SDRP Journal of Cellular and Molecular Physiology(ISSN: 2574-4046)

THE ROLES OF MELATONIN IN PARKINSON'S DISEASE: AN OVERVIEW

DOI: 10.25177/JCMP.2.1.6

Research

Author: Chye Soi Moi

August 2017

Received Date: 29th Jun 2017
Accepted Date: 26th Jul 2017
Published Date:10th Aug 2017

Xue Zhen Lim[1], Rhun Yian Koh[1], Khuen Yen Ng[2], Soi Moi Chye[1,*]

[1]Division of Applied Biomedical Science and Biotechnology, School of Health Sciences, International Medical University, Kuala Lumpur 57000, Malaysia
[2]School of Pharmacy, Monash University Sunway Campus, Bandar Sunway, Selangor 47500, Malaysia

CORRESPONDENCE AUTHOR
Soi Moi Chye
Email: chye_soimoi@imu.edu.my
Address: Division of Applied Biomedical Science and Biotechnology, School of Health Sciences, International Medical University, Kuala Lumpur 57000, Malaysia. Phone: +603- 27317220 Fax: +603-8656 7229

CONFLICTS OF INTEREST
There are no conflicts of interest for any of the authors.

ABSTRACT
When the central nervous system loses its nerve cell functions over a period of time, symptoms and problems arise leading to the progression of neurodegenerative diseases. Statistical data shows that more than 5 million people worldwide are affected by Parkinson's disease [PD], and the data is undesirably rising every year. In PD patients, structural and functional changes are shown in the brain, especially the substantia nigra region. The underlying cause that correspond to the development of PD remains unclear. Nevertheless, α-synuclein aggregation has been reported to be neuropathologically linked to PD. On the other hand, several evidences successfully demonstrate the importance and significance of mitochondrial dysfunction in PD models. Treatments available for PD are limited. Recently, as shown in some studies, the antioxidant properties and hypnotic benefits of melatonin bring remarkable contribution to the PD patients. Hence, in this article, we focus on the effect of melatonin associating with the pathology and physiology of PD.

Keywords: Antioxidant; Melatonin; Parkinson's disease; Pathophysiology

INTRODUCTION
Parkinson's disease (PD) is associated with irreversible neuronal dysfunction, specifically the progressive depletion of dopaminergic neurons in the substantia nigra pars compacta, which play a role in dopamine neurotransmission [1-2]. Many studies proved that the dopaminergic cell loss in substantia nigra contributes significant effects to PD patients. Other related studies proposed some possible underlying causes of PD, for example, mitochondrial dysfunction, activation of glial cells due to oxidative stress in micro-environment, as well as gene mutations [3-6]. In PD models, oxidative stress built in dopaminergic neuronal cells is suggested to be the major cause of neuronal cell death [7]. Monoamine oxidase initiates the production of reactive oxygen species (ROS) by catalyzing dopamine oxidation, which can eventually lead to the pathogenesis of PD [8]. On the other hand, α-synuclein (α-syn) is the first and most important gene found to be closely related to PD. It is responsible for the formation of Lewy bodies and variation at its locus is the major genetic risk factor for sporadic PD [9-10].

The main clinical manifestations of PD are akinesia, rigidity and tremor at rest. There are also a wide spectrum of cognitive symptoms [11-13]. Most fre-

quently, patients develop PD symptoms gradually over a period of years. Patients with PD often show notable body movements and features such as tremor in hand or foot, limbs rigidity, postural instability, insomnia, rapid eye movement sleep behavior disorder and motor impairment [14-17]. There is currently no cure for PD. The treatments available are mostly used to improve symptoms of the disease [18]. Hence, new or alternative therapies for PD are in demand.

Melatonin (*N*-acetyl-5-methoxytryptamine) is a tryptophan which is secreted by pineal gland in the brain. It is a major product during dark phase [19-21]. Melatonin also plays an autocrine or paracrine role due to its secretion in various cells and organs such as bone marrow, thymus, skin and eyes [22]. Circulating melatonin binds to albumin and metabolized by liver enzymes, cytochrome P450 monooxygenases A2 and 1A, to produce 6-hydroxymelatonin. A series of reactions are continued with the conjugation with sulphuric acid to yield 6-sulfatoxymelatonin, which is a major melatonin metabolite found in urine [23]. Melatonin carries out many functions in the body including sleep regulation, seasonal reproduction, control of circadian rhythms and free radical scavenging [24-25]. Melatonin shows its sleep-promoting effect in many studies. However, the results are debatable due to the short half -life of melatonin and inadequate dosing while conducting the study [26-27].

