Dysregulation of Circadian System in Parkinson's Disease

9

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Contents

Abstract

Circadian rhythms are physiological and behavioral cycles with a periodicity of approximately 24 h, generated by the endogenous biological clock, the suprachiasmatic nucleus (SCN). These rhythms influence most physiological processes, including the sleep–wake cycle. The exact pathophysiology of sleep–wake disturbances in Parkinson's disease (PD) remains largely unknown, but the etiology is likely to be multifactorial, including influence of motor PD symptoms on sleep, adverse effects of antiparkinsonian medications, and neurodegeneration of

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central sleep regulatory areas. The circadian system and its main central pacemaker, the SCN, have a major influence on sleep–wake homeostasis. A growing body of evidence points to significant alterations of the circadian system in PD. Despite this, little is known about the role of the circadian system in the regulation of sleep–wake cycles in PD. In this chapter, we discuss the role of the circadian system in the regulation of the sleep–wake cycle and outline implications of circadian timekeeping in PD.

9.1   Introduction

The human circadian system regulates numerous biological rhythms. The daily sleep–wake cycle is the most notable human behavior that is regulated by the circadian system. The two-process model of sleep regulation has been proposed to explain the relationship between the circadian system and sleep. This model proposes a sleep homeostatic process (process S) that interacts with the circadian process (process C), which is independent of sleep. Thus, process S, which is described in detail in Chap. 1 of this book, represents an internal homeostatic requirement for sleep that increases during wakefulness and decreases with sleep. The sleep homeostatic process regulates the amount and depth of sleep. Although the precise mechanisms of circadian regulation of sleep and alertness are not fully elucidated, it appears that the circadian system functions to consolidate wakefulness and regulate the timing of sleep. In this chapter, we discuss the role of the circadian system in the regulation of the sleep–wake cycle and outline implications of circadian timekeeping in PD.

9.2   Overview of the Human Circadian System

Nearly all physiological and behavioral processes in humans exhibit daily rhythms, regulated by the endogenous circadian timing system. These rhythms recur with a periodicity of approximately 24 h, under the governance of the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus [1]. The timing of human biological rhythms is synchronized to the rotation of earth and is under the influence of numerous external and internal time clues. This synchronization may become disrupted leading to misalignment or *internal desynchronization*. This loss of coordination of rhythms may have negative consequences on sleep–wake cycles and numerous other biological functions.

9.2.1   Neuroanatomy and Neurochemistry
of the Circadian System

The circadian timing system has three distinct components: a circadian pacemaker – SCN, afferent pathways for light and other stimuli that synchronize the pacemaker to the environment, and efferent output rhythms that are regulated by the SCN.

The SCN is composed of "core" and "shell" subnuclei. Each of the subnuclei has distinct neurochemical properties [1]. Gamma-aminobutyric acid (GABA) is the dominant neurotransmitter in the SCN, present in nearly all SCN neurons. The SCN core contains high density of vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), and bombesin-containing neurons. Somatostatin and neurophysin are dominant neurochemicals within the SCN shell.

The main afferent pathways to the SCN emerge from the retina and reach the SCN directly via the retinohypothalamic tract, or indirectly via retinogeniculate pathways [2]. The melanopsin-containing retinal ganglion retinal cells are the primary photoreceptors for the circadian system. The SCN also receives nonphotic information from the raphe nuclei, basal forebrain, pons, medulla, and posterior hypothalamus.

The major efferents from the SCN project to the subparaventricular zone and the paraventricular nucleus of the hypothalamus, dorsomedial hypothalamus, thalamus, preoptic and retrochiasmatic areas, stria terminalis, lateral septum, and the intergeniculate nucleus. In addition to these distinct neuroanatomical networks, the SCN also communicates via diffusion of humoral signals such as transforming growth factor (TGF)-α, cardiotrophin-like cytokine (CLC), and prokineticin 2 (PK2).

The SCN represents the main clock of the circadian system. Almost all peripheral tissues as well as brain regions outside the SCN contain circadian clocks influenced by the SCN in addition to their own distinct circadian synchronizers [3] (Fig. 9.1).

