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REVIEW PAPER

Melatonin and Parkinson Disease: Current Status and Future Perspectives for Molecular Mechanisms

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Abstract

Parkinson disease (PD) is a chronic and neurodegenerative disease with motor and nonmotor symptoms. Multiple pathways are involved in the pathophysiology of PD, including apoptosis, autophagy, oxidative stress, inflammation, α-synuclein aggregation, and changes in the neurotransmitters. Preclinical and clinical studies have shown that melatonin supplementation is an appropriate therapy for PD. Administration of melatonin leads to inhibition of some pathways related to apoptosis, autophagy, oxidative stress, inflammation, α-synuclein aggregation, and dopamine loss in PD. In addition, melatonin improves some nonmotor symptom in patients with PD. Limited studies, however, have evaluated the role of melatonin on molecular mechanisms and clinical symptoms in PD. This review summarizes what is known regarding the impact of melatonin on PD in preclinical and clinical studies.

Keywords Melatonin · Parkinson disease · Apoptosis · Autophagy · Oxidative stress

Introduction

Parkinson disease is a chronic and neurodegenerative disease with motor (Swallowing disorder, speech disorder, bradykinesia, hypokinesia and tremor), and nonmotor (cognitive and sleep disorder) symptoms (Connolly and Lang 2014). Diagnosis of PD usually is occurred by the first motor symptoms Hughes et al. (2007). Swallowing problems is occurred in 40–80% of the PD patients (Kalf et al. 2011). Speech disorder also is occurred in more than half of the PD patients (Perez-Lloret et al. 2012). In addition, cognitive impairment was noted in a quarter of the patients with PD without any dementia disorder (Aarsland et al. 2010). Patients with PD have low quality of life due to pain and depression (Balash et al. 2019). Decreased dopamine secreting and its neurons are apparent in the substantia nigra (SN) (Connolly and Lang 2014). Up to 80% of dopaminergic neurons are lost before the revealing motor symptoms of PD (Chung et al. 2001). The dysregulation of cytosolic dopamine and reactive metals, especially iron, plays an essential role in pathogenesis of PD (Zucca et al. 2017). Oxidative stress, inflammatory factors, aquaporin 4, and apoptosis pathways seem to contribute to the pathophysiology of PD (Anglade et al. 1997; Jenner 2003; Zucca et al. 2017; Hughes et al. 2007). The etiology of PD is multifactorial, and there is no definitive treatment that will stop development of the disease. Existing treatments are symptomatic, aim of which is correcting the motor disorders. For example, levodopa is a standard drug and the most common treatment for patients with PD (Jankovic and Stacy 2007). However, it has been reported that it develops different complications on consuming levodopa in PD patients (Toth et al. 2008; Thanvi and Lo 2004). Today, beneficial effects of different diets and supplements, including vitamins (Lima et al. 2018), medical plants (Venkatesh et al. 2019; Mahboubi et al. 2016), probiotics bacteria (Borzabadi et al. 2018; Thanvi and Lo 2004; Tamtaji et al. 2019c), and melatonin (Delucca et al. 2018; Tamtaji et al. 2019a) were indicated in controlling PD or other age-related disorders.

Melatonin (*N*-acetyl-5-methoxy tryptamine) is best known for its synthesis within the pineal gland (Lerner et al. 1958). Melatonin is produced in mammals, unicellular

