CIM
eISSN 2635-9162 / https://chronobiologyinmedicine.org
Chronobiol Med 2022;4(4):137-140 / https://doi.org/10.33069/cim.2022.0031

REVIEW ARTICLE

Circadian Rhythms in Parkinson's Disease

Yoonha Hwang

Department of Neurology, The Catholic University of Korea Eunpyeong St. Mary's Hospital, Seoul, Korea

Circadian rhythm is a biological process that regulates neuronal, metabolic, and hormonal functions following a 24-hour cycle. Parkinson's disease (PD) is a progressive neurodegenerative disorder, and it exhibits diurnal fluctuations in motor and non-motor symptoms. Recently, increasing attention has been paid to circadian dysfunction in PD patients. This review summarizes the existing research on the circadian rhythms in PD especially endogenous markers, clinical symptoms, and available treatment options.

Keywords: Circadian rhythm; Parkinson's disease; Sleep; Chronobiology

Received: December 5, 2022 Revised: December 9, 2022 Accepted: December 11, 2022
Corresponding author: Yoonha Hwang, MD, MS, Departments of Neurology, The Catholic University of Korea Eunpyeong St. Mary's Hospital, 1021 Tongil-ro, Eunpyeong-gu, Seoul 03312, Korea.
Tel: 82-2-2030-4502, E-mail: yoonhaha10@gmail.com

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by bradykinesia, rigidity, tremor, impaired balance, and non-motor symptoms such as cognitive dysfunction, sleep disturbance, autonomic system dysfunctions, pain, and mood disorders. These symptoms exhibit diurnal oscillations, so increasing attention has been paid to circadian rhythms in PD patients.

The sleep-wake cycle in PD is profoundly disrupted in both motor and non-motor symptoms [1]. The pathophysiological mechanisms are not yet clear, several evidence have shown reciprocal interactions between dopamine (DA) system and circadian rhythms. Dopamine receptor system may mediate psychostimulant-induced changes in clock gene expression [2]. On the other hand, circadian-associated genes (e.g. *Clock*) regulate the expression and phosphorylation of tyrosine hydroxylase that the rate-limiting enzyme in dopamine synthesis [3]. Moreover, production of melatonin, that is regulator of the sleep-wake cycle, by the pineal gland is regulated by a circadian-related heteromerization of adrenergic and dopamine receptors [4].

Neuroanatomical sites of circadian disruption in PD may be along the afferent pathways to the suprachiasmatic nucleus (SCN), within the SCN itself, or within the downstream peripheral efferents of the SCN [5]. In an alpha-synuclein overexpressing transgenic mouse study, the peak/trough expression of the clock gene *PERIOD2* was normal in the SCN; however, the daytime firing rate of SCN neurons was reduced in the mutant mice [6].

Mechanisms underlying circadian fluctuations of symptoms and signs of PD remain unknown. This review summarizes the existing research on the circadian rhythms in PD especially endogenous markers, clinical symptoms, and available treatment options.

MARKERS OF CIRCADIAN SYSTEM IN PD PATIENTS

Circadian rhythms are physiological and behavioral cycles with a periodicity of approximately 24 hours, generated by the endogenous biological clock in the SCN, and can be characterized by analyzing well-established endogenous circadian markers such as melatonin and cortisol [7].

Initial studies about melatonin revealed no significant differences in the amplitude of the melatonin rhythm and its phase advance relative to healthy controls [8,9]. Later studies investigated melatonin levels in different stages of PD with or without levodopa treatment. One found that the plasma melatonin level phase is more advanced in patients receiving a dopaminergic treatment compared with untreated PD patients [10]. And the dopaminergic treatment also increases the secretion of melatonin (measured by salivary melatonin) and induces delayed sleep onset, suggesting dopaminergic therapy in PD results in an uncoupling of circadian and sleep regulation [11]. On the other hand, some studies

reported reduced melatonin production and blunted melatonin rhythm in PD patients, especially with excessive daytime sleepiness [12,13].