9.2.2   Genetic Regulation of the Circadian System

Circadian rhythms are generated by a core set of clock genes, including three Period genes (Per1, Per2, Per3), Clock, Bmal1, and two plant cryptochrome gene homologues (Cry1 and Cry2) [4]. The proteins encoded by these genes interact to create a self-sustaining negative transcription–translation feedback loop that drives the timing system. The intracellular levels of CLOCK remain steady during the 24-h period. BMAL1 levels, which are high at the beginning of the day, promote the formation of BMAL1-CLOCK heterodimers. These proteins activate transcription of the PER and CRY genes resulting in high levels of these transcripts. As PER accumulates in the cytoplasm, it becomes phosphorylated and degraded by ubiquitination. Cry accumulates in the cytoplasm late in the subjective day and translocates to the nucleus to inhibit Clock-Bmal1-mediated transcription. During the night, the PER-CRY complex is degraded, and the cycle starts again. This feedback loop ensures a high level of BMAL1 and low levels of PER and CRY at the beginning of a new circadian day.

Circadian clock genes control a significant proportion of genome. It is estimated that approximately 10 % of all expressed genes are under regulation of the clock genes. Furthermore, peripheral tissues contain independent clocks. It is likely that peripheral clocks are synchronized by an input directly from the SCN or SCN-mediated messages. For a detailed overview of the molecular regulation of the circadian system, please see the excellent review by Dardente and Cermakian [2].
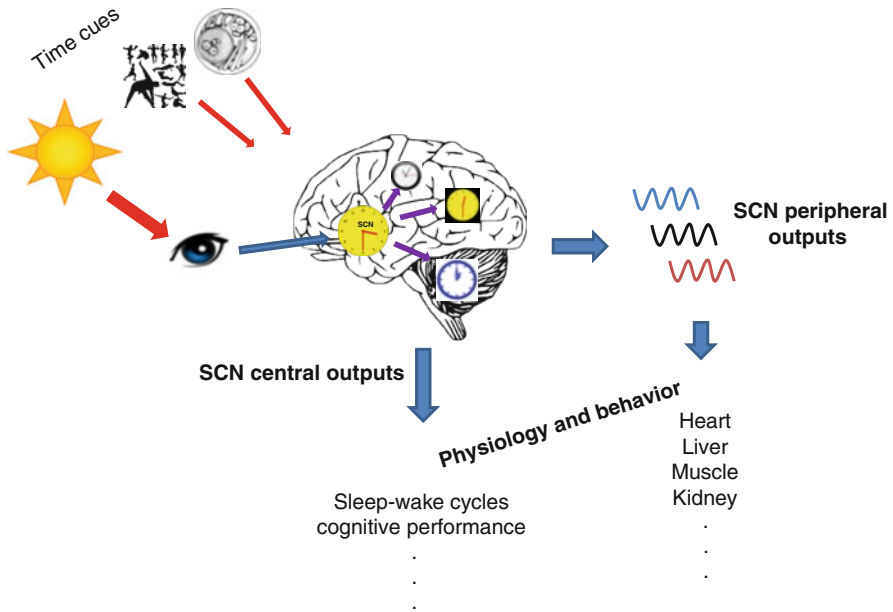
Fig. 9.1 A simplified scheme of the circadian system. The environmental photic (light) and non-photic (feeding schedules, physical activity) zeitgebers synchronize the central circadian pacemaker (*SCN*) to daily light–dark and social rhythms. The SCN synchronizes other central and peripheral clocks via neuronal and humoral efferents. This internal synchronization is important for optimal physiologic function and behavior

9.2.3 Circadian Entrainment and Markers of Circadian Rhythmicity

Circadian rhythms are synchronized with the solar day by daily adjustments in the timing of the SCN, following the exposure to stimuli that signal the time of day. These stimuli are known as "zeitgebers" (German for "time-giver"). Light is the most important and potent zeitgeber. In addition to light, feeding schedules, activity, and the hormone melatonin also influence the circadian timing [1].

Circadian rhythms can be described by their phase and amplitude. Circadian output rhythms are used to estimate the time (the phase) of the clock [5]. In humans, timing of the circadian core body temperature and hormonal rhythms are the most commonly used phase markers. The hormone melatonin is one of the best understood output rhythms of the SCN. The timing of melatonin secretion by the pineal gland is regulated by the SCN, with the onset of secretion being approximately 2 h before natural sleep time and being highest during the middle of the night [1]. Melatonin onset measured in dim light melatonin onset (DLMO) is a stable marker of circadian phase and is used in research as well as clinical practice to determine the timing of the endogenous circadian rhythm. The amplitude of a circadian rhythm refers to the half-distance from the maximum to the minimum of the observed rhythm. Plasma melatonin has been proven

reliable as a marker of the amplitude of the circadian clock [6–8]. Since markers of circadian rhythms may be influenced by environmental stimuli and behavior (light–dark, rest–activity, meals), the underlying endogenous circadian rhythms are best assessed under the protocols that minimize exposure to stimuli that evoke responses in the physiological variables being monitored. The constant routine and forced desynchrony are prototypes of protocols used to assess endogenous circadian rhythms. The detailed description of these protocols is beyond the scope of this chapter.