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eukaryotes, plants, and bacteria (Slominski et al. 2012). Obviously many species that produce melatonin have no pineal gland. Melatonin exists widely in many types of food including meat, eggs, nuts, and medical herbs (Reiter et al. 2001; Mercolini et al. 2012; Tan et al. 2003, 2014). Melatonin precursor is L-tryptophan is converted to melatonin via four enzymes including N-acetyltransferase, N-acetylserotonin methyltransferase, tryptophan hydroxylase, and L-aromaticamino acid decarboxylase (Tan et al. 2016). Function of melatonin often is triggered through interactions with its membrane receptors (MT1 and MT2) which are G protein-coupled receptors (Dubocovich and Markowska 2005; Reppert 1997; Hattori et al. 1995). Several physiological/pathological conditions also change the morphology of the pineal gland (Grosshans et al. 2016; Bumb et al. 2014). The degree of pineal calcification might be an indicator of diminished ability of the pineal gland to produce melatonin. The reduced 6-sulfatoxymelatonin excretion with age is associated with the increased pineal calcification (Kunz et al. 1999). There are calcium deposits in 21% and cysts in 59% of the glands in older men (Sigurdardottir et al. 2016). Calcified pineal volumes in various age groups are different (Beker-Acay et al. 2016). The changes of pineal gland lead to lower pineal melatonin and B-cells in aging (Paltsev et al. 2016). In addition to melatonin, melatonin receptors drop with aging (Hill et al. 2013). Melatonin levels are also related to aging (Waldhauser et al. 1988).

The severe damping of a bioenergetic oscillatory pattern was seen in the fibroblasts of PD patients. Clock genes are deregulated in PD fibroblasts (Pacelli et al. 2019). Dysfunctional circadian clock in PD is involved in abnormal antioxidative response through SIRT1-dependent brain and muscle Arnt-like protein 1 (*BMAL1*) pathway (Wang et al. 2018). *BMAL1* and *rPer1* significantly decreased in PD patients (Cai et al. 2010; Mattam and Jagota 2015). The expression of *BMAL1* in patients with PD has significant correlation with disease severity (Cai et al. 2010). *Per1* genes are changed in PD, which has important role in pathogenesis of PD (Gu et al. 2015). It has been reported that melatonin affects clock gene expression. Torres-Farfan et al.(Torres-Farfan et al. 2006) found that maternal melatonin affects clock genes such as *BMAL1* and *Per* in primate fetus. Melatonin regulates different clock genes such as *mPer1, mCry1*, and *BMAL1* via MT1 receptor (von Gall et al. 2005). In a study, administration of melatonin led to the restoration of *rPer1* daily rhythm in PD (Mattam and Jagota 2015).

The biological effects of melatonin are extremely widespread. Melatonin could control molecular action such as oxidative stress signaling (Galano et al. 2011; Reiter et al. 2000), inflammatory pathways (Li et al. 2005; Kim et al. 2012), immune responses (Moore and Siopes 2000; Carrillo-Vico et al. 2006), apoptosis (Mayo et al. 1998; Muñoz-Casares et al. 2006), physiological rhythm (Zawilska et al. 2009; Skene and Arendt 2006) as well as influencing chronic diseases, such as, diabetes (Winiarska et al. 2006; Espino et al. 2011), obesity (Agil et al. 2011; Hussein et al. 2007), kidney injuries (Hussein et al. 2007; Leibowitz et al. 2016), cardiovascular diseases (Dominguez-Rodriguez 2012; Dominguez-Rodriguez et al. 2012), cancers (Tamtaji et al. 2019b), neurological disorders (Wang and Wang 2006; Yang et al. 2011; Farez et al. 2015) and aging-related conditions (Karasek and Reiter 2002; Wu and Swaab 2005). Circulating melatonin levels are reduced in patients with PD (Breen et al. 2014). Decreased melatonin levels markedly are correlated with disease severity and hypothalamic gray matter volume in patients with PD (Breen et al. 2016). Melatonin decreased the degenerating neurons, oxidative stress, and apoptosis in paraquat and maneb-induced PD in mice (Singhal et al. 2011). In addition, a study reported that melatonin led to formation of scavenged ·OH, increased GSH, and increase in the activity of cytosolic SOD in neuronal perikarya of PD mice (Thomas and Mohanakumar 2004). Also, this supplement prevented upregulation of CDK5 in the striatum and decreased a-synuclein aggregation in animal model of PD (Su et al. 2015). Kunz and Mahlberg (2010) noted that melatonin improved sleep behavior in patients with PD. The aim of this review is to assess the current knowledge related to the effects of melatonin supplementation on PD and its pathophysiology.

The Effects of Melatonin on Clinical Symptom in Patients with PD

Rare studies evaluated the effects of melatonin on patients with PD. A study reported that administration of melatonin improved nonmotor disorders in patients with PD (Dowling et al. 2005). Kunz et al. (2010) noted that melatonin improved sleep behavior in patients with PD. Many studies have shown that melatonin supplementation improves the quality of sleep. However, motor symptoms were not improved in PD patients (Medeiros et al. 2007). There are no studies on the effects of melatonin supplementation on molecular mechanism in PD patients. More studies clearly need to evaluate the effects of melatonin on clinical symptoms and molecular mechanisms in clinical studies.

The Effects of Melatonin on Molecular Mechanisms in the In Vitro and In Vivo Model of PD

Melatonin and Oxidative Stress in PD

Oxidative stress is involved in neurodegeneration in PD and activation of c-Jun N-terminal kinase (JNK) and c-Jun that

are important role in cell death (Jenner 2003; Wang et al. 2008). Few studies reported the effects of melatonin on oxidative stress signaling in PD. Administration of melatonin (20 and 30 mg/kg) increased superoxide dismutase (SOD), mitochondrial complex-I activity, and glutathione (GSH) in SN in a rat model of PD induced by homocysteine. In addition, melatonin at dosage of 10, 20 and 30 mg/kg decreased hydroxyl radical (·OH) and increased catalase in the SN of rat model of PD induced by homocysteine (Paul et al. 2018). In a study, melatonin 10 mg/kg was administered, and this led to increases of GSSG/GSH ratio and increased GSH in some part of brain in rat model of PD induced by MPP+ (Chen et al. 2002). Melatonin also decreased 8-Oxoguanine in rat model of PD induced by MPTP (Chen et al. 2005). Jin et al. (1998) reported that melatonin decreased MDA in rat model of PD induced by MPTP. In addition, melatonin decreased MDA, increased SOD, decreased dopaminergic neuron death, increased CAT, and increased GPx in the SN of rat model of PD induced by 6-OHDA (Ozsoy et al. 2015). Melatonin increased GSH and CAT in SN, increased GSH in the striatum and increased SOD contents in the SN in rat model of PD induced by rotenone (Saravanan et al. 2007). Melatonin decreased the number of degenerating neurons and lipid peroxidation in the paraquat and maneb-induced PD in mice (Singhal et al. 2011). Thomas and Mohanakumar (2004) reported that melatonin led to scavenged ·OH formed, increased GSH, increase in the activity of cytosolic SOD in neuronal perikarya of PD mice. In addition, a study reported that melatonin significantly decreased oxidative stress in in vitro model of PD induced by MPP (+) (Chuang et al. 2016). Another study also indicated that administration of melatonin significantly decreased oxidative stress caused by MPTP-induced PD in mice (Ortiz et al. 2013).

Melatonin and Apoptosis Pathways in PD

Increased oxidative stress, decreased antioxidant enzymes, and mitochondrial dysfunction lead to apoptosis and cell death of neurons (Annunziato et al. 2003; Jenner 2003). Some animal models of PD are induced using 6-hydroxydopamine (6-OHDA) (Simola et al. 2007; Thiele et al. 2012), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Meredith and Rademacher 2011; Jackson-Lewis and Przedborski 2007), homocysteine (Mansouri et al. 2012), and rotenone (Sherer et al. 2003; Tanner et al. 2011). 6-OHDA causes cell apoptosis in both in vivo (Zuch et al. 2000) and in vitro (Blum et al. 1997). The different proteins such as p38 MAPK, Bax, and caspases are activated in apoptotic cascade by 6-OHDA (Mei and Niu 2014; Cheng et al. 2007; Gomez-Lazaro et al. 2008; Ochu et al. 1998). 6-OHDA downregulates Bcl-2 and Bcl-w gene expressions and upregulates Bax and Bad expressions. However, Glial cell line derived neurotrophic factor (GDNF) is reversed these changes (Cao et al. 2013). Caspase-3 activation is associated to MPTP-induced PD in rodents (Yamada et al. 2010). MPTP activate caspase-9 via cytochrome *c* release that leads to activation of caspase-8 and Bid cleavage which trigger to dopaminergic cell death (Viswanath et al. 2001). MPTP neurotoxicity leads to dopaminergic cell death via activation of the caspase-11 cascade and inflammatory cascade, in addition to mitochondrial apoptotic process (Furuya et al. 2004). MPTP/MPP+ also leads to the activation and phosphorylation of JNK, JNK kinase (MKK4), and c-Jun (Xia et al. 2001). Rotenone induces the activation of caspase-3 which leads to dopaminergic cell death (Ahmadi et al. 2003). Increased caspase-3, caspase-9, and Hsp60 are observed in the rotenone-induced PD model (Angeline et al. 2012).