Cortisol, another marker of circadian function, is also impaired in PD patients. Cortisol secretion is dominated by the hypothalamic-pituitary-adrenal (HPA) axis, which receives the circadian flow from the hypothalamic paraventricular nucleus. So the secretory rhythm of cortisol could be regarded as a sensitive marker of circadian function [14]. Breen et al. [12] examined cortisol levels in 30 patients with early PD, there was an elevated total serum cortisol level and half of the patients had arrhythmic cortisol profiles but with no phase shifting. Moreover, salivary diurnal cortisol level is not affected by L-dope treatment, duration, and severity of PD [15]. In an animal study, neuroendocrine abnormality of the HPA was investigated in 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP)-treated dogs as a model of PD. The concentrations of plasma cortisol increased by 60% after MPTP treatment, and circadian rhythm of plasma cortisol concentration was observed. This implied that the HPA axis is modulated by the circadian rhythm and dopamine function [16].

Although these investigations suggest modifications of circadian rhythmicity in PD, results are to be interpreted with caution due to small sample sizes and study designs that reflect influences of both endogenous circadian and exogenous (e.g., light exposure, physical activity, meals, social schedules) rhythms on PD [5].

CLINICAL EXPRESSION OF CIRCADIAN RHYTHMS DISRUPTION IN PD

Motor fluctuation

Circadian fluctuations of motor symptoms in PD are very common. Several studies reported actigraphy results that showed the absence of normal diurnal motor activity changes in advanced PD patients [1,17], and these changes are in strong correlation with the disease severity [18,19]. Also, responsiveness of PD motor symptoms to dopaminergic medications decreased later in the day than in the morning and may be more closely related to circadian regulation of dopaminergic systems [20,21]. In animal studies, there are no direct evidence for circadian fluctuation in PD. 6-Hydroxydopamine (6-OHDA) PD rat model had reduced locomotor activity, while the overall diurnal distribution of motor activity remained unchanged [22]. Also, in the 6-OHDA lesioned rodent model dyskinesia L-dopa-induced are not influenced by the time of L-dopa administration, nor the genetic variance, nor the time of the day it was administered [23]. Considering these studies, the disease stage may be a major contributor while the pharmacokinetic factors also affect the motor fluctuation.

Blood pressure and heart rate alteration

Signs or symptoms of impaired autonomic regulation of circulation, including blood pressure and heart rate, often attend PD patients, may increase long-term morbidity [24,25]. Twenty-four-hour (24-h) ambulatory blood pressure monitoring (ABPM) showed presence of reversal of circadian rhythm (93%), postprandial hypotension (100%), and nocturnal hypertension (100%) in PD patients [26]. Patients with a non-dipper or riser pattern on 24-h ABPM exhibited a higher prevalence of autonomic disorders (orthostatic hypotension) and received higher doses of dopaminergic treatment. A day-night variation in diastolic blood pressure was the most important marker of these findings. Orthostatic hypotension and supine hypertension lead patients to visceral damage and increased mortality rates [27].

Heart rate variability (HRV) change in PD is also very common. Circadian autonomic fluctuation of HRV has been evaluated in untreated PD patients indicating that spectral components of HRV were significantly suppressed especially during the nighttime [28,29]. However, some say it could only be a consequence of reduced motor activity besides being a marker of cardiovascular dysautonomia. Devos et al. [30] found a loss of HRV and distinct sympathetic morning peak with decreased nocturnal vagal parameters in moderate and severe L-dopa-treated patients. They speculated that the evolutive HRV decrease is correlated with the disease severity. On the other hand, Harnod et al. [24] reported impaired HRV is significantly correlated with the duration of PD, but not with disease severity and patient age. A case-control study, including 20 PD patients with REM sleep behavior disorder (PD-RBD) and 20 PD patients without RBD (PD), showed cardiac sympathetic and parasympathetic index were significantly higher in PD-RBD patients than in PD patients. The night-to-day ratio of low-frequency values (cardiac sympathetic index) accurately distinguished PD-RBD patients from those with PD on an individual basis [29].

Cardiovascular dysautonomia is increasingly accepted as a prodromal 'window' in which PD can be detected [25,31]. Monitoring of dysautonomia is recommended because it could increase the risk of cardio-cerebral vascular incidents, affecting the patients' life quality and life spans.

Visual impairment

Experimental evidence has shown that the mammalian retina contains a complete circadian clock system−biochemical machinery that generates temperature-compensated 24-h oscillations, an input pathway by which light synchronizes the cycling of the retinal clock to the environmental light/dark cycle, and neurochemical output pathways that transmit the clock's influence throughout the retina and into the rest of the brain. The circadian clock system in the retina allows the anticipation of the normal cycle of photopic and scotopic visual conditions that alternate with the cycling of solar day and night [32]. In the rat study, retinal dopamine concentration and synthetic rate exhibit a circadian rhythm and it persists in the absence of time cues [33]. Dopamine is a chemical messenger for light adaptation and is involved in trophic functions of the retina, including growth, development, and cell death [34].

The study about visual performance in PD assessed by 2-hour intervals contrast sensitivity showed fluctuation during early morn-

ing and afternoon. Visual performance gets worse at 2:30 PM than at 8:30 AM, but in controls, it was unchanged throughout the day. The results suggest that visual performance fluctuation may be related to dopamine deficiency [35]. Dearry and Burnside [36] reported that dopamine induces light-adaptive retinomotor movements in cones, rods, and retinal pigment epithelium cells by activating D2 receptors by animal in vivo study. Van Hook et al. [37] also revealed that dopamine modulates the function of the intrinsically photosensitive retinal ganglion cells by regulating the expression of the photopigment melanopsin. So, loss of dopaminergic neurons in PD may cause circadian fluctuations.

CIRCADIAN THERAPIES IN PD PATIENTS

Exposure to bright light can reset the human circadian pacemaker, which controls daily variations in physiologic, behavioral, and cognitive function [38]. Light is the most important and potent stimulus to "zeitgebers" which makes circadian rhythms synchronized with the solar day. Also, exposure to light could increase retinal dopamine activity [39]. So, there were several studies using light to treatment in a variety of sleep and neuropsychiatric conditions including circadian rhythm disorders, seasonal affective disorder, and dementia [40,41]. Paus et al. [42] examined effects of bright light therapy on motor symptoms, depression, and sleep in PD in a randomized placebo-controlled double-blind study in 36 PD patients. In the results, light therapy led to significant improvement of depression, tremor, and other motor symptoms. Another exploratory study also examined the effects of bright light in PD, and documented significant improvements in depression, bradykinesia, rigidity, and dyskinesias [43]. Currently, the available pharmacological and lifestyle-based therapeutic interventions for circadian alterations have at best modest impact on the symptoms with little or no effect on the intrinsic neuropathology [44-46]. Therefore, further validation studies including larger cohorts and employing objective outcome measures are needed.

CONCLUSIONS AND FUTURE DIRECTIONS

Increasing evidence suggest disruptions of the circadian system in PD, and these circadian impairments likely contribute to the progressive deterioration of the clinical signs and symptoms. From this review, we could understand about melatonin, cortisol as the circadian system markers, clinical symptoms, and bright light therapy as a treatment option. A major question which arises is whether circadian disruption is a causal factor for PD pathogenesis or a consequence of PD progression. Further systematic longitudinal investigations are needed to examine more thoroughly neuronal network underlying the generation of circadian rhythms. It will make us could develop mechanism-based therapies for circadian disruption and shed new insights about the neurodegenerative process of PD itself.

Funding Statement
None

Conflicts of Interest
The author has no potential conflicts of interest to disclose.