9.3   Dopamine in the Circadian Timing System

Dopaminergic neurotransmission has been implied at several levels in the circadian system, starting with the photic afferent connection with the SCN. In the retina, dopamine (DA) plays an important role in light adaptation [9], and regulates the rhythmic expression of melanopsin, a photopigment of photosensitive retinal ganglion cells which has been implied in circadian entrainment [10]. Dopaminergic retinal cells express circadian rhythms in core clock genes Per, Cry, Clock, and Bmal1 [11]. In addition, DA modulates rhythms in retinal second messengers like cAMP, therefore interacting directly with retinal physiology and sensitivity [12]. Dopamine also affects the phase and amplitude of specific clock genes presumably through dopaminergic D1 receptors in the retina [13]. In the SCN, dopaminergic D1 receptors are present in both fetuses and adults [14, 15].

Several lines of evidence suggest that clock genes play a role in DA metabolism. The *clock* gene regulates dopaminergic activity in the ventral tegmental area (VTA) [16]. Several genes involved in dopaminergic signaling are differentially regulated in the VTA of *Clock* mutant mice, which also exhibits altered circadian rhythmicity, indicating a role of this gene in DA-related transcription in the VTA [16]. Circadian fluctuations in extracellular DA levels have been reported in the striatum and nucleus accumbens [17]. DA also regulates clock gene expression in the dorsal striatum [18, 19]. Promoter regions of the DA active transporter (DAT), D1A receptor, and tyrosine hydroxylase (TH) genes include an E-Box element, which is the target of the canonical molecular clock.

Dopaminergic activity and metabolism can also be considered an output of the circadian clock. DA and its metabolites and receptors exhibit daily fluctuations in their levels in different brain regions [20]. In particular, DA metabolism exhibits a diurnal rhythm in striatal regions, related to cyclic variations in the expression of DAT, D1A receptors, and TH [21]. There is a clear interaction between DA and melatonin, a well-known circadian output, which acts as a marker for both daily and seasonal variations in physiology and behavior, in several areas of the central nervous system [22]. Seasonal variations of DA have also been described in humans, although its importance and consequences remain to be established [23].

In summary, DA exhibits a two-way interaction with the circadian system at several levels. It has been hypothesized that diurnal and circadian changes in dopaminergic neurotransmission influence mood-related behavior [24] as well as addiction-related behavior [21, 25].

9.4   Circadian Rhythm Dysfunction in PD

Circadian biology of PD has not been systematically studied. Exciting emerging evidence suggests that circadian dysregulation plays an important role in PD. Answers to the question "Is PD affected by chronobiology?" require a multidirectional approach that includes a better understanding of common diurnal variations of symptoms and signs in PD as well as the assessment of physiologic and molecular markers of circadian rhythmicity in the PD population. Further, our understanding of circadian regulation in PD will be substantially enriched by examining the effects of potent modulators of the circadian system, such as light and other nonphotic zeitgebers, on PD symptoms and disease progression.

9.4.1   Diurnal Clinical Fluctuations in PD: Are they Driven by Circadian Dysregulation?

Diurnal rhythms of symptoms and signs associated with PD have been reported in numerous studies. Examples include fluctuations in daily motor activity [26–29], autonomic function [30–35], sleep–wake cycles [36–40], visual performance [41], as well as responsiveness to dopaminergic treatments [26, 42]. These observations are suggestive of possible circadian influences on the expression of clinical features of PD.

Fluctuations of motor symptoms in PD are very common. An actigraph, a wrist-worn monitor that detects movements, has been employed in numerous studies that assessed rest–activity rhythms in PD population. These actigraphy studies demonstrate lower peak activity levels and lower amplitude of the rest–activity cycle in PD patients compared to healthy older adults [36–40]. Increased levels of physical activity and shorter periods of immobility during the night result in an almost flat diurnal pattern of motor activity in PD [43, 44]. In addition, PD patients have a more fragmented pattern of activity with transitions from high to low activity periods, leading to less predictable rest–activity rhythm [45]. Motor symptoms tend to be more prominent in the afternoon and evening, both in stable patients and in those with wearing off symptoms [26, 42]. This daily pattern appears to be independent of the timing of dopaminergic medications and may be related to circadian regulation of dopaminergic systems. Furthermore, responsiveness of PD motor symptoms to dopaminergic treatments declines throughout the day, despite the absence of significant changes in levodopa pharmacokinetics [26]. While the presence of motor artifact in PD poses challenges to the interpretation of actigraphy studies in this population, actigraphy can be used in conjunction with PD sleep–wake diaries and newer nonparametric circadian rhythm analysis in order to minimize shortcoming of the actigraphy recordings of the rest–activity cycles in the PD population.

Output rhythms of the autonomic nervous system are influenced by circadian timekeeping. Alterations in the circadian regulation of the autonomic system in PD have been reported. Twenty-four hour ambulatory blood pressure monitoring in patients with PD demonstrates reversal of circadian rhythm of blood pressure,

increased diurnal blood pressure variability, postprandial hypotension, and a high nocturnal blood pressure [32, 46–48]. Holter electrocardiographic monitoring in PD patients reveals a decrease of sympathetic activity during the day with a loss of the circadian heart rate variability and a disappearance of the sympathetic morning peak [31]. The spectral analysis of heart rate variability reveals a significant decrease of the daytime low frequency power, decreased daytime low–high frequency ratio, and decreased nighttime high frequency power [31, 35, 49, 50]. These abnormalities, more prominent in advanced PD, are also present in untreated patients with early PD [49]. The prognostic significance and pathophysiological mechanisms leading to altered autonomic circadian variability in PD remain to be determined. While observed abnormalities may arise within the peripheral autonomic ganglia, the influence of central networks including hypothalamus may be significant as well [51–53].

Similarly to motor performance and autonomic function, circadian fluctuations of sensory systems have been reported in PD. For example, visual performance, measured by contrast sensitivity, is altered in PD [41]. Impairment of retinal DA, which exhibits an endogenous circadian rhythm independent of light–dark cycles, is most likely responsible for these changes [54]. Since circadian changes in contrast sensitivity may occur independently of circadian oscillations in motor symptoms, it is possible that various anatomical networks (retina, striatum, and cortex) may have differential threshold to the circadian signaling of DA [55].

The sleep–wake cycle is a prototype of a biological rhythm strongly influenced by circadian system. Disruption of sleep and impaired daytime alertness are common manifestations of PD, affect majority of PD patients, and may emerge early in the course of the disease. Sleep fragmentation and excessive daytime sleepiness are the most common abnormalities of the sleep–wake cycle in PD. While the etiology of insomnia and hypersomnia associated with PD is multifactorial, circadian disruption should be considered as one of the contributing factors. Several lines of evidence stemming from research on animal models of PD support this hypothesis. Transgenic mice overexpressing human alpha-synuclein (Thy1-aSyn) exhibits disrupted circadian behaviors including the temporal distribution of sleep and activity. Furthermore, the firing rate of SCN neurons early in the progression of experimentally induced parkinsonism in the Thy1-aSyn mice may result in impairments of neural and hormonal output rhythms of the SCN.

9.4.2 Circadian Markers in PD

Physiologic and molecular markers of the circadian system may provide insight into the function of circadian timekeeping in PD. Only a few studies attempted to characterize profiles of circadian markers in PD. In a cohort of 26 PD patients, the amplitude of melatonin rhythm was decreased, and the phase was advanced in treated patients with and without motor complications compared to de novo patients [56]. These results suggest a trend toward advanced melatonin phase and amplitude reduction during the evolution of PD. Circadian rhythms of temperature and plasma

cortisol did not differ between the groups in this study. In a separate study, nine patients with de novo PD had a preserved melatonin rhythm compared with healthy controls [57]. In a study of 12 PD patients, 24-h mean cortisol production rate was significantly higher and the mean secretory cortisol curve was flatter, leading to significantly reduced diurnal variation in the PD group relative to controls [58]. Body temperature is an excellent marker of endogenous circadian rhythmicity. While 24-h rhythms of core body temperature remain similar in PD relative to healthy controls [59], basal body temperature is significantly lower in parkinsonian patients [60]. PD patients with coexistent depression have altered circadian rhythms of rectal temperature and lower amplitudes of core body temperature [61]. These circadian modifications of temperature regulation have been confirmed in the 6-hydroxydopamine (6-OHDA) animal model of parkinsonism where a significant decrease of the mesor and a phase advance of temperature rhythm have been reported [62]. 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. In a recent study of 20 patients with mild to moderate PD and 12 age-matched controls that employed modified constant routine experimental protocol that minimize exogenous influences on circadian rhythms, significant blunting of circadian rhythm of melatonin secretion and reduced amplitude of melatonin rhythm was observed [63]. PD patients with excessive daytime somnolence had a more prominent reduction in the amplitude of their melatonin rhythm compared to PD patients without EDS. Significant reductions in the amplitude of melatonin secretion was also demonstrated in de novo PD patients [64]. In contrast to these findings, Bolitho et al. recently reported a threefold increase in melatonin secretion in a cohort of PD patients [65]. While further investigations are needed, these observations provide a rationale for the role of circadian disruption in excessive sleepiness associated with PD.

Several studies have demonstrated strong oscillatory expression patterns of core clock genes in human whole blood and peripheral blood mononuclear cells (PBMCs) [66–68], demonstrating the feasibility of using clock gene expression as a circadian marker. Time-related variations in the expression of circadian clock genes have been recently reported in patients with PD [69]. In a study of 17 individuals with PD and 16 age-matched controls, the relative abundance of the clock gene *Bmal1* was significantly lower during the night in PD patients versus controls. Expression levels of *Bmal1* in PD patients correlated with PD severity as assessed by the UPDRS [69]. A lack of time-dependent variation in Bmal1 expression in PD patients was recently confirmed in another study [64]. Exciting emerging evidence suggests alterations in molecular regulation of circadian timekeeping in animal models of PD. Depletion of striatal DA by 6-OHDA or blockade of D2 DA receptors by raclopride blunts the circadian rhythm of striatal Per2. Furthermore, timed daily activation of D2 DA receptors restores and entrains the Per2 rhythm in DA-depleted striatum. These observations suggest a role of dopaminergic stimulation of D2 DA receptors in the maintenance of circadian molecular oscillations in the striatum.

9.4.3   Light Exposure and Nonphotic Circadian Entrainment in PD

Light, the main synchronizer for the human circadian system, is increasingly applied as therapy in a variety of sleep and neuropsychiatric conditions including circadian rhythm disorders, seasonal affective disorder, and dementia [70]. Light therapy is usually a well tolerated and easily applied nonpharmacological treatment modality. Numerous studies have demonstrated beneficial effects of light therapy on sleep quality, daytime sleepiness, mood, and quality of life in healthy elderly and in patients with dementia. Several lines of evidence support the rationale for exploring supplemental light exposure in PD. For example, DA is likely a mediator of light signaling to the retinal circadian clock which provides direct input to the SCN [9]. Exposure to light facilitates the recovery of motor function in a chronic experimental model of PD [71]. Only a few exploratory studies, however, examined the effects of bright light in patients affected by PD.

In a case series of 12 PD patients, daily exposure to supplemental bright light of 1,000–1,500 lux prior to habitual bedtime resulted in improved sleep quality and mood [72]. Evening exposure to bright light was also associated with improvements in bradykinesia and rigidity. Beneficial effects of supplemental light exposure emerged several days after initiating the treatment. Similar beneficial effects of supplemental bright light on sleep, mood anxiety, and motor performance were reported in an open-label retrospective study of 129 levodopa-treated PD patients followed up to 8 years [73]. In another study, 36 PD patients were randomized to receive treatment with bright light therapy of 7,500 lux (active arm) or 950 lux (placebo arm) in 30-min sessions every morning for 2 weeks [74]. Exposure to bright light of 7,500 lux was associated with improvements in UPDRS part I, II, IV scores, and daytime sleepiness. While these studies demonstrated good feasibility and positive effects of bright light therapy on nonmotor and motor manifestations of PD, further validation studies involving larger cohorts and employing objective outcome measures are needed. The timing, duration, intensity, and spectral qualities of light therapy will need to be optimized for use in the PD population.

9.4.4   Circadian Disruption in PD: Potential Mechanisms

Mechanisms underlying circadian dysregulation in PD are not fully elucidated. Primary neurodegenerative processes of PD leading to progressive depletion of DA likely have negative consequences on circadian timekeeping as dopaminergic transmission is an integral part of circadian homeostasis. Fluctuations in DA metabolism, overnight DA accumulation, or diurnal receptor downregulation may be in part driving diurnal fluctuations of PD clinical features [75–77]. Neuroanatomical sites of circadian disruption in PD may be along the afferent pathways to the SCN, within the SCN itself, or within the downstream peripheral efferents of the SCN. Circadian entrainment may be compromised in the population as PD patients

tend to be less active and spend more time indoors. For example, reduced light exposure and/or impaired light transmission, partly due to dopaminergic retinal degeneration [78], may affect circadian timekeeping in the PD population. While the structure and function of the SCN in PD has not been rigorously examined to date, degeneration of this central circadian pacemaker may be yet another possible mechanism of impaired circadian rhythmicity in PD. Hypothalamic dopaminergic neurons, however, do not appear to be involved in the disease [79]. Finally, alterations in SCN output may be primarily responsible for fluctuations in biological rhythms and symptoms of PD.

Conclusion

Increasing evidence suggests disruptions of the circadian system in PD. Further, systematic investigations directed at circadian timekeeping may provide additional insight into the pathogenesis of daytime sleepiness and sleep dysfunction, and may possibly shed new insights into the neurodegenerative processes of PD itself. Furthermore, better understanding of the circadian biology of Parkinson's disease may lead to the development of novel, circadian-based treatment approaches for motor and nonmotor manifestations of PD.

References

1. Golombek DA, Rosenstein RE. Physiology of circadian entrainment. Physiol Rev. 2010;90(3):1063–102.
2. Dardente H, Cermakian N. Molecular circadian rhythms in central and peripheral clocks in mammals. Chronobiol Int. 2007;24(2):195–213.
3. Cermakian N, Boivin DB. The regulation of central and peripheral circadian clocks in humans. Obes Rev. 2009;10 Suppl 2:25–36.
4. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev. 2008;9(10):764–75.
5. Daan S, Pittendrigh CS. A functuional analysis of circadian pacemakers in nocturnal rodents. II. The variability of phase response curve. J Comp Physiol. 1976;106:253.
6. Lewy AJ. Melatonin as a marker and phase-resetter of circadian rhythms in humans. Adv Exp Med Biol. 1999;460:425–34.
7. Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. J Biol Rhythms. 1999;14(3):227–36.
8. Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. Life Sci. 2003;73(26):3339–49.
9. Witkovsky P. Dopamine and retinal function. Doc Ophthalmol. 2004;108(1):17–40.
10. Sakamoto K, Liu C, Kasamatsu M, Pozdeyev NV, Iuvone PM, Tosini G. Dopamine regulates melanopsin mRNA expression in intrinsically photosensitive retinal ganglion cells. Eur J Neurosci. 2005;22(12):3129–36.
11. Dorenbos R, Contini M, Hirasawa H, Gustincich S, Raviola E. Expression of circadian clock genes in retinal dopaminergic cells. Vis Neurosci. 2007;24(4):573–80.
12. Jackson CR, Chaurasia SS, Hwang CK, Iuvone PM. Dopamine D receptor activation controls circadian timing of the adenylyl cyclase 1/cyclic AMP signaling system in mouse retina. Eur J Neurosci. 2011;34(1):57–64.
13. Ruan GX, Allen GC, Yamazaki S, McMahon DG. An autonomous circadian clock in the inner mouse retina regulated by dopamine and GABA. PLoS Biol. 2008;6(10):e249.

14. Weaver DR, Rivkees SA, Reppert SM. D1-dopamine receptors activate c-fos expression in the fetal suprachiasmatic nuclei. Proc Natl Acad Sci U S A. 1992;89(19):9201–4.

15. Ishida Y, Yokoyama C, Inatomi T, Yagita K, Dong X, Yan L, et al. Circadian rhythm of aromatic L-amino acid decarboxylase in the rat suprachiasmatic nucleus: gene expression and decarboxylating activity in clock oscillating cells. Genes Cells. 2002;7(5):447–59.

16. Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, et al. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A. 2007;104(15):6406–11.

17. Castaneda TR, de Prado BM, Prieto D, Mora F. Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light. J Pineal Res. 2004;36(3):177–85.

18. Hood S, Cassidy P, Cossette MP, Weigl Y, Verwey M, Robinson B, et al. Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors. J Neurosci. 2010;30(42):14046–58.

19. 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(2):537–44.

20. Kafka MS, Benedito MA, Roth RH, Steele LK, Wolfe WW, Catravas GN. Circadian rhythms in catecholamine metabolites and cyclic nucleotide production. Chronobiol Int. 1986;3(2):101–15.

21. McClung CA. Circadian rhythms, the mesolimbic dopaminergic circuit, and drug addiction. ScientificWorldJournal. 2007;7:194–202.

22. Zisapel N. Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting. Cell Mol Neurobiol. 2001;21(6):605–16.

23. Eisenberg DP, Kohn PD, Baller EB, Bronstein JA, Masdeu JC, Berman KF. Seasonal effects on human striatal presynaptic dopamine synthesis. J Neurosci. 2010;30(44):14691–4.

24. Hampp G, Albrecht U. The circadian clock and mood-related behavior. Commun Integr Biol. 2008;1(1):1–3.

25. Hampp G, Ripperger JA, Houben T, Schmutz I, Blex C, Perreau-Lenz S, et al. Regulation of monoamine oxidase A by circadian-clock components implies clock influence on mood. Curr Biol. 2008;18(9):678–83.

26. 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(1):28–33.

27. Nutt JG, Woodward WR, Carter JH, Trotman TL. Influence of fluctuations of plasma large neutral amino acids with normal diets on the clinical response to levodopa. J Neurol Neurosurg Psychiatry. 1989;52(4):481–7.

28. 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(3):171–7.

29. van Hilten JJ, Middelkoop HA, Kerkhof GA, Roos RA. A new approach in the assessment of motor activity in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1991;54(11):976–9.

30. Arias-Vera JR, Mansoor GA, White WB. Abnormalities in blood pressure regulation in a patient with Parkinson's disease. Am J Hypertens. 2003;16(7):612–3.

31. 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. 2003;110(9):997–1011.

32. 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(6):417–20.

33. Mihci E, Kardelen F, Dora B, Balkan S. Orthostatic heart rate variability analysis in idiopathic Parkinson's disease. Acta Neurol Scand. 2006;113(5):288–93.

34. Pathak A, Senard JM. Blood pressure disorders during Parkinson's disease: epidemiology, pathophysiology and management. Expert Rev Neurother. 2006;6(8):1173–80.

35. Pursiainen V, Haapaniemi TH, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV. Circadian heart rate variability in Parkinson's disease. J Neurol. 2002;249(11):1535–40.

36. Comella CL. Sleep disorders in Parkinson's disease: an overview. Mov Disord. 2007;22(S17):S367–73.

37. Placidi F, Izzi F, Romigi A, Stanzione P, Marciani MG, Brusa L, et al. Sleep-wake cycle and effects of cabergoline monotherapy in de novo Parkinson's disease patients. An ambulatory polysomnographic study. J Neurol. 2008;255(7):1032–7.

38. Porter B, Macfarlane R, Walker R. The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. Eur J Neurol. 2008;15(1):50–4.

39. van Hilten JJ, Weggeman M, van der Velde EA, Kerkhof GA, van Dijk JG, Roos RA. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J Neural Transm. 1993;5(3):235–44.

40. Verbaan D, van Rooden SM, Visser M, Marinus J, van Hilten JJ. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. Mov Disord. 2008;23(1):35–41.

41. Struck LK, Rodnitzky RL, Dobson JK. Circadian fluctuations of contrast sensitivity in Parkinson's disease. Neurology. 1990;40(3 Pt 1):467–70.

42. 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(6):219–24.

43. van Hilten B, Hoff JI, Middelkoop HA, van der Velde EA, Kerkhof GA, Wauquier A, et al. Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. Arch Neurol. 1994;51(9):922–8.

44. van Hilten JJ, Hoogland G, van der Velde EA, Middelkoop HA, Kerkhof GA, Roos RA. Diurnal effects of motor activity and fatigue in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1993;56(8):874–7.

45. 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(8):1137–45.

46. Kallio M, Haapaniemi T, Turkka J, Suominen K, Tolonen U, Sotaniemi K, et al. Heart rate variability in patients with untreated Parkinson's disease. Eur J Neurol. 2000;7(6):667–72.

47. Plaschke M, Trenkwalder P, Dahlheim H, Lechner C, Trenkwalder C. Twenty-four-hour blood pressure profile and blood pressure responses to head-up tilt tests in Parkinson's disease and multiple system atrophy. J Hypertens. 1998;16(10):1433–41.

48. Senard JM, Chamontin B, Rascol A, Montastruc JL. Ambulatory blood pressure in patients with Parkinson's disease without and with orthostatic hypotension. Clin Auton Res. 1992;2(2):99–104.

49. Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV. Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001;70(3):305–10.

50. Mastrocola C, Vanacore N, Giovani A, Locuratolo N, Vella C, Alessandri A, et al. Twenty-four-hour heart rate variability to assess autonomic function in Parkinson's disease. Acta Neurol Scand. 1999;99(4):245–7.

51. Mochizuki A, Komatsuzaki Y, Shoji S. Association of Lewy bodies and glial cytoplasmic inclusions in the brain of Parkinson's disease. Acta Neuropathol. 2002;104(5):534–7.

52. Wakabayashi K, Takahashi H. Neuropathology of autonomic nervous system in Parkinson's disease. Eur Neurol. 1997;38 Suppl 2:2–7.

53. Langston J. The hypothalamus in Parkinson's disease. Ann Neurol. 1978;3:129–33.

54. Wirz-Justice A, Da Prada M, Reme C. Circadian rhythm in rat retinal dopamine. Neurosci Lett. 1984;45(1):21–5.

55. 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(4):1006–21.

56. 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(2):65–72.

57. 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. 1993;5(3):227–34.

58. Hartmann A, Veldhuis JD, Deuschle M, Standhardt H, Heuser I. Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: ultradian secretory pulsatility and diurnal variation. Neurobiol Aging. 1997;18(3):285–9.

59. Pierangeli G, Provini F, Maltoni P, Barletta G, Contin M, Lugaresi E, et al. Nocturnal body core temperature falls in Parkinson's disease but not in Multiple-System Atrophy. Mov Disord. 2001;16(2):226–32.
60. Cagnacci A, Bonuccelli U, Melis GB, Soldani R, Piccini P, Napolitano A, et al. Effect of naloxone on body temperature in postmenopausal women with Parkinson's disease. Life Sci. 1990;46(17):1241–7.
61. Suzuki K, Miyamoto T, Miyamoto M, Kaji Y, Takekawa H, Hirata K. Circadian variation of core body temperature in Parkinson disease patients with depression: a potential biological marker for depression in Parkinson disease. Neuropsychobiology. 2007;56(4):172–9.
62. Ben V, Blin O, Bruguerolle B. Time-dependent striatal dopamine depletion after injection of 6-hydroxydopamine in the rat. Comparison of single bilateral and double bilateral lesions. J Pharm Pharmacol. 1999;51(12):1405–8.
63. Videnovic A, Noble C, Reid KJ, Peng J, Turek FW, Marconi A, et al. Circadian melatonin rhythm and excessive sleepiness in Parkinson disease. JAMA Neurol. 2014;71(4):463–9.
64. Breen DA, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythms regulation in early Parkinson disease. JAMA Neurol. 2014;71(5):589–95.
65. Bolitho SJ, Naismith SL, Rajaratnam SM, Grunstein RR, Hodges JR, Terpering Z, et al. Disturbances of melatonin secretion and circadian sleep-wake regulation in Parkinson disease. Sleep Med. 2014;15(3):324–7.
66. Boivin DB, James FO, Wu A, Cho-Park PF, Xiong H, Sun ZS. Circadian clock genes oscillate in human peripheral blood mononuclear cells. Blood. 2003;102(12):4143–5.
67. Takimoto M, Hamada A, Tomoda A, Ohdo S, Ohmura T, Sakato H, et al. Daily expression of clock genes in whole blood cells in healthy subjects and a patient with circadian rhythm sleep disorder. Am J Physiol. 2005;289(5):R1273–9.
68. Teboul M, Barrat-Petit MA, Li XM, Claustrat B, Formento JL, Delaunay F, et al. Atypical patterns of circadian clock gene expression in human peripheral blood mononuclear cells. J Mol Med (Berl, Germany). 2005;83(9):693–9.
69. Cai Y, Liu S, Sothern RB, Xu S, Chan P. Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson's disease. Eur J Neurol. 2010;17(4):550–4.
70. Shirani A, St Louis EK. Illuminating rationale and uses for light therapy. J Clin Sleep Med. 2009;5(2):155–63.
71. Harrell LE, Balagura S. The effects of dark and light on the functional recovery following lateral hypothalamic lesions. Life Sci. 1974;15(12):2079–87.
72. 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(3):521–37.
73. Willis GL, Moore C, Armstrong SM. A historical justification for and retrospective analysis of the systematic application of light therapy in Parkinson's disease. Rev Neurosci. 2012;23(2):199–226.
74. Paus S, Schmitz-Hubsch T, Wullner U, Vogel A, Klockgether T, Abele M. Bright light therapy in Parkinson's disease: a pilot study. Mov Disord. 2007;22(10):1495–8.
75. Bruinink A, Lichtensteiger W, Schlumpf M. Ontogeny of diurnal rhythms of central dopamine, serotonin and spirodecanone binding sites and of motor activity in the rat. Life Sci. 1983;33(1):31–8.
76. Khaldy H, Leon J, Escames G, Bikjdaouene L, Garcia JJ, