities, offering a possible treatment option. There is evidence that melatonin administration may somewhat enhance motor performance in PD patients, particularly in early-stage patients, despite the fact that clinical study outcomes are currently conflicting.[24]

Melatonin and Non-Motor Symptoms are Correlated

Melatonin imbalances and non-motor symptoms in PD patients have a complicated interaction. Numerous non-motor symptoms, such as anxiety, sadness, and sleep difficulties, have been discovered to be closely linked to changes in melatonin levels. Reduced levels of melatonin, a hormone involved in the control of the sleep-wake cycle, may be linked to an aggravation of the poor sleep quality that patients with PD commonly report.[26] Melatonin supplementation was linked to improvements in non-motor symptoms and dramatically enhanced sleep quality in PD patients in a randomized controlled experiment.[24] Additionally, melatonin may affect patients' anxiety and depression levels by improving their quality of life.[12] Consequently, melatonin regulation may help with both motor and non-motor symptoms in individuals with PD.

Mechanistic Viewpoint: Melatonin Disruption's Impact on Parkinson's Disease

Melatonin, a hormone mostly produced at night and involved in regulating the biological clock and sleep cycle, is secreted by the pineal gland. In recent years, a growing body of research has shown that PD patients have dramatically altered melatonin levels. Many symptoms of PD may be closely related to this disturbance. In addition to influencing patients' sleep quality, changes in melatonin levels may have a number of effects on the degenerative process of PD.

First off, one of the key ways that melatonin influences PD is through its function in controlling biological rhythms. Melatonin levels have been shown to be generally lower in PD patients, which may lead to biological rhythm irregularities that affect waking and sleeping cycles. According to one study, PD patients' much greater melatonin levels than those of healthy controls may be linked to their non-motor symptoms, which include gastrointestinal problems, sleep issues, and cardiovascular symptoms.[21] Moreover, melatonin improves the quality of sleep for PD patients by regulating the expression of genes linked to the biological clock and aiding in the restoration of regular biological rhythms.[27]

Second, the pathogenesis of PD also heavily relies on the anti-inflammatory and antioxidant properties of melatonin. Melatonin's ability to scavenge free radicals and lessen oxidative stress damage to neuronal cells is particularly important for PD patients, as oxidative stress is believed to be a significant contributing factor to the pathogenesis of PD.[6] Research has shown that melatonin can reduce neuroinflammation by blocking the activation of inflammatory vesicles called NOD-Like Receptor Pyrin Domain Containing 3 Inflammasome (NLRP3), so shielding dopaminergic neurons from harm.[28] Furthermore, by controlling mitochondrial activity and enhancing energy consumption, melatonin amplifies its neuroprotective benefits.[29]

Thirdly, it is important to consider melatonin's function in neurotransmitter modulation. A number of neurotransmitters, including dopamine, norepinephrine, and 5-hydroxytryptophan, are strongly related to the production and release of these neurotransmitters through their receptors (MT1 and MT2), and individuals with PD frequently have abnormalities in these neurotransmitters. Melatonin is closely linked to the synthesis and release of these neurotransmitters, which affect mood and sleep patterns, through its receptors (MT1 and MT2).[30] For example, melatonin supplementation has been demonstrated to aid individuals with Rapid Eye Movement Sleep Behavior Disorder (RBD) who have PD. This might be a result of melatonin's neurotransmitter modulation.[31]

Furthermore, cognitive impairment in PD patients may potentially be linked to melatonin insufficiency. Research has indicated a negative relationship between PD patients' cognitive impairment and lower melatonin levels, indicating that melatonin may be crucial for preserving cognitive function.[32] Consequently, melatonin-targeting supplementary medication may offer novel therapeutic approaches for enhancing cognitive performance in PD patients.

Lastly, melatonin has promise as a PD treatment. Melatonin has been shown in several clinical studies to significantly improve motor symptoms and sleep quality in individuals with PD, particularly in the early stages of the illness.[24] Further investigation is required to ascertain the optimal dosage and timing of melatonin administration in order to provide a firmer basis for therapeutic usage. In conclusion, melatonin disruption has a substantial influence on the development and course of PD via a variety of mechanisms that alter neurotransmitter balance, oxidative stress, biological rhythms, and cognitive function (Table 1). Future studies should focus on the specific mechanisms of melatonin's activity in PD and its therapeutic applications in order to provide PD patients with better therapy options.

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Table 1 This Table Summarizes the Potential Mechanisms Through Which Melatonin, Acting via MT1 (Melatonin Receptor 1) and MT2 (Melatonin Receptor 2) Receptors, Influences the Clinical Manifestations of Parkinson's Disease. The Table Details Various Mechanisms by Which Melatonin Exerts Its Effects, Including the Reduction of Oxidative Stress, Mitigation of Mitochondrial Structure and Function Disorders, Anti-Inflammatory Actions, Regulation of Circadian Rhythm, Modulation of Endocrine Rhythm, Inhibition of α-Synuclein Toxicity, Anti-Apoptosis, and Anti-Autophagy. These Mechanisms Collectively May Contribute to Alleviating Symptoms Such as Sleep Disorders, Dystonia in the Morning, Constipation, Postural/Ortho-Static Hypotension, Cognitive Disorders, and Affective Disorders, Which are Commonly Associated with Parkinson's Disease. The Table Highlights the Specific Mechanisms of Action of Melatonin and Its Potential Impact on the Clinical Presentations of Parkinson's Disease, Underscoring the Substance's Significance in the Treatment of the Condition

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Hu et al, (2023)[27]	To investigate the neuroprotective effects of melatonin on sleep disorders related to Parkinson's disease	Experimental study	Melatonin	Parkinson's disease model	Melatonin improves sleep disorders in Parkinson's disease through antioxidant, anti-excitotoxicity, and circadian rhythm regulation mechanisms	Melatonin may significantly improve sleep disorders in Parkinson's disease patients and is worthy of further clinical research
Asemi-Rad et al, (2022)[22]	To study the effects of melatonin combined with dopaminergic neuron transplantation on cell death induced by oxidative stress in Parkinson's disease	Experimental study	Melatonin combined with dopaminergic neuron transplantation	Parkinson's disease model	Melatonin combined with transplantation significantly reduces cell death induced by oxidative stress	Melatonin may enhance neuroprotective effects through antioxidant mechanisms
Zheng et al, (2021)[28]	To investigate the regulatory effects of melatonin on the NLRP3 inflammasome in MPTP-induced Parkinson's disease models	Experimental study	Melatonin	Parkinson's disease model	Melatonin downregulates the NLRP3 inflammasome through a SIRT1-dependent pathway, reducing neuroinflammation	Melatonin may improve the pathological process of Parkinson's disease through anti-inflammatory mechanisms
Kato et al, (2025)[29]	To study the effects of melatonin on MPP+-induced cytotoxicity	Experimental study	Melatonin	Neuronal cell model	Melatonin inhibits MPP+ toxicity through two antioxidant activities	Melatonin may protect neuronal cells through multiple antioxidant mechanisms
Pérez-Lloret et al, (2021)[30]	To explore the role of melatonin as a circadian regulator and cell protector in Parkinson's disease	Experimental study	Melatonin	Parkinson's disease model	Melatonin provides neuroprotection through circadian rhythm regulation and antioxidant effects	Melatonin may become an adjunctive treatment for Parkinson's disease, improving patients' quality of life
Song et al, (2024)[33]	To study the regulatory effects of melatonin on neuroinflammatory responses and microglial activation in mice exposed to night-time blue light	Experimental study	Melatonin	Mouse model	Melatonin significantly reduces neuroinflammation and microglial activation	Melatonin may improve neuroinflammation by regulating microglial cell activity
Liu et al, (2019)[34]	To study the protective effects of melatonin on ischemic stroke	Experimental study	Melatonin	Stroke model	Melatonin reduces inflammation by regulating microglial/macrophage polarization	Melatonin may become a potential treatment option for ischemic stroke
Lazarević et al, (2024)[35]	To study the regulatory effects of melatonin on cardiac tissue damage under sepsis conditions	Experimental study	Melatonin	Sepsis model	Melatonin significantly reduces cardiac tissue damage	Melatonin may protect the heart through antioxidant and anti-inflammatory effects
Zhang et al, (2024)[36]	To study the regulatory effects of melatonin on cough sensitivity and microglial activation in guinea pigs exposed to PM2.5	Experimental study	Melatonin	Guinea pig model	Melatonin significantly reduces cough sensitivity and microglial activation	Melatonin may improve respiratory inflammation by regulating microglial cell activity
Hsieh et al, (2023)[37]	To study the effects of thyroid dysfunction on traumatic brain injury	Experimental study	Melatonin	Brain injury model	Melatonin significantly reduces oxidative stress and inflammation	Melatonin may improve brain injury through antioxidant and anti-inflammatory effects

Lv et al, (2024)[38]	To study the protective effects of melatonin through MT1 receptor regulation of the Sirt1/Nrf2/Ho-1/Gpx4 pathway in preventing ferroptosis induced by α-synuclein in Parkinson's disease	Experimental study	Melatonin	Parkinson's disease model	Melatonin inhibits ferroptosis by activating the MT1 receptor	Melatonin may delay the progression of Parkinson's disease by regulating antioxidant pathways
Shao et al, (2024)[39]	To study the effects of melatonin on gut microbiota and colitis inflammation	Experimental study	Melatonin	Colitis model	Melatonin significantly reduces colitis inflammation	Melatonin may improve colitis inflammation by regulating gut microbiota
Kim et al, (2023)[40]	To study the role of microRNAs in the circadian rhythm and molecular links to autism spectrum disorder	Experimental study	Melatonin	Autism model	Melatonin may improve autism symptoms through circadian rhythm regulation	Melatonin may become a potential treatment option for autism spectrum disorder
Mishima et al, (2024)[41]	To study the regulatory effects of melatonin on voltage-gated potassium channel KV 4.2 in rat pineal gland	Experimental study	Melatonin	Rat model	Melatonin significantly inhibits the KV 4.2 channel	Melatonin may improve neuronal function through ion channel regulation
Yuksel et al, (2023)[42]	To study the protective effects of melatonin receptor agonists on endotoxin-induced uveitis	Experimental study	Melatonin receptor agonist	Uveitis model	Melatonin significantly reduces inflammation	Melatonin may become a potential treatment option for uveitis
Jung et al, (2022)[43]	To study the effects of melatonin on MPP+-induced apoptosis	Experimental study	Melatonin	Neuronal cell model	Melatonin inhibits apoptosis through heat shock proteins	Melatonin may protect neuronal cells through anti-apoptotic mechanisms
Bocheva et al, (2022)[44]	To study the protective effects of melatonin and its metabolites in skin aging	Experimental study	Melatonin	Skin cell model	Melatonin significantly reduces oxidative stress and inflammation	Melatonin may improve skin aging through antioxidant and anti-inflammatory effects
Zhang et al, (2022)[45]	To study the effects of melatonin on gut microbiota and secondary injury after spinal cord injury	Experimental study	Melatonin	Spinal cord injury model	Melatonin significantly improves gut microbiota and reduces secondary injury	Melatonin may improve spinal cord injury through gut microbiota regulation
Chen et al, (2020)[46]	To study the protective effects of melatonin on intervertebral disc degeneration	Experimental study	Melatonin	Intervertebral disc model	Melatonin reduces inflammation by activating the NF-κB signaling pathway	Melatonin may become a potential treatment option for intervertebral disc degeneration
Xu et al, (2020)[47]	To study the regulatory effects of melatonin on pressure overload-induced cardiac hypertrophy	Experimental study	Melatonin	Cardiac hypertrophy model	Melatonin significantly reduces cardiac hypertrophy	Melatonin may protect the heart through autophagy and Akt/mTOR pathway regulation
Wakahara et al, (2022)[48]	To study whether the definition of pancreatic fistula is applicable to post-gastrectomy	Experimental study	Melatonin	Pancreatic fistula model	Melatonin significantly reduces pancreatic fistula	Melatonin may become a potential treatment option for pancreatic fistula
Gu et al, (2021)[49]	To study the regulatory effects of microglial MT1 activation on LPS-induced neuroinflammation	Experimental study	Melatonin	Neuronal cell model	Melatonin reduces neuroinflammation through metabolic reprogramming	Melatonin may improve the pathological process of Parkinson's disease by regulating microglial cell activity
Rasheed et al, (2023)[50]	To study the effects of melatonin on oxidative stress and mitochondrial dysfunction in fruit fly models of Parkinson's disease	Experimental study	Melatonin	Fruit fly model	Melatonin reduces oxidative stress and mitochondrial dysfunction	Melatonin may improve the pathological process of Parkinson's disease through antioxidant and mitochondrial protection mechanisms

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Melatonin Disorders and Oxidative Stress

Recent research has revealed that PD, which is intimately linked to oxidative stress, frequently causes patients' melatonin levels to fluctuate. Oxidative stress, which damages and malfunctions cells, is brought on by an imbalance between the body's antioxidants and reactive oxygen species (ROS). Oxidative stress is a major contributing factor in PD, a neurodegenerative disorder with both motor and non-motor symptoms. The pathological process of PD may be made worse by disruptions in melatonin, an endogenous hormone with antioxidant qualities.

According to studies, people with PD have much lower melatonin levels. This condition may be caused by degenerative changes in the pineal gland, irregularities in the circadian rhythm, or a decrease in the activity of melatonin synthases, such as aromatic amine N-methyltransferase. Melatonin is a strong antioxidant and scavenger of free radicals that directly neutralizes a range of ROS and reactive nitrogen species (RNS), reducing lipid peroxidation, protein oxidation, and DNA damage.[51] Melatonin's antioxidant protective action is diminished when levels are low. This results in less scavenging of free radicals, which raises intracellular ROS and RNS levels and worsens oxidative stress. Melatonin has been demonstrated to significantly enhance neurological function, reduce neuronal apoptosis, and increase cellular antioxidant capacity by increasing the activity of antioxidant enzymes such as glutathione peroxidase (GPX) and superoxide dismutase (SOD) in an animal model of PD.[52] Melatonin may protect against the degenerative progression of PD by controlling the body's redox status. Melatonin, for instance, has been demonstrated to improve motor symptoms and sleeping conditions in PD patients by reducing neuronal damage through the inhibition of intracellular oxidative stress.[21] Second, by triggering intracellular signal transduction pathways, melatonin also improves cell viability. For instance, melatonin can stimulate the transcription of Nrf2, a crucial transcription factor that controls the expression of antioxidant enzymes, aids cells in scavenging ROS, and shields them from oxidative damage, as well as activate the PI3K/Akt signaling pathway through its receptors (MT1 and MT2)[29] (Figure 1). Melatonin's potent antioxidant ability, which neutralizes free radicals, prevents oxidative stress, and shields cells from oxidative damage, is one of its key characteristics. Oxidative stress is closely linked to dopaminergic neuron loss in PD, and melatonin imbalances may exacerbate oxidative stress.[53]

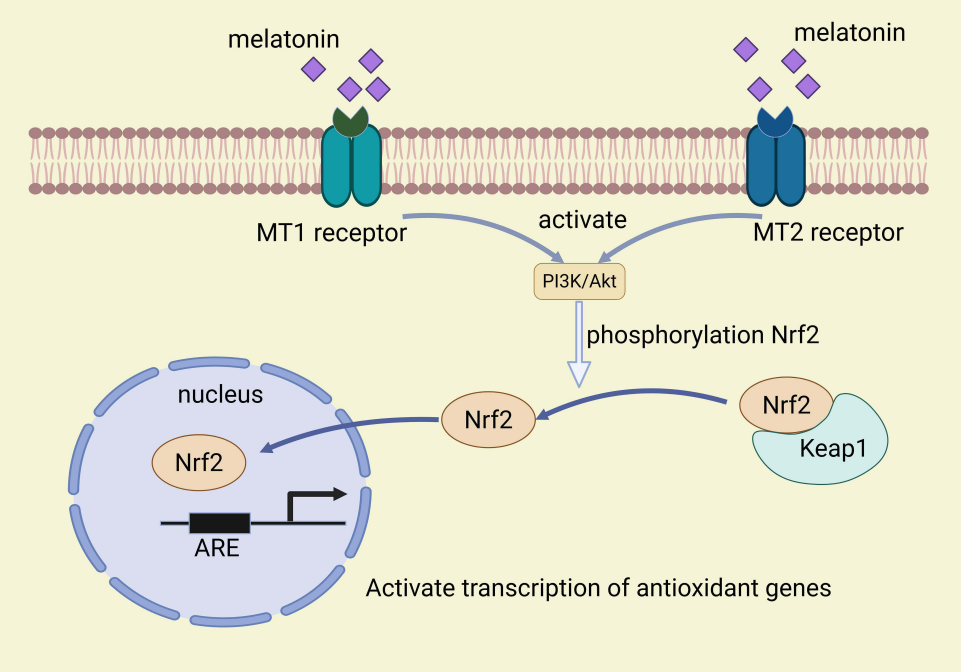

Figure 1 This diagram illustrates the mechanism by which melatonin activates the transcription of antioxidant genes through its interaction with MT1 (Melatonin Receptor 1) and MT2 (Melatonin Receptor 2) receptors. Melatonin binds to these receptors, initiating the PI3K/Akt (Phosphoinositide 3-kinase/Akt signaling pathway) signaling pathway. Activation of this pathway leads to the phosphorylation of Nrf2 (Nuclear factor erythroid 2-related factor 2), which is normally bound to Keap1 (Kelch-like ECH-associated protein 1) in the cytoplasm. Upon phosphorylation, Nrf2 is released from Keap1 and translocates to the nucleus. In the nucleus, Nrf2 binds to the ARE (Antioxidant response element), promoting the transcription of genes involved in antioxidant defense. This process is crucial for protecting cells against oxidative stress and maintaining cellular homeostasis. Created in BioRender. yiwei, s. (2025) https://BioRender.com/h55lapb.

Disorders of Melatonin and Mitochondrial Structure and Function

The structure and function of mitochondria are directly linked to melatonin levels, which are frequently disturbed in people with PD. Mitochondria are referred to as the energy factories of cells because they produce ATP (adenosine triphosphate) and are a part of several physiological functions, including apoptosis, cellular metabolism, and redox reactions. PD patients have been shown to have altered mitochondrial activity, as shown by decreased potential of the mitochondrial membrane, increased ROS, and decreased ATP synthesis. Strong antioxidant melatonin scavenges radicals that cause damage and reduces oxidative stress, protecting mitochondria and enhancing their function.[21]

Neuronal cell death and morphological and functional alterations in mitochondria are tightly linked in the pathophysiology of PD. Neuronal degeneration may worsen due to mitochondrial malfunction brought on by melatonin depletion. Melatonin, for instance, has been shown in a PD model to activate SIRT1 (Silent Information Regulator 1), which promotes mitochondrial production and functional recovery.[23] In addition to improving mitochondrial energy metabolism, SIRT1 activation also prevents mitochondrial death and reduces neuroinflammatory reactions, both of which slow the course of PD.[31]

Furthermore, by controlling mitochondrial dynamics, melatonin preserves mitochondrial health. The operation of mitochondria depends on their dynamic equilibrium, which includes fusion and division. Melatonin improves overall mitochondrial function by promoting mitochondrial fusion and preventing excessive mitochondrial division, according to studies.[27] Melatonin therapy dramatically enhanced ATP generation and mitochondrial membrane potential in a PD model, reducing apoptosis and mitochondrial damage.[25]

These effects of melatonin are intimately linked to its signaling pathways, which are regulated by melatonin receptors (MT1 and MT2), in addition to its antioxidant properties. It has been demonstrated that melatonin binds to MT1 and MT2 receptors and activates downstream signaling pathways, hence enhancing mitochondrial synthesis and functional recovery.[1] Since melatonin receptor expression is much lower in PD patients, this process is especially crucial since it may exacerbate sleep difficulties and other non-motor symptoms.[21]

In conclusion, mitochondrial structure and function in PD patients are intimately linked to melatonin abnormalities. Enhancing melatonin levels and function may lead to novel approaches to PD therapy. In order to provide PD patients with better therapy choices, future research should investigate the possible pathways of melatonin in neuroprotection and mitochondrial function recovery.

Inflammation is Triggered by Low Melatonin

Melatonin's function in immunological modulation and neuroinflammation has drawn a great deal of attention in recent years. Inflammatory reactions are strongly linked to melatonin abnormalities, and inflammatory responses are triggered when pro-inflammatory cytokines rise as a result of decreased melatonin levels or dysregulated circadian rhythms. Melatonin decreases the release of pro-inflammatory cytokines (like TNF-α, IL-1β, and IL-6) and enhances the synthesis of anti-inflammatory cytokines (like TGF-β and IL-10) to maintain a balance between pro-inflammatory and anti-inflammatory responses.[54] Additionally, via regulating the overactivation of glial cells (such as microglia), melatonin abnormalities might worsen neuroinflammation.[55] According to research, melatonin regulates the polarization of microglia from a pro-inflammatory to an anti-inflammatory phenotype via the STAT3 pathway and prevents the activation of NF-κB and NLRP3 inflammatory vesicles[33,34] (Figure 2).

Motor dysfunction is a hallmark of PD, a neurodegenerative illness whose pathological hallmarks include dopaminergic neuron loss and neuroinflammatory activation.[1] In addition to controlling sleep, melatonin also has an impact on neurodegenerative conditions like PD through anti-inflammatory and antioxidant pathways. Because it lowers inflammatory reactions, melatonin may be crucial in decreasing the course of PD.

Through a number of methods, melatonin has been shown to suppress the inflammatory response. First, pro-inflammatory cytokines that are crucial to the pathophysiology of PD, such as Interleukin 6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α), can be directly inhibited by melatonin.[35] Melatonin was shown to possess anti-inflammatory properties in research where it dramatically decreased the levels of TNF-α and IL-6 in cardiac tissues

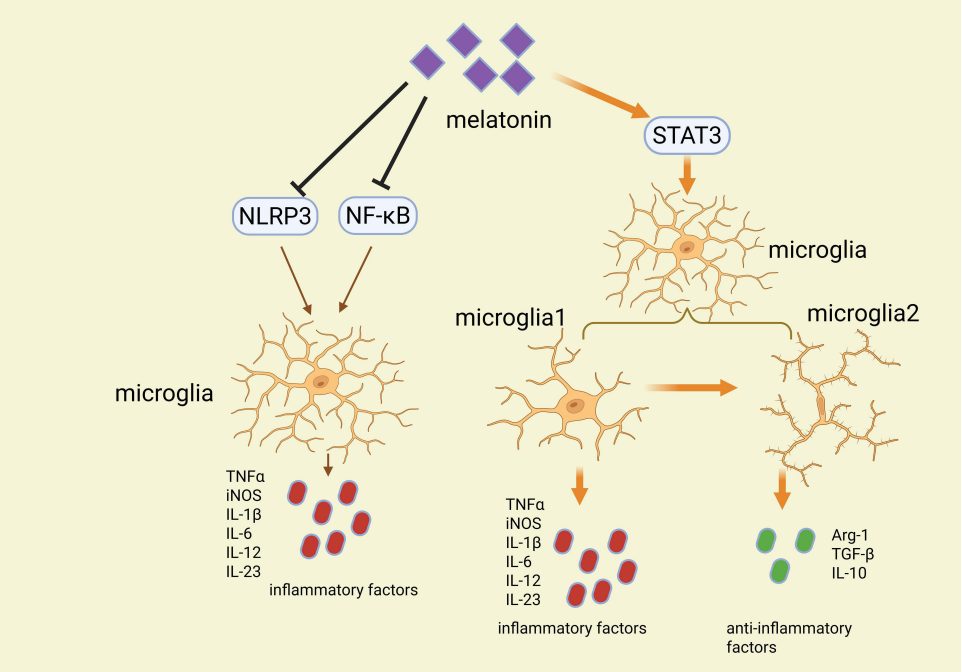

Figure 2 The diagram illustrates the effects of melatonin on microglial activation and inflammation. Melatonin inhibits the NLRP3 inflammasome (Nucleotide-binding domain, Leucine-rich repeat-containing family, Pyrin domain-containing 3) and NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) pathways, which reduces the production of inflammatory factors such as TNFα (Tumor Necrosis Factor alpha), IL-1β (Interleukin-1 beta), IL-6 (Interleukin-6), IL-12 (Interleukin-12), and IL-23 (Interleukin-23). Concurrently, melatonin activates STAT3 (Signal Transducer and Activator of Transcription 3), leading to the secretion of anti-inflammatory cytokines including IL-10 (Interleukin-10), TGF-β (Transforming Growth Factor beta), and Arg-1 (Arginase-1). This dual modulation by melatonin indicates its potential role in managing neuroinflammation. Created in BioRender. yiwei, s. (2025) https://BioRender.com/lg2sd3x.

caused by lipopolysaccharide (LPS).[35] Furthermore, by preventing the activation of NLRP3 inflammatory vesicles and reducing the release of inflammatory mediators, melatonin decreased neuroinflammation.[36]

Second, melatonin's anti-inflammatory qualities also help to lower inflammation. Melatonin scavenges free radicals and minimizes oxidative damage, which lowers neuronal cell mortality. One of the main pathogenic mechanisms in PD is oxidative stress.[37] According to one study, melatonin activated the Nrf2 pathway, which increased cells' antioxidant capacity and reduced oxidative stress-induced cellular damage.[36]

Aggregation of α-synuclein (α-syn) causes increased iron accumulation and iron mortality in a rat model of PD.[38] These modifications were made worse by MT1 receptor knockdown, which resulted in a greater loss of dopamine (DA) neurons and significant motor impairments. Additionally, MT1 knockdown reduced iron death resistance by blocking the Sirt1/Nrf2/Ho1/Gpx4 pathway and decreased ferritin Fth1 expression, which increased ferrous ion release. In vitro investigations validated these findings. Iron death was exacerbated by MT1 knockdown, which increased intracellular α-syn aggregation generated by precast fiber (PFF) and inhibited the production of the Fth1 protein and the Sirt1/Nrf2/Ho1/Gpx4 pathway. Conversely, these effects were reversed by MT1 overexpression. The results underscore the neuroprotective effect of MT1 in PD by revealing a unique mechanism by which MT1 activation reduces α-syn-induced iron death in PD.

Furthermore, it has been discovered that melatonin alters the gut flora, which in turn affects the systemic inflammatory state indirectly. According to research, melatonin improves gut health, decreases intestinal inflammation by blocking NLRP3 inflammatory vesicles, and boosts the number of bacteria that produce short-chain fatty acids.[39] Given the strong correlation between gut health and brain health, this modulatory function of the microbiota may be significant for people with PD.

Melatonin Controls the Circadian Cycle

Melatonin, a hormone mostly produced and released at night and crucial to the regulation of circadian rhythms, is secreted by the pineal gland. Its secretion is affected by variations in light, usually reaching its maximum in darkness and sharply declining in light. By attaching to melatonin receptors (MT1 and MT2) in the brain, melatonin controls the biological clock's operation, impacting alertness, sleep, and other physiological functions. Melatonin's regulating function is especially crucial in PD, which frequently causes circadian rhythm disruption and sleep difficulties.

Research suggests that melatonin levels may be linked to non-motor symptoms in people with PD. For example, one study found that plasma melatonin levels were much higher in individuals with PD than in healthy controls, and that these levels were negatively correlated with non-motor symptoms such as cardiovascular and sleep issues.[21] This implies that, whereas melatonin is a key regulator of normal physiology, anomalies in its production may be strongly linked to the pathological condition in PD patients.

By altering the expression of genes related to the biological clock, melatonin has also been shown to help restore the regular operation of circadian rhythms. For instance, it has been demonstrated that melatonin controls genes like Bmal1 and Per2 that are linked to the biological clock, which in turn impacts how stable biological rhythms are.[40]

Melatonin Controls Endocrine Cycles

By influencing the hypothalamic-pituitary-adrenal axis (HPA axis), a crucial system for controlling the body's stress response, melatonin not only influences sleep but also other endocrine processes. By preventing the release of stress hormones like cortisol, melatonin can reduce the body's stress response and enhance the psychological well-being and quality of life of PD patients.[26]

By controlling the gut microbiome, melatonin may also affect endocrine function. According to studies, the gut microbiota may convert tryptophan into melatonin, which enhances the operation of the gut barrier and the makeup of the microbiota, both of which have an impact on general health.[12] As a result, melatonin may have a variety of effects on endocrine control in PD patients, including direct effects on hormone secretion and indirect effects on sleep quality and microbiota modulation.

Melatonin Prevents α-Syn's Harmful Effects

One of the main pathogenic features of PD is alpha-synuclein (α-syn), and neuronal degeneration is directly linked to its aggregation to produce Lewy bodies. Through a variety of methods, melatonin prevents α-syn's harmful effects, which may affect how PD develops. First off, melatonin is thought to have potent antioxidant qualities that lower oxidative stress and scavenge free radicals from the body. One of the main causes of neuronal damage is oxidative stress, which is particularly significant in PD patients. Aggregation of α-syn is strongly linked to elevated oxidative stress. Research has demonstrated that by triggering the Nrf2 pathway and increasing the production of intracellular antioxidant enzymes, melatonin can prevent oxidative damage and shield neurons from α-syn-induced toxicity.[41]

Second, by regulating the inflammatory response, melatonin also prevents alpha-syn damage. Patients with PD frequently have a persistent inflammatory response in their neurological systems, and the activation of inflammatory cells makes α-syn aggregation worse. Melatonin reduces neuroinflammation and α-syn toxicity by blocking the production of pro-inflammatory cytokines such as IL-6 and TNF-α.[37]

Additionally, by controlling apoptotic pathways, melatonin may prevent α-syn toxicity. Melatonin has been shown to reduce neuronal apoptosis and preserve the life of neuronal cells by suppressing the production of apoptosis-related proteins, including caspase-3. Melatonin enhances neuronal survival and regeneration through this mechanism, while simultaneously reducing α-syn toxicity.[42]

Melatonin's Anti-Apoptotic Properties

Loss of dopaminergic neurons and increased apoptosis are two pathogenic hallmarks of PD, a neurodegenerative condition that mostly affects mobility. Melatonin (MT), an endogenous antioxidant and neuroprotective component,

has been demonstrated to be able to prevent apoptosis, lessen the death of dopaminergic neurons, and postpone the degenerative process of PD through a number of routes. Apoptosis is a key feature in the pathophysiology of PD.[56]

Research has demonstrated that melatonin uses a variety of pathways to prevent apoptosis. First of all, melatonin is a strong antioxidant that scavenges the body's ROS, minimizing oxidative stress-induced cellular damage. Melatonin prevented the activation of apoptosis-related proteins (such as Caspase-3) and dramatically decreased intracellular ROS levels in a PD model, shielding dopaminergic neurons from harm.[22] Oxidative stress is a major contributor to apoptosis in PD. Strong antioxidant melatonin may scavenge free radicals and shield against oxidative stress-related damage. Melatonin has been shown to inhibit apoptosis by increasing the activity of enzymes in the electron transport chain complex and the mitochondrial membrane potential (MPT). Additionally, melatonin lessens the damage that oxidative stress does to dopaminergic neurons by boosting the activity of antioxidant enzymes (including SOD and GSH-Px).[43]

In addition, it has been demonstrated that melatonin regulates the synthesis of endogenous nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), both of which are critical for the growth and survival of neurons. Melatonin counteracts the neurodegenerative alterations linked to PD by promoting neuronal survival and regeneration through the enhancement of these factors' expression.[41] Through a number of signaling channels, melatonin can suppress the production of proteins linked to apoptosis. Melatonin, for instance, decreases apoptosis in the MPP-induced PD cell model by preventing caspase-3 activation and increasing the Bax/Bcl-2 ratio via upregulating heat shock protein 70 (HSP70) and heat shock factor 1 (HSF1).[56] Melatonin also prevents apoptosis in dopaminergic neurons by suppressing the expression of caspase-9, Bax, and p53.

One of the main causes of apoptosis in PD is mitochondrial malfunction. By reducing mitochondrial oxidative stress, preserving the mitochondrial membrane potential, and triggering the SIRT3-SOD2 signaling cascade, melatonin prevents apoptosis.[44] This process preserves mitochondrial function while simultaneously lowering mitochondrial malfunction. The degenerative process of PD is significantly influenced by neuroinflammation, and over-activated microglia can trigger apoptosis by releasing a range of pro-inflammatory molecules, such as TNF-α and IL-1β. By preventing microglia from activating and lowering the production of inflammatory molecules, melatonin reduces inflammation-mediated apoptosis.[45]

Melatonin's Anti-Cellular Autophagy Effects

To preserve cellular homeostasis, cellular autophagy—a crucial intracellular degradation pathway—removes misfolded proteins and damaged organelles. However, disruption of the autophagic process may result in damage and death of neuronal cells in neurodegenerative illnesses like PD.

Research has demonstrated that melatonin regulates autophagy via a variety of pathways to provide its neuroprotective benefits. First, by stimulating the AMPK (adenylate-activated protein kinase) signaling pathway, which serves as a gauge of the energy level of cells, melatonin encourages autophagy. This signaling pathway also inhibits the mTOR (mammalian target of rapamycin) signaling pathway, which lessens the inhibition of autophagy. Applying melatonin to a PD model was shown to dramatically raise the expression of proteins linked to autophagy (such as LC3 and Beclin-1) and lower the amount of p62, indicating that melatonin stimulates autophagy.[37,46]

Second, through its antioxidant properties, melatonin also reduces intracellular oxidative stress, which influences the autophagy process. By scavenging ROS, melatonin reduces oxidative damage and creates an environment that is conducive to autophagy. Oxidative stress is thought to have a significant role in the pathophysiology of PD. In a PD model, melatonin was found to dramatically lower intracellular ROS levels and enhance mitochondrial function, both of which are strongly linked to autophagy activation.[37,41]

Furthermore, by regulating intracellular inflammatory responses, melatonin may influence autophagy. Impaired autophagy frequently coexists with increased inflammatory responses in PD. Autophagy is enhanced when melatonin suppresses the production of inflammatory molecules, such as TNF-α and IL-6. Melatonin supplementation has been shown to significantly decrease the activation of signaling pathways associated with inflammation, hence promoting autophagy recovery.[47,48]

In conclusion, melatonin has a variety of neuroprotective benefits on Parkinson's disease (PD) via a number of pathways (Figure 3), such as its anti-inflammatory, antioxidant, and circadian rhythm-modulating effects as well as its influence on autophagy and mitochondrial function. By lowering oxidative stress, maintaining mitochondrial integrity, reducing neuroinflammation, and promoting neuronal survival, these mechanisms work together to potentially delay the progression of Parkinson's disease (PD) and improve patients' quality of life (Figure 4).

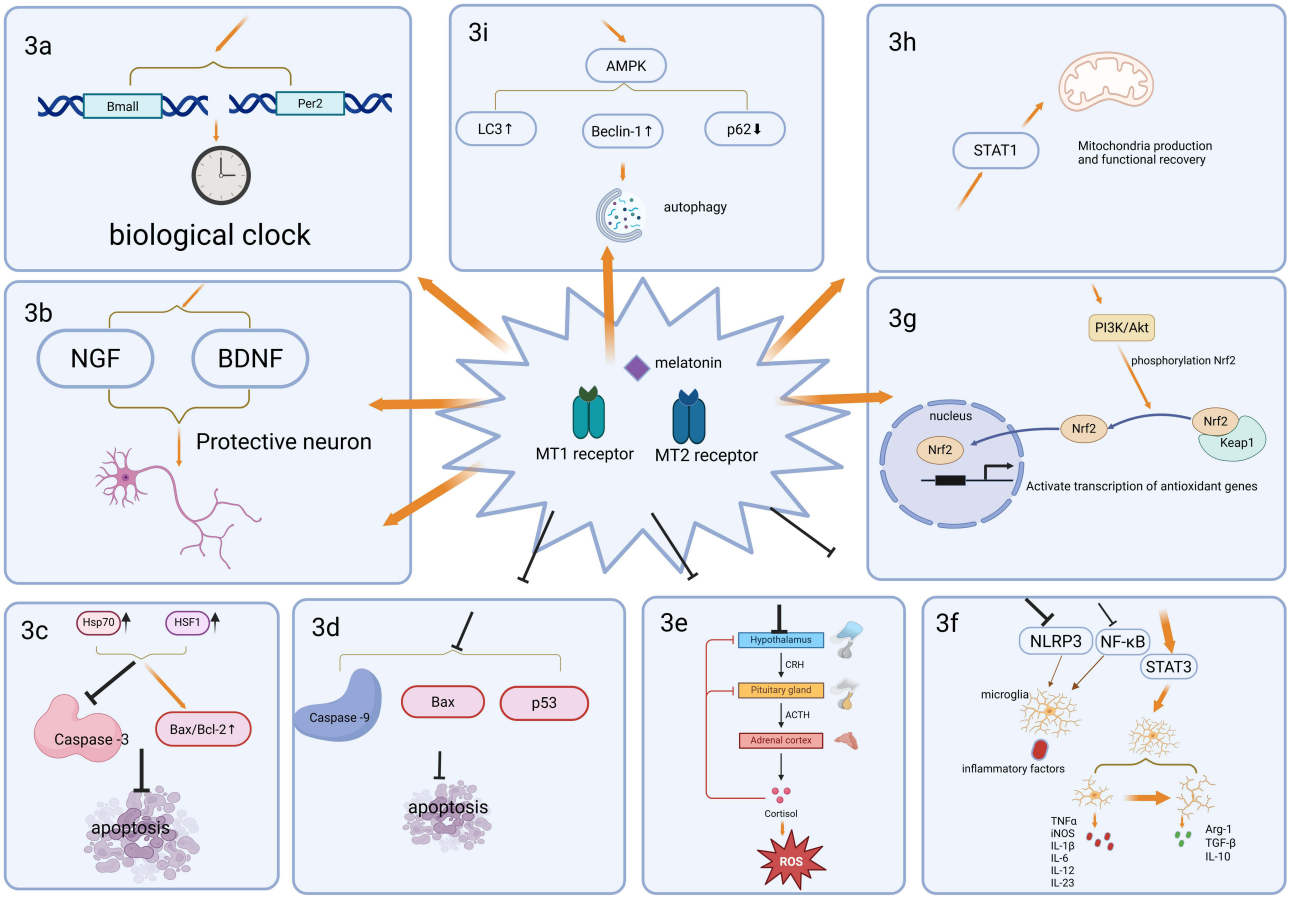

Figure 3 The diagram illustrates the complex interactions between melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) with various cellular and molecular pathways, highlighting their roles in neuroprotection, inflammation, autophagy, and mitochondrial function. (**a**) Melatonin affects the circadian rhythm through Bmal1 (Brain and Muscle Arnt-Like Protein 1) and Per2 (Period 2). (**b**) It promotes the expression of neurotrophic factors, such as NGF (Nerve Growth Factor) and BDNF (Brain-Derived Neurotrophic Factor), thereby protecting neurons. (**c**) Melatonin enhances the expression of HSP70 (Heat Shock Protein 70) and HSF1 (Heat Shock Factor 1), which in turn inhibits the expression of Caspase-3 and promotes the expression of Bax (Bcl-2-Associated X Protein) and Bcl-2 (B-Cell Lymphoma 2), ultimately protecting neurons from apoptosis. (**d**) Melatonin also inhibits the expression of Caspase-9 (Cysteine Aspartate-Specific Protease-9), Bax (Bcl-2-Associated X Protein), and p53 (Tumor Protein p53) to protect neurons from apoptosis. (**e**) Melatonin inhibits the hypothalamic-pituitary-adrenal (HPA) axis, showing how CRH (Corticotropin-Releasing Hormone) released from the hypothalamus stimulates the pituitary gland to release ACTH (Adrenocorticotropic Hormone), which then acts on the adrenal cortex to produce cortisol. This ultimately leads to the generation of ROS (Reactive Oxygen Species), which can influence inflammation and oxidative stress. (**f**) Melatonin inhibits the NLRP3 inflammasome (Nucleotide-binding domain, Leucine-rich repeat-containing family, Pyrin domain-containing 3) and NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) pathways, thereby reducing the production of pro-inflammatory factors such as TNFα (Tumor Necrosis Factor alpha), IL-1β (Interleukin-1 beta), IL-6 (Interleukin-6), IL-12 (Interleukin-12), and IL-23 (Interleukin-23). Concurrently, melatonin activates STAT3 (Signal Transducer and Activator of Transcription 3), leading to the secretion of anti-inflammatory cytokines, including IL-10 (Interleukin-10), TGF-β (Transforming Growth Factor beta), and Arg-1 (Arginase-1). This dual regulatory action of melatonin indicates its potential role in managing neuroinflammation. (**g**) Melatonin binds to these receptors, initiating the PI3K/Akt (Phosphoinositide 3-kinase/Akt signaling pathway). Activation of this pathway leads to the phosphorylation of Nrf2 (Nuclear factor erythroid 2-related factor 2), which is normally bound to Keap1 (Kelch-like ECH-associated protein 1) in the cytoplasm. Upon phosphorylation, Nrf2 is released from Keap1 and translocates to the nucleus. In the nucleus, Nrf2 binds to the ARE (Antioxidant response element), promoting the transcription of genes involved in antioxidant defense. This process is crucial for protecting cells against oxidative stress and maintaining cellular homeostasis. (**h**) The diagram also shows that melatonin promotes the role of STAT1 (Signal Transducer and Activator of Transcription 1) in mitochondrial biogenesis and functional recovery, which is essential for cell survival. (**i**) The diagram also illustrates that melatonin promotes the AMPK (AMP-Activated Protein Kinase) pathway, thereby increasing the expression of LC3 (Microtubule-Associated Protein 1A/1B-Light Chain 3) and Beclin-1 (Beclin 1) while inhibiting the expression of p62 (Sequestosome 1), regulating autophagy, which is crucial for cellular homeostasis. Overall, the diagram provides a comprehensive overview of how melatonin receptors integrate with various cellular pathways to maintain neuronal health and respond to stressors. Created in BioRender. yiwei, s. (2025) https://BioRender.com/rquuae4.

A Look at Clinical Presentations: How Melatonin Abnormalities Affect Parkinson's Disease

Sleep Disorders and Melatonin Disorders

One of the main causes of the increased frequency of sleep disruptions in PD patients is melatonin abnormalities. The indoleamine hormone melatonin, which is essential for regulating the sleep-wake cycle, is primarily produced by the pineal gland. Melatonin secretion has been shown to be severely disrupted in PD patients, as demonstrated by

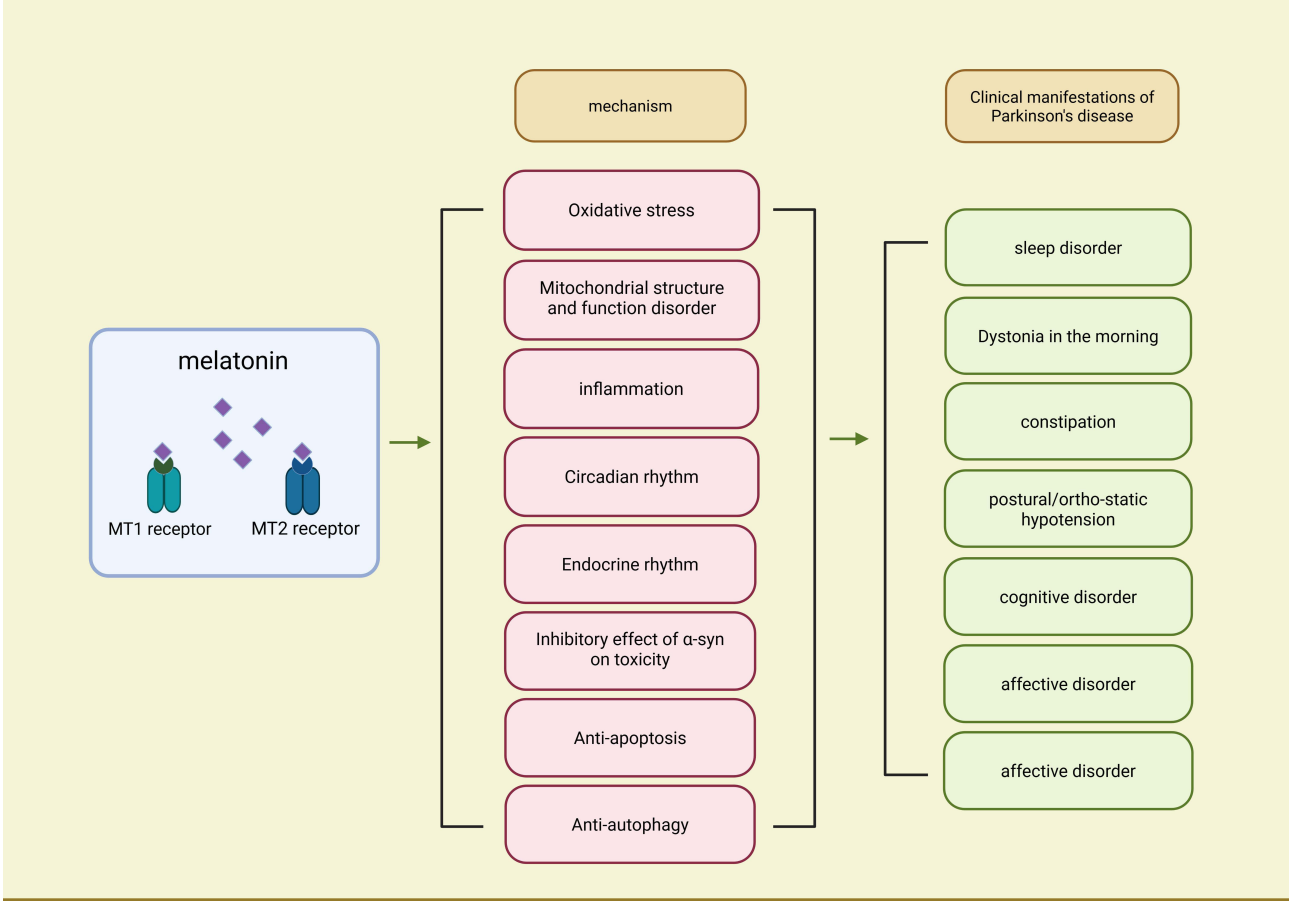

Figure 4 This diagram illustrates the potential mechanisms by which melatonin influences clinical manifestations of Parkinson's disease. Melatonin acts through MT1 (Melatonin Receptor 1) and MT2 (Melatonin Receptor 2) receptors, impacting various physiological processes. The mechanisms include reduction of oxidative stress, mitigation of mitochondrial structure and function disorders, anti-inflammatory effects, regulation of circadian and endocrine rhythms, inhibition of α-synuclein toxicity, anti-apoptotic actions, and anti-autophagy effects. These mechanisms collectively contribute to alleviating symptoms such as sleep disorders, dystonia in the morning, constipation, postural/ortho-static hypotension, cognitive disorders, and affective disorders, which are common clinical manifestations of Parkinson's disease. Created in BioRender. yiwei, s. (2025) https://BioRender.com/j4kk6ic.

a significant reduction in the 24-hour area under the curve (AUC) and the amplitude of the circadian rhythm.[26] This interruption can lead to circadian rhythm dysregulation, which may affect sleep quality.[26]

PD sleep-wake problems are largely caused by melatonin rhythm abnormalities, which have an impact on daytime waking, sleep maintenance, and sleep start. The most common sleep complaint among people with PD is difficulty falling asleep. Research has shown that delayed melatonin secretion phases (mean delay of 1.8 hours) directly result in significantly longer sleep latency[57](increase of 42 minutes compared to controls, $p<0.001$). These temporal phase shifts are closely linked to abnormal optical input signaling and degenerative neuronal changes in the suprachiasmatic nucleus (SCN).[58] PD patients had a noticeably earlier time to peak melatonin, which is inversely connected with depression symptoms and sleep quality.[59] Moreover, light exposure affects melatonin secretion, inhibiting it, and PD patients frequently have heightened light sensitivity, which may make their sleep difficulties worse.[52,60]

A distinct pattern of melatonin production in PD patients with respect to sleep maintenance problems is a 2.3-fold increase in the amplitude of changes in nocturnal melatonin levels57 (95% CI 1.7–3.1) as compared to healthy controls.[61] This irregular hormonal secretion rhythm also contributes to sleep fragmentation by influencing the generation of sleep spindle waves (12–15 Hz), which raises the sleep fragmentation index by 37%.[61] Melatonin levels were shown to be strongly and favorably connected with patients' sleep quality scores, and they were found to be considerably lower in PD patients than in healthy controls.[62] By acting on melatonin receptors in the suprachiasmatic nucleus, melatonin controls biological clock rhythms. If its production is decreased, the biological clock may be disrupted, which might result in trouble falling asleep, irregular sleep maintenance, and fragmented sleep.[63]

By decreasing sleep desire, attenuation may be a contributing factor to pathological daytime drowsiness. At the level of circadian rhythms, aberrant SCN function results in delayed temporal phases of melatonin secretion; at the level of sleep microstructure, aberrant melatonin fluctuation affects the stability of the sleep spindle wave; and at the level of circadian rhythmic strength, reduced melatonin amplitude causes blurring of the sleep-wake boundary. Furthermore, PD patients' sleep problems are linked to the brain-gut axis, and melatonin's part in this is slowly becoming clear. Intestinal flora imbalance in PD patients has been linked to aberrant tryptophan metabolism in the gut, which impacts the availability of precursors for melatonin production.[64] Sleep is further disrupted by tryptophan, a crucial raw material for the production of melatonin, and its metabolic abnormalities, which reduce melatonin synthesis.

To carry out its role in regulating sleep, melatonin mainly binds to melatonin receptors (MT1 and MT2). Studies have shown that melatonin improves sleep indices such as sleep onset latency, sleep efficiency, and sleep quality.[50,65] In individuals with PD, melatonin therapy has shown promise in enhancing sleep quality and lowering non-motor symptoms.[50,65] For example, melatonin levels over 10 mg/day have been shown to improve subjective sleep quality and reduce Unified PD Rating Scale (UPDRS) scores in PD patients. Additionally, melatonin-treated PD patients performed significantly better on sleep quality assessments than the placebo group.[65] After receiving 3 mg of melatonin for 8 weeks, individuals with PD showed notable improvements in their Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) ratings in a randomized, double-blind, placebo-controlled study.[26] By controlling circadian cycles and enhancing sleep architecture, melatonin also lessens the symptoms of RBD and Excessive Daytime Sleepiness (EDS).[26]

Even though melatonin's ability to treat sleep problems has been well researched, more excellent clinical trials are required to ascertain the best dosage and time of administration in order to maximize its effectiveness.[50,65] Furthermore, specific patient variables, including age, gender, and comorbidities, must be considered while using melatonin since they may impact its safety and effectiveness.[60,65]

Dystonia in the Morning

In addition to being crucial for controlling the sleep-wake cycle, melatonin may also have an impact on motor symptoms, such as morning dystonia, in people with PD. One of the most prevalent non-motor symptoms in people with PD is morning dystonia (MD), which typically shows up as stiff muscles and trouble moving when you wake up. Melatonin levels and the patient's biological clock are intimately linked to this phenomena. According to studies, people with PD frequently have low melatonin levels and circadian disorders, which may result in poorer quality sleep at night, which may then affect morning dystonia. They also frequently have disturbed melatonin levels, which may exacerbate morning dystonia.

According to one study, PD patients had considerably higher plasma melatonin levels than healthy controls (12.82 ± 4.85 vs 19.40 ± 4.23, $P < 0.001$), which may indicate that melatonin abnormalities are linked to the emergence of non-motor symptoms.[21] Melatonin's function in controlling biological cycles and the quality of sleep may be connected to the onset of morning dystonia. A patient may have dystonia upon waking up in the morning due to disruption of their biological clock caused by a melatonin deficiency or aberrant amounts. The receptors for melatonin (MT1 and MT2) are located in several brain areas, including those related to motor control. By influencing the release of neurotransmitters like dopamine, melatonin may have an impact on motor function in people with PD.[26] Furthermore, the anti-inflammatory and antioxidant properties of melatonin may be crucial for safeguarding dopaminergic neurons. Reduced melatonin levels in PD patients may result in compromised antioxidant defenses in nerve cells, which might hasten dopaminergic neuron death and worsen morning dystonia.[26] Melatonin and its receptor agonists have some promise in the treatment of PD because of the possible influence of melatonin abnormalities on PD morning dystonia. In PD patients, exogenous melatonin treatment might enhance sleep quality, perhaps reducing morning dystonia.[26]

Constipation

Known as the "second brain", the gut contains its own separate enteric nervous system (ENS) with over 500 million neurons. The modulation of intestinal peristalsis, the release of digestive juices, and other physiological processes are all significantly influenced by ENS. Multiple routes allow melatonin to influence ENS function. Melatonin receptors are

found on intestinal neurons in large quantities.[66] By interacting with enteric neurons' MT1 and MT2 receptors, melatonin has been shown to control the release of neurotransmitters.[67] Dopaminergic neurons are damaged in lesions in the enteric nervous system of PD patients, and melatonin imbalances may further disrupt the regular control of neurotransmitters. Serotonin primarily controls gastrointestinal motility through 5-HT_3 and 5-HT_4 receptors, and neurotransmitters like this one often play a significant part in the regulation of intestinal peristalsis in the gut.[68] Reduced serotonin levels are frequently seen in PD patients, which may result in less smooth muscle activity in the gastrointestinal tract, ultimately leading to constipation.[68] Furthermore, serotonin regulates the intestinal tract's secretory function; a drop in serotonin levels may impact intestinal water secretion, aggravating the symptoms of constipation.[68] Tryptophan may be transformed by gut microorganisms into a number of signaling chemicals, such as serotonin, melatonin, tryptamine, and various derivatives of indole.[69] Disturbances in melatonin may impact serotonin production and metabolism, which in turn may impact intestinal neurons that regulate intestinal peristalsis, resulting in a delayed intestinal transit time and constipation.

Conversely, neuroinflammation is frequently present in PD patients, and the inflammatory response will impact the ENS's normal function. According to some research, melatonin has anti-inflammatory qualities and can decrease the release of pro-inflammatory factors,[70] but when melatonin is disrupted, its anti-inflammatory effects are diminished and intestinal neuroinflammation is worsened, which interferes with the ENS's normal nerve conduction and impairs intestinal peristalsis, raising the risk of constipation.

Postural Hypotension

A substantial drop in blood pressure during postural changes (such as getting out of a sitting or reclining posture) is known as orthostatic hypotension (OH), and it can cause symptoms including weakness, dizziness, and even syncope. A growing body of research in recent years has demonstrated that postural hypotension is more common in PD patients and is strongly linked to a range of non-motor symptoms. The autonomic nervous system's malfunction and melatonin-related physiological alterations might be the factors behind this occurrence.

Melatonin insufficiency has been linked to aberrant sympathetic nerve activity, which may worsen the symptoms of postural hypotension. Melatonin levels are often low in PD patients.[21,27] By blocking NLRP3 inflammatory vesicle activation through Nrf2 pathway activation, the current study[71] showed that melatonin may protect against HG-induced vascular endothelial cell scorching. Additionally, melatonin was found to decrease HG-induced vascular endothelial cell damage via activating the Nrf2 pathway through its contact with receptors (MT1/MT2).[71]

The incidence of postural hypotension in PD patients is positively connected with the disease's severity. In particular, more severe motor and non-motor symptoms, such as anxiety, sadness, and sleep difficulties, are frequently present in individuals with postural hypotension. According to studies, individuals with postural hypotension frequently have an increased chance of falling while going about their everyday lives, which can significantly impair their quality of life and cause significant challenges.[23]

It should be noted that one of the early indicators of PD might be postural hypotension. Prior to the beginning of motor symptoms, many PD patients have signs of postural hypotension, according to studies. According to this, postural hypotension might be a helpful early screening method in clinical evaluation to assist in finding possible individuals with PD.[27,30]

Impairment of Cognition

Cognitive impairment is one of the most common non-motor symptoms in patients with PD. By controlling neurotransmitter balance, melatonin enhances cognitive function in addition to its anti-inflammatory and antioxidant qualities.[21,27]

Several variables, such as age, gender, the severity of the disease, and other comorbidities, are linked to the start of cognitive impairment in PD patients. According to studies, cognitive loss is closely linked to longer illness duration, and cognitive deficiencies may not be noticeable in the early stages of the disease until other non-motor symptoms appear in the patient.[6,23] Furthermore, using melatonin supplements may help people with PD improve their cognitive function,

particularly if they have poor sleep quality. Melatonin might also indirectly enhance cognitive performance by promoting better sleep.[24,72]

Cognitive diseases have different clinical manifestations and usually involve attention difficulties, memory loss, and executive dysfunction. It has been discovered that people with PD tend to demonstrate more difficulties in doing complicated activities, especially in circumstances that need rapid reflexes and flexible thinking.[49,73] In addition to impairing the patient's capacity for self-management, these cognitive impairments may cause social interaction issues, which would add to the patient's psychological load.

Melatonin has demonstrated promise as a possible supplementary therapy to enhance cognitive function from a therapeutic standpoint. Numerous studies have demonstrated that melatonin supplements help PD patients sleep better, and sound sleep is closely linked to enhanced cognitive performance.[65,74] Additionally, melatonin's antioxidant qualities could aid in delaying the onset of neurodegeneration, thereby partially preserving cognitive function.

Chronic rapid eye movement sleep deprivation (CRSD) prolonged swimming distance and escape latency in the Morris water maze and significantly decreased recognition indices in the new object location test, indicating that CRSD primarily affects hippocampus-dependent spatial learning and memory.[75] According to a study,[75] melatonin administration dramatically restored the substantial decrease in HDAC3 (histone deacetylase 3) protein levels in the hippocampus caused by CRSD. By controlling gene expression through deacetylation, HDAC3, a crucial protein in the management of circadian rhythms and cognitive function, influences both neuroplasticity and circadian rhythms. By regulating HDAC3 activity and boosting circadian gene expression, melatonin may enhance cognitive performance. Melatonin, therefore, modulates HDAC3-Bmal1/Clock connections to reduce cognitive abnormalities caused by CRSD. In particular, melatonin therapy markedly corrected the cognitive deficiencies caused by CRSD in the Morris water maze and Novel Object Position Test.

In a dose-dependent way, $CoCl_2$ decreased the survival of SH-SY5Y cells, caused apoptosis, and hampered neuronal synaptic plasticity.[76] Reduced performance on the Y maze test and the Novel Object Recognition Test (ORT), together with fewer neurons in the hippocampus and cortex, are indicators of neurological damage and cognitive dysfunction in stroke mice. In vitro and in vivo, melatonin attenuates stroke-induced cognitive impairment and neurological damage by reducing apoptosis, inhibiting excessive mitochondrial autophagy, and improving synaptic plasticity.[76] By encouraging the expression of synaptic proteins like PSD-95 and synaptophysin, improving synaptic transmission and long-duration potentiation (LTP), safeguarding synaptic structures, modifying the BDNF signaling pathway, and preventing excessive mitochondrial autophagy, melatonin enhances synaptic plasticity. These benefits, which considerably reduce stroke-induced impairment of synaptic plasticity and cognitive dysfunction, have been shown in both a mouse model of stroke and a $CoCl_2$-induced hypoxic damage cell model.[76] In conclusion, melatonin has the potential to be used in neuroprotection and cognitive recovery as it reduces neurological damage and cognitive dysfunction brought on by CRSD and stroke through a variety of pathways.

Disorders of the Emotions

According to studies, mood disorders can take many different forms in people with PD, including anxiety, depression, and mood swings. These symptoms are closely linked to melatonin imbalances in addition to the disease's physiological mechanisms. The hormone melatonin, which primarily regulates the sleep-wake cycle, is secreted by the pineal gland. Variations in its levels may have a significant effect on mood states. There is a negative correlation between elevated depression symptoms and lower melatonin levels in PD patients. According to one study, PD patients' plasma melatonin levels were noticeably lower than those of healthy controls.[21] Furthermore, sleep disturbances can result from melatonin deprivation, and mood disorders and poor sleep quality are mutually reinforcing. According to studies, depression symptoms are present in around 40% of PD patients and frequently appear before motor symptoms.[27]

There are many ways in which melatonin influences depression symptoms in PD. First of all, it controls neurotransmitter systems, such as the 5-hydroxytryptamine (5-HT) and dopamine systems. Degeneration of dopaminergic neurons in the substantia nigra-striatal pathway reduces dopamine levels and results in depressed symptoms in patients with PD. By modifying melatonin receptors (MT1 and MT2), which in turn control dopamine production and release, melatonin influences the activity of dopaminergic neurons.[74] Melatonin, on the other hand, interacts with 5-HT receptors

to control 5-HT levels and alleviate depression symptoms.[77] Second, melatonin boosts synaptic plasticity and facilitates the rebuilding of brain networks by controlling the production of BDNF (Brain-derived neurotrophic factor), which in turn promotes neuroplasticity, neurogenesis in the hippocampus, and the number of newborn neurons.[78,79]

Melatonin's anti-inflammatory and antioxidant qualities may be linked to its mode of action in mood modulation. Melatonin plays a key role in the pathogenesis of PD by scavenging free radicals and lowering oxidative stress in the body. Oxidative stress is thought to play a major part in neuronal death and damage, which can result in mood disorders.[6] It has been discovered that melatonin supplements help PD patients with their depression symptoms, particularly when their sleep quality improves Melatonin Ameliorates Abnormal Sleep.[72]

Furthermore, it is important to consider how melatonin affects mood disorders by controlling circadian rhythms and the biological clock. Normal melatonin output can aid in restoring circadian rhythms, which can enhance mood states in PD patients who frequently have disturbed rhythms.[80] Melatonin supplementation can successfully enhance the emotional state of people with PD, particularly in the initial phases, according to many clinical studies.[24]

Additionally, melatonin contains anti-inflammatory[81] and antioxidant[82] properties that protect neurons by lowering oxidative stress levels in PD patients' brains, preventing the production of inflammatory cytokines, and minimizing the inflammatory response. Lastly, via activating MT1 and MT2 receptors, melatonin reduces depression symptoms by modifying neuronal excitability and synaptic transmission.[74] In the 6-OHDA-impaired model of PD, melatonin treatment significantly reduced depressive-like behaviors like reduced immobility time and increased swimming frequency. In a PD model, melatonin and the MT2 receptor agonist, 4-P-PDOT, demonstrated synergistic antidepressant-like effects. Melatonin receptors are located together with dopamine neurons in the globus pallidus of the olfactory bulb, suggesting a role in mood and olfactory function.[74]

In conclusion, melatonin imbalances and mood abnormalities in PD patients are closely related. PD patients' mood symptoms may be lessened and their quality of life may be enhanced by raising their melatonin levels. Through a variety of mechanisms, such as neurotransmitter system modulation, neuroplasticity promotion, circadian rhythm regulation, antioxidant and anti-inflammatory effects, and melatonin receptor modulation, melatonin improves depressive symptoms in PD patients and enhances their quality of life.

Obstacles and Opportunities for Clinical Use

The use of melatonin, a crucial bioregulatory hormone, in PD patients is fraught with difficulties. First, even though melatonin has been shown to have potential benefits in regulating sleep and reducing non-motor symptoms, more research is necessary to prove its safety and efficacy in therapeutic settings. One research study, for instance, discovered that plasma melatonin levels were considerably greater in PD patients than in healthy controls; however, it is unknown how these levels relate to non-motor symptoms such as gastrointestinal dysfunction, sleep problems, and cardiovascular symptoms.[21] This implies that although melatonin may help PD patients in certain ways, further research is required to fully understand its precise mode of action and indications.

Second, a significant obstacle in clinical use is determining the appropriate dosage and method of melatonin delivery. Clinical studies have demonstrated that melatonin, particularly at levels of 10 mg/day or higher, can help people with PD with their motor symptoms and sleep issues.[24] Responses might differ greatly from patient to patient, and there is currently no agreement on the ideal melatonin dosage and course of therapy. Furthermore, further randomized controlled trials are required to confirm the safety of melatonin for long-term usage.

Individual patient characteristics also impact the usage of melatonin in clinical practice. The effectiveness of melatonin may be impacted by the range of non-motor symptoms that are frequently present in people with PD, including sadness, anxiety, and cognitive impairment.[72] As a result, customized treatment programs are especially crucial for various patients, and in order to create a logical treatment plan, physicians must consider the patient's unique symptoms as well as the course of the illness.

The use of melatonin, an essential bio-regulatory hormone, in the treatment of Parkinson's disease (PD) remains controversial. On one hand, studies of plasma melatonin levels in PD patients have yielded conflicting results. Some research indicates that PD patients have significantly higher plasma melatonin levels compared to healthy controls. For instance, in a study by Li, the plasma melatonin level in PD patients was 19.40±4.23 pg/mL, while in the control group, it

was 12.82±4.85 pg/mL (P<0.001).[21] This suggests that abnormal melatonin secretion may be associated with non-motor symptoms such as sleep disorders and cardiovascular symptoms. However, other studies[25] have found a negative correlation between melatonin levels and levodopa dosage, implying that pharmacological treatment may interfere with melatonin rhythm. This contradiction may stem from the disruption of the circadian rhythm of melatonin secretion. In PD patients, the nocturnal peak of melatonin may occur earlier or later, leading to inconsistent changes in the area under the 24-hour curve (AUC), rather than a uniform increase or decrease in overall levels.

On the other hand, the clinical efficacy of melatonin in treating PD is also a matter of debate. Regarding the improvement of motor symptoms, high doses of melatonin (≥10 mg/d) have shown modest benefits in some randomized controlled trials (RCTs), as evidenced by a reduction in UPDRS scores. Yet, other studies[57] have found no significant effect of melatonin on motor symptoms, especially in patients with moderate to severe disease. In terms of sleep improvement, melatonin at doses of 3–5 mg/d can significantly reduce sleep latency in PD patients. For example, an RCT by Sugumaran demonstrated a 42-minute reduction in sleep latency. However, doses exceeding 10 mg/d may induce daytime somnolence, indicating a narrow therapeutic window.[26]

Given these controversies and the need for further clarification, the following integrated directions are suggested for future research:

First, large-scale, multicenter randomized controlled trials (RCTs) with a follow-up period of at least 1 year and a sample size of at least 300 participants should be conducted. These trials should evaluate the long-term effects of different melatonin doses (3 mg/d, 10 mg/d, and 20 mg/d) on both motor and non-motor symptoms in PD patients. This will help determine the optimal dosing regimen and therapeutic window for melatonin.

Second, biomarker-oriented studies should be carried out to measure the expression levels of MT1/MT2 receptors and oxidative stress markers (such as 8-OHdG) in the peripheral blood of PD patients. Establishing a biomarker model for predicting melatonin efficacy will aid in personalized treatment planning and early diagnosis.

Third, PET imaging techniques should be employed to observe the effects of melatonin on α-synuclein deposition and microglial activation in the brains of PD patients. This will provide direct evidence of melatonin's neuroprotective effects and elucidate its mechanisms of action.

Additionally, further research should focus on understanding how melatonin exerts its neuroprotective, antioxidant, and anti-inflammatory properties in PD. Extensive clinical trials should be conducted to evaluate melatonin's safety and effectiveness at various stages of the disease and to investigate its potential for use in combination with other therapies. Examining how melatonin affects PD biomarkers will also aid in early diagnosis and the creation of tailored treatment plans.

Conclusion

The medical world has progressively begun to pay close attention to melatonin's possible benefits in treating PD in recent years. It has been demonstrated that melatonin not only regulates sleep and the biological clock, but it may also influence the progression of PD by controlling neurotransmitter release and having anti-inflammatory, antioxidant, and other effects. This finding implies that we can expand our therapy ideas and provide fresh insights into the intricate physiological systems behind PD.

According to a review of the research, melatonin imbalances are believed to be intimately linked to both motor and non-motor symptoms in PD patients. Melatonin deficit is directly linked to the worsening of several non-motor symptoms that patients frequently display, including depression, sleep difficulties, and cognitive deterioration. Some patients' non-motor symptoms have improved after taking melatonin supplements, which suggests that melatonin may be utilized as an adjuvant therapy. It's crucial to remember that not all research backs up this theory; others indicate that melatonin is less beneficial and may even have negative side effects. Therefore, a key area of future study will be how to balance the opinions and conclusions of many investigations.

To guarantee the validity of the findings, future clinical studies should focus more on increasing the sample size and maintaining trial design rigor. Research should also focus on individualized therapy methods because individual characteristics among patients (eg, age, gender, length of illness, etc.) may affect the benefits of melatonin. We may

be able to develop more specialized treatment plans by classifying patients and examining how each subgroup of individuals responds to melatonin.

Meanwhile, a critical topic for future research is determining the optimal dosage and timing of melatonin administration. There are currently no established guidelines for the use of melatonin in PD, leaving doctors perplexed about when and how to provide dosages. Thus, a solid foundation for therapeutic use will be provided by methodical investigation of the pharmacokinetic properties of melatonin and its interactions with other medications.

Melatonin's potential benefits in the treatment of PD will become clearer when more study is done on the hormone. People with PD may have new hope because of melatonin, a reasonably safe and affordable therapeutic option. But scientific research needs time and patience to advance, so we anticipate more excellent clinical trials in the future to uncover melatonin's full potential in PD treatment and to provide patients with better management choices.

Abbreviations

BDNF, Brain-derived neurotrophic factor; CNS, Central Nervous System; DA, Dopamine; EDS, Excessive Daytime Sleepiness; ENS, Enteric Nervous System; HDAC3, Histone Deacetylase 3; HPA, Hypothalamic-Pituitary-Adrenal Axis; IL-6, Interleukin 6; LPS, Lipopolysaccharide; MD, Morning Dystonia; MT1/MT2, Melatonin Receptor 1/Melatonin Receptor 2; NGF, Nerve Growth Factor; NLRP3, NOD-Like Receptor Pyrin Domain Containing 3 Inflammasome; PD, Parkinson's Disease; RBD, Rapid Eye Movement Sleep Behavior Disorder; ROS, Reactive Oxygen Species.

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