Few studies reported the effects of melatonin on cell death and apoptosis signaling in PD. Melatonin (10 mg/kg) decreased DNA fragmentation in striatum and midbrain, lowered apoptosis cells in midbrain in PD rats induced by MPTP (Acuna-Castroviejo et al. 1997). Administration of melatonin (500 µg/kg, i.p) limited DNA fragmentation in PD rats induced by MPTP (Antolin et al. 2002). In a study, melatonin 10 mg/kg was administered, and this led to decreased apoptosis cell in the striatum in rat model of PD induced by MPP + (Chen et al. 2002). Patki and Lau (2011) reported that melatonin improved mitochondrial deficit in mice model of PD induced by MPTP. Melatonin decreased P-p53, Bax, and caspase 9 expressions and increased the levels of p53 in the paraquat- and maneb-induced PD in mice (Singhal et al. 2011) In addition, melatonin decreased caspase-3 and dopaminergic neuron death, and increased expression of Bcl-2 in PD rats (Yildirim et al. 2014). In addition, a study reported that melatonin significantly decreased neuron death and mitochondrial fragmentation in vitro model of PD induced by MPP (+) (Chuang et al. 2016). Moreover, melatonin has neuroprotective effects through inhibition of calpain/cdk5 signaling in in vitro model of PD (Alvira et al. 2006).

Melatonin and Autophagy Pathway in PD

Autophagy has an essential role the pathogenesis of PD (Lynch-Day et al. 2012). MPTP as an inductor of PD leads to increase in CDK5 in MPTP-induced PD in mice. CDK5 is involved in the regulation of autophagy to mediation of neuronal cell death and neurotoxicity (Naskar et al. 2015b). However, melatonin decreased kainic acid-induced neurotoxicity through inhibition of autophagy (Chang et al. 2012). Another study also reported that melatonin improved CDK5-induced autophagy and cell death in PD induced by MPTP in monkey (Su et al. 2015). More studies are required to evaluate the effects of melatonin on autophagy pathways in PD.

Melatonin and Neuroinflammation in PD

Cyclooxygenase type-2 (COX-2) is involved in neuroinflammation in PD (Choi et al. 2009). Moreover, it has been reported that MPTP elevated Inducible nitric oxide synthase (iNOS) activity in striatum and substantia nigra. In addition, iNOS-dependent increased nitric oxide was seen that is known as a pathological hallmark of neuroinflammation in PD (López et al. 2017). However, melatonin prevented elevation of iNOS in MPTP-induced PD mice (López et al. 2017). In addition, administration of melatonin significantly decreased COX-2 activity in MPTP-induced PD in mice (Ortiz et al. 2013). Rare studies evaluated the effects of melatonin on neuroinflammation in PD. More studies are required to evaluating the effects of melatonin on neuroinflammation in PD.

Melatonin and Pathological Hallmarks

The overexpression of α-synuclein has an important role in the pathogenesis of PD (Eller and Williams 2011; Zarranz et al. 2004). α-Synuclein induces dopaminergic nerve terminal degeneration (Saha et al. 2000; Masliah et al. 2000). Aggregation of non β amyloid component (NAC) and α-synuclein proteins induced neuronal apoptosis (El-Agnaf et al. 1998; Lee et al. 2001). α-Synuclein induces apoptosis through the activation of caspases, while Hsp70 inhibits these processes as by sequestering and binding to α-synuclein (Flower et al. 2005).

Studies that evaluated the effects of melatonin on α-synuclein in PD are rare. Melatonin at a dosage of 10 mg/kg decreased alpha-synuclein in striatum in rat model of PD induced by rotenone (Lin et al. 2008). Also, this supplement prevented upregulation of CDK5 in the striatum and decreased a-synuclein aggregation in PD induced by MPTP in monkey (Su et al. 2015). In addition, a study reported that α-synuclein triggers impairment of respiration in yeast; however, melatonin improved this condition (Zampol and Barros 2018). More studies are required to evaluate the effects of melatonin on α-synuclein in PD.

Melatonin and Neurotransmitters

Decreases in dopamine levels and dopaminergic neurons are induced in PD (Berendse et al. 2001). Few studies evaluated the effects of melatonin on dopamine in PD. Patki and Lau (2011) reported that melatonin increased nigral and striatal dopamine concentrations and improved locomotor deficit and mitochondrial deficit in mice model of PD induced by MPTP. Another study indicated that striatal dopamine loss induced by MPTP was not improved by melatonin in MPTP-induced PD in mice. However, low doses of L-DOPA along with melatonin significantly decreased striatal dopamine loss and improved in both akinesia and catalepsy MPTP-induced PD in mice (Naskar et al. 2013). A study by Brito-Armas et al. (2013) reported that melatonin prevented dopaminergic cell loss caused by mutant alpha-synuclein.

Daily rhythms related to serotonin metabolism and gene expression of various clock genes in the animal model of PD induced by rotenone. Decreases in mean 24-h levels of melatonin, 5-hydroxytryptophan, serotonin, and N-acetyl serotonin and in the suprachiasmatic nucleus of animal model of PD induced by rotenone in rats could be due to reduction of activity of tryptophan hydroxylase. However, administration of melatonin restored these changes (Naskar et al. 2015b). More studies are required to evaluate the effects of melatonin on dopamine and other neurotransmitters in PD.

Genetical Changes

Mutations of leucine-rich repeat kinase2 (*LRRK2*) gene have important role in pathogenesis of PD (Gilks et al. 2005), whish mutations of *LRRK2* leads to cell death and neurodegeneration (Iaccarino et al. 2007). A study reported that melatonin decreased hLRRK2-induced memory dysfunction in the drosophila model of PD (Ran et al. 2018). In addition, a study indicated that hLRRK2 is involved in the synaptic dysfunction and sleep disorder in PD, while melatonin decreased hLRRK2-induced synaptic dysfunction and sleep disorders (Sun et al. 2016). Moreover, administration of melatonin led to rescue of zebrafish embryos from the MPTP-induced PD phenotype restoring the parkin/PINK1/DJ-1/MUL1 (Díaz-Casado et al. 2016).

Melatonin, an Ideal Adjuvant to Treatment with L-DOPA

It is an interesting point to note that the combination of melatonin with L-DOPA was more effective than monotherapy. A study indicated that combination of melatonin with L-DOPA had more neuroprotective effects in animal model of PD (Naskar et al. 2013). Melatonin increased treatment effects of L-DOPA, and decreased its dosage in animal model of PD (Naskar et al. 2015a). Therefore, melatonin may be a perfect and ideal adjuvant to treatment with L-DOPA in PD.