Melatonin is well characterized to be highly related to PD diagnosis. Hence, it could be one of the great indexes to be measured for the severity of PD. Study found that levels of melatonin in PD patients are lesser as compared with controls [28-29]. Melatonin receptors, MT1 and MT2 are expressed in several parts of the central nervous system. A previous study reported that the receptors are down-regulated in PD patients, hence suggesting the possible involvement of melatonin in the disease [30]. Furthermore, melatonin shows some relationships with dopamine such as its turnover, content modulation and receptor activation [28]. Considering the important involvement of melatonin in PD, we have thus reviewed the roles of melatonin in the pathophysiology of PD in this article.

MELATONIN ACTS AS ANTIOXIDANT IN PD

Due to its well-known neuroprotective and antioxidative stress properties, melatonin's actions on PD are conducted in many *in vivo* and *in vitro* studies [31-32]. Melatonin is well-known with its antioxidant properties that block prooxidant enzymes' expression while promoting antioxidant enzymes genes expression [33]. Previous study proved that melatonin has several desirable characteristics which make it a good antioxidant. It binds to iron and attenuates Fenton reaction as well as hydroxyl radical generation. The highly reactive hydroxyl radical is produced via the Fenton reaction in the presence of excess iron [34-35].

Melatonin has been shown to prevent oxidative stress in the early stages of neurodegenerative process. Brain contains high amount of polyunsaturated fatty acids and requires high energy input, which makes it susceptible to free radical-mediated insults [36]. To evaluate the potential anti-PD effects of melatonin, 6-hydroxydopamine (6-OHDA) was used to destroy the dopaminergic neurons in the study models. 6-OHDA is known to cause increase in ROS production and mitochondrial dysfunction. The ability of melatonin in elevating several antioxidant enzymes is discovered in the studies [37]. Besides, melatonin is proved to be able to modulate astrocyte activity by regulating antioxidative defenses [38].

MELATONIN RESCUES MITOCHONDRIAL DYSFUNCTION IN PD

The major function of mitochondria is to produce energy by generating adenosine triphosphate (ATP) through the electron transport chain (ETC). ETC, which is found in the inner mitochondrial membrane, comprises oxido-reductant protein complexes such as Complex I, II, III and IV. It mediates signals among cells to generate energy from atmospheric oxygen [39]. Under normal circumstances, incomplete oxygen reduction produces less than 2% of electrons. The leakage of electrons causes the superoxide radicals to be rapidly converted into hydrogen peroxide (H_2O_2). Subsequently, mitochondria become a site where it is responsible for the overproduction of ROS, therefore the main source of free radicals in cells. The elevation in hydrogen ion-electrochemical gradient is another result obtained from the transferring of metabolic substrates via ETC to molecular oxygen [40]. Evidences of Complex I and glutathione (GSH) deficiencies in substantia nigra are reported in most of the PD patients, hence supported the relationship between PD and mitochondrial dysfunction. Due to the lack of catalase in mitochondria, neuronal cells have to rely on GSH to act as antioxidant and protect against H_2O_2-induced apoptosis. In previous research, melatonin showed to restore GSH in the isolated GSH-depleted brain mitochondria, thus increase the glutathione peroxidase and glutathione reductase activities [41].

Recent *in vivo* studies proved that melatonin when added to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced zebrafish embryo, successfully restored brain function and prevented parkinsonian phenotypes. MPTP injection is used to mimic the characteristics of PD patients. In this study model, mitochondrial dysfunction is noted when mitochondrial Complex I is inhibited. Incredibly, melatonin helped in mitochondrial homeostasis and integrity, thus protecting mitochondria from being destroyed by the deleterious effects of MPTP [42]. Additionally, melatonin has been shown to act as a protective agent against excitotoxicity by reducing the autoxidation of dopamine in MPTP-induced mice [43]. Apart from that, melatonin-treated mice were reported to have normalized Complex I ac-

tivity and oxidative status in mitochondria of substantia nigra and striatum regions [44].

Melatonin is particularly picked up by mitochondria. It prevents the inhibition of mitochondrial respiration by limiting the interaction of 1-methyl-4-phenylpyridinium with Complex I [44]. The deficiency in Complex I activity is believed to be associated with reduction in GSH levels and induction of oxidative stress. Furthermore, ROS production and lipid peroxides are demonstrated to cause mitochondrial DNA (mtDNA) damage [45]. In this case, melatonin was found to provide protection to mitochondrial respiratory chain and mtDNA from oxidative damage, leading to an effective increase in Complex I and Complex IV expressions and activities. In mitochondrial dysfunction, inducible nitric oxide synthase (iNOS) activity and nitric oxide (NO) synthesis are enhanced, therefore inhibit the ETC and mitochondrial permeability transition [46]. However, melatonin with its powerful antioxidative properties, is proved to possibly inhibit iNOS and terminate the NO production. Moreover, by reducing mitochondrial oxygen consumption and its membrane potential, melatonin effectively increases mitochondrial ETC efficiency that in turn reduces electron leakage such as superoxide and H_2O_2 production [47].

Aging process also evidently reduced the mitochondrial capacity and neuronal functions. Here, melatonin is suggested as a therapeutic agent to delay the aging process in normal brain and to treat neurodegenerative disorders [48]. Melatonin was found to inhibit mitochondrial cell death pathways, hence promoting neuronal cell survival [49].

MELATONIN REGULATES CIRCADIAN RHYTHM IN PD

Another important topic related to the pathophysiology of PD is the adjustment of patient's circadian rhythm. Circadian rhythm or wake-promoting system, is one of the central factors controling the physiology and behaviors of PD patients [50]. In PD patients, non-motor symptoms such as insomnia, excessive morning sleepiness, rapid-eye-movement sleep behavior disorder and obstructive sleep apnea are very frequently reported upon examination [11, 13]. Depression in fact is associated with a disturbed circadian rhythm [51-52].

MT1 and MT2 are deprived in PD, and this explains on the wakefulness that is experienced by most of the PD patients [30]. Melatonin plays a role in regulating sleep pattern specifically through the inhibition of circadian signal at the suprachiasmatic nucleus via the MT1 and MT2 receptors [30]. Additional dose of melatonin to ongoing levodopa treatment before bedtime resulted in longer hours of sleep and higher sleep efficiency as compared with untreated group in animal models of PD [53]. In a clinical trial, PD patients that were given melatonin showed a minimal improvement in sleep disorders, with no adverse effect resulted from the treatment [54]. Other studies also indicated that melatonin administration resulted in restoration in daily rhythm of various clock genes expression, hence resetting the disturbed circadian pacemaker [55]. Morover, agomelatine, an antidepressant that produces melatonergic effects shows promising results in treating a variety of sleep disorders in PD [56].

Despite all the evidences presented, there is still lack of sufficient data to fully support the use of melatonin in managing PD as the known treatment benefits are limited [57].

OTHER EFFECTS OF MELATONIN ON PD

Melatonin activates the cells through G-protein coupled membrane receptors, mainly the MT1 and MT2, and nuclear receptors like retinoid orphan receptors and retinoid Z receptor (RZR) . MT1 and MT2 receptors have seven membrane domains which are categorized into the superfamily of G-protein coupled receptors. MT2 receptor has lower affinity (Kd=160pmol/l) for ^{125}I-melatonin as compared with the human MT1 receptor (Kd=20-40pmol/l) [59]. Studies on PD models reported that RZRα & RZRβ receptors, which can be found in the nervous system, lymphocytes and monocytes, have great association with cell differentiation and inflammatory reactions [58]. Melatonin exhibits potent anti-inflammatory properties such as inhibiting TNF-α, which is responsible for proinflammatory cytokines synthesis and suppression of iNOS gene expression [59].

Melatonin shows its antiapoptotic effects in many PD models. It protects neuronal cells from damages induced by neurotoxic substances such as MPTP, 6-OHDA and rotenone [60-62]. *In vivo* study concluded that melatonin possesses an unprecedented ability to prevent neurons in the midbrain from apoptotic cell death [60]. Study also showed that melatonin effectively attenuates kainic acid-induced neurotoxicity and arsenite-induced apoptosis by inhibiting the aggregation of α-syn [63-64]. Other than that, melatonin is reported to block and suppress the expression of α-syn fibril formation, which contribute greatly to the management of PD [63-64].

CONCLUSION

Effects of melatonin in the pathophysiology of PD were investigated in many studies to understand its roles and mechanisms. From the *in vivo* and *in vitro* studies, melatonin showed to prevent oxidative stress-induced mitochondrial dysfunction and help in managing sleep disorders in PD. However, melatonin has short half-life, and late melatonin administration due to the delay in PD diagnosis make the treatment benefits debatable. Furthermore, PD is characterized by irreversible dopaminergic neurons degeneration, and there is no evidence proving that melatonin is able to regenerate damaged neurons in the nigostriatal pathway. Thus, further related studies are crucial to fully understand the role of melatonin in the pathophysiology of PD.

ACKNOLEDGEMENTS
The authors wish to thank International Medical University, Malaysia in supporting the project.

AUTHOR CONTRIBUTIONS
X.Z.L drafted the manuscript. R.Y.K, K.Y.N and S.M.C edited and revised the manuscript. All authors approved the final version of the manuscript.

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