Availability of Data and Material
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iD
Yoonha Hwang
https://orcid.org/0000-0002-2624-9336

REFERENCES

1. Whitehead DL, Davies AD, Playfer JR, Turnbull CJ. Circadian rest-activity rhythm is altered in Parkinson's disease patients with hallucinations. Mov Disord 2008;23:1137-1145.
2. Imbesi M, Yildiz S, Dirim Arslan A, Sharma R, Manev H, Uz T. Dopamine receptor-mediated regulation of neuronal "clock" gene expression. Neuroscience 2009;158:537-544.
3. McClung CA, Sidiropoulou K, Vitaterna M, Takahashi JS, White FJ, Cooper DC, et al. Regulation of dopaminergic transmission and cocaine reward by the clock gene. Proc Natl Acad Sci U S A 2005;102:9377-9381.
4. González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, Mallol J, et al. Circadian-related heteromerization of adrenergic and dopamine D_4 receptors modulates melatonin synthesis and release in the pineal gland. PLoS Biol 2012;10:e1001347.
5. Videnovic A, Golombek D. Circadian and sleep disorders in Parkinson's disease. Exp Neurol 2013;243:45-56.
6. Kudo T, Loh DH, Truong D, Wu Y, Colwell CS. Circadian dysfunction in a mouse model of Parkinson's disease. Exp Neurol 2011;232:66-75.
7. Videnovic A, Willis GL. Circadian system — A novel diagnostic and therapeutic target in Parkinson's disease? Mov Disord 2016;31:260-269.
8. Fertl E, Auff E, Doppelbauer A, Waldhauser F. Circadian secretion pattern of melatonin in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1991;3:41-47.
9. Fertl E, Auff E, Doppelbauer A, Waldhauser F. Circadian secretion pattern of melatonin in de novo parkinsonian patients: evidence for phase-shifting properties of l-dopa. J Neural Transm Park Dis Dement Sect 1993;5:227-234.
10. Bordet R, Devos D, Brique S, Touitou Y, Guieu JD, Libersa C, et al. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin Neuropharmacol 2003;26:65-72.
11. Bolitho SJ, Naismith SL, Rajaratnam SM, Grunstein RR, Hodges JR, Terpening Z, et al. Disturbances in melatonin secretion and circadian sleep-wake regulation in Parkinson disease. Sleep Med 2014;15:342-347.
12. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol 2014;71:589-595.
13. Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, Marconi A, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol 2014;71:463-469.
14. Li S, Wang Y, Wang F, Hu LF, Liu CF. A new perspective for Parkinson's disease: circadian rhythm. Neurosci Bull 2017;33:62-72.
15. Törnhage CJ, Skogar Ö, Borg A, Larsson B, Robertsson L, Andersson L, et al. Short- and long-term effects of tactile massage on salivary cortisol concentrations in Parkinson's disease: a randomised controlled pilot study. BMC Complement Altern Med 2013;13:357.
16. Mizobuchi M, Hineno T, Kakimoto Y, Hiratani K. Increase of plasma adrenocorticotrophin and cortisol in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyr-

idine (MPTP)-treated dogs. Brain Res 1993;612:319-321.
17. van Hilten JJ, Kabel JF, Middelkoop HA, Kramer CG, Kerkhof GA, Roos RA. Assessment of response fluctuations in Parkinson's disease by ambulatory wrist activity monitoring. Acta Neurol Scand 1993;87:171-177.
18. Niwa F, Kuriyama N, Nakagawa M, Imanishi J. Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. Auton Neurosci 2011;165:195-200.
19. Pan W, Kwak S, Li F, Wu C, Chen Y, Yamamoto Y, et al. Actigraphy monitoring of symptoms in patients with Parkinson's disease. Physiol Behav 2013;119: 156-160.
20. Bonuccelli U, Del Dotto P, Lucetti C, Petrozzi L, Bernardini S, Gambaccini G, et al. Diurnal motor variations to repeated doses of levodopa in Parkinson's disease. Clin Neuropharmacol 2000;23:28-33.
21. Piccini P, Del Dotto P, Pardini C, D'Antonio P, Rossi G, Bonuccelli U. [Diurnal worsening in Parkinson patients treated with levodopa]. Riv Neurol 1991;61:219-224. Italian
22. Baier PC, Branisa P, Koch R, Schindehütte J, Paulus W, Trenkwalder C. Circadian distribution of motor-activity in unilaterally 6-hydroxy-dopamine lesioned rats. Exp Brain Res 2006;169:283-288.
23. Monville C, Torres EM, Pekarik V, Lane EL, Dunnett SB. Genetic, temporal and diurnal influences on L-dopa-induced dyskinesia in the 6-OHDA model. Brain Res Bull 2009;78:248-253.
24. Harnod D, Wen SH, Chen SY, Harnod T. The association of heart rate variability with parkinsonian motor symptom duration. Yonsei Med J 2014;55: 1297-1302.
25. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol Dis 2012;46:572-580.
26. Ejaz AA, Sekhon IS, Munjal S. Characteristic findings on 24-h ambulatory blood pressure monitoring in a series of patients with Parkinson's disease. Eur J Intern Med 2006;17:417-420.
27. Berganzo K, Díez-Arrola B, Tijero B, Somme J, Lezcano E, Llorens V, et al. Nocturnal hypertension and dysautonomia in patients with Parkinson's disease: are they related? J Neurol 2013;260:1752-1756.
28. Pursiainen V, Haapaniemi TH, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV. Circadian heart rate variability in Parkinson's disease. J Neurol 2002;249:1535-1540.
29. Salsone M, Vescio B, Fratto A, Sturniolo M, Arabia G, Gambardella A, et al. Cardiac sympathetic index identifies patients with Parkinson's disease and REM behavior disorder. Parkinsonism Relat Disord 2016;26:62-66.
30. Devos D, Kroumova M, Bordet R, Vodougnon H, Guieu JD, Libersa C, et al. Heart rate variability and Parkinson's disease severity. J Neural Transm (Vienna) 2003;110:997-1011.
31. Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. Clin Auton Res 2006;16:46-54.
32. McMahon DG, Iuvone PM, Tosini G. Circadian organization of the mammalian retina: from gene regulation to physiology and diseases. Prog Retin Eye Res 2014;39:58-76.
33. Wirz-Justice A, Da Prada M, Remé C. Circadian rhythm in rat retinal dopamine. Neurosci Lett 1984;45:21-25.
34. Witkovsky P. Dopamine and retinal function. Doc Ophthalmol 2004;108: 17-40.
35. Struck LK, Rodnitzky RL, Dobson JK. Circadian fluctuations of contrast sensitivity in Parkinson's disease. Neurology 1990;40(3 Pt 1):467-470.
36. Dearry A, Burnside B. Dopaminergic regulation of cone retinomotor movement in isolated teleost retinas: I. Induction of cone contraction is mediated by D2 receptors. J Neurochem 1986;46:1006-1021.
37. Van Hook MJ, Wong KY, Berson DM. Dopaminergic modulation of ganglion-cell photoreceptors in rat. Eur J Neurosci 2012;35:507-518.
38. Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sánchez R, Ríos CD, et al. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 1986;233:667-671.
39. Witkovsky P, Veisenberger E, Haycock JW, Akopian A, Garcia-Espana A, Meller E. Activity-dependent phosphorylation of tyrosine hydroxylase in dopaminergic neurons of the rat retina. J Neurosci 2004;24:4242-4249.
40. Terman M. Evolving applications of light therapy. Sleep Med Rev 2007;11:497-507.
41. Shirani A, St Louis EK. Illuminating rationale and uses for light therapy. J Clin Sleep Med 2009;5:155-163.
42. Paus S, Schmitz-Hübsch T, Wüllner U, Vogel A, Klockgether T, Abele M. Bright light therapy in Parkinson's disease: a pilot study. Mov Disord 2007;22: 1495-1498.
43. Willis GL, Turner EJ. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. Chronobiol Int 2007;24:521-537.
44. Fifel K, Videnovic A. Light therapy in Parkinson's disease: towards mechanism-based protocols. Trends Neurosci 2018;41:252-254.
45. Fifel K, Videnovic A. Chronotherapies for Parkinson's disease. Prog Neurobiol 2019;174:16-27.
46. Fifel K, Videnovic A. Circadian alterations in patients with neurodegenerative diseases: neuropathological basis of underlying network mechanisms. Neurobiol Dis 2020;144:105029.