Conclusions

Increasing evidence documents that melatonin has a profound influence on PD. Herein we summarized the effects of melatonin on apoptosis, autophagy, oxidative stress, inflammation, α-synuclein aggregation, and changes in the neurotransmitters in preclinical and clinical investigations related

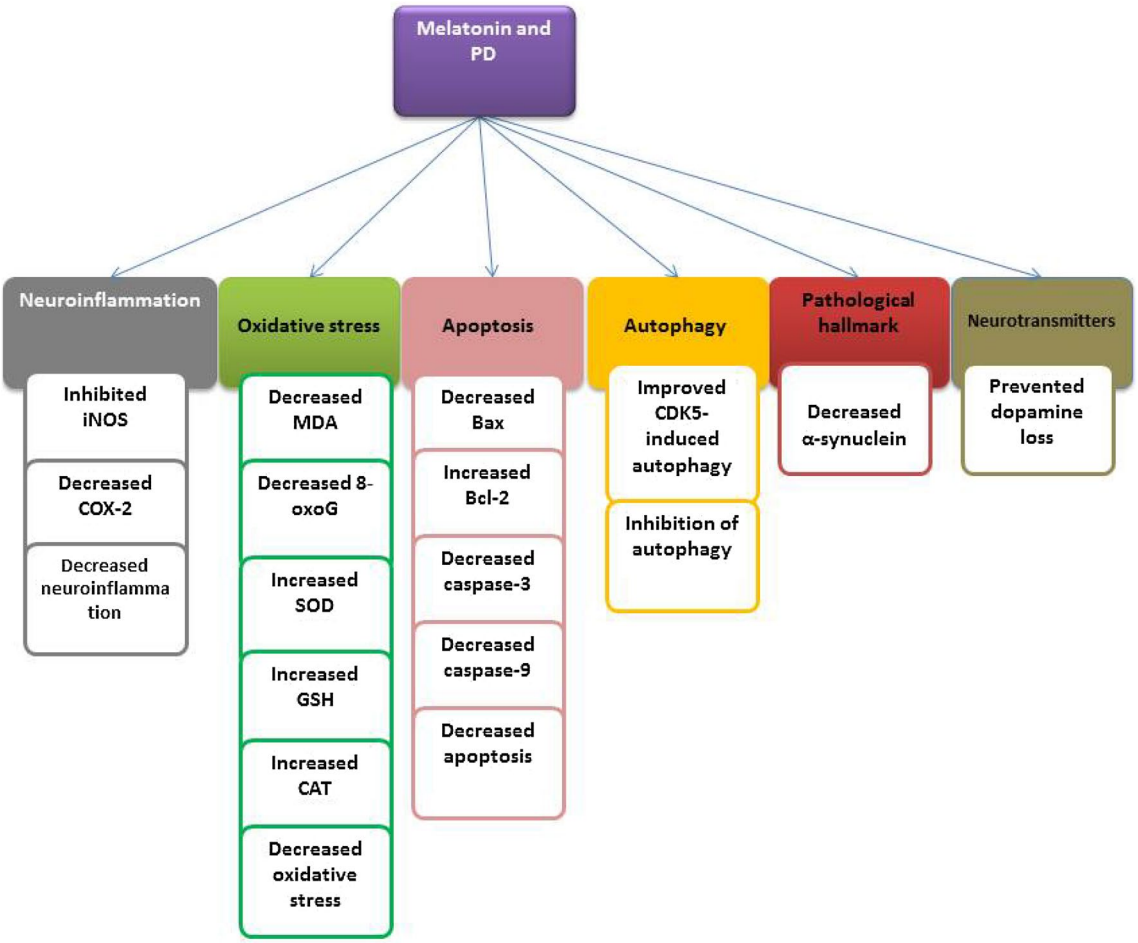

Fig. 1 Schematic representation of targeting molecular signaling pathway by melatonin in the PD

to PD. Administration of melatonin led to inhibition of some pathways related to apoptosis, autophagy, oxidative stress, inflammation, α-synuclein aggregation, and dopamine loss in PD (Fig. 1). In addition, melatonin improved some non-motor symptoms in patients with PD. Further assessments on the impacts of melatonin on PD-related pathways at the molecular level and clinical symptoms are required. Moreover, preclinical studies documented that melatonin may be a perfect and ideal adjuvant for treatment with L-DOPA in PD, to confirm which finding more clinical studies are needed.

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Compliance with Ethical Standards

Conflict of interest The authors declare there are no conflicts of interest.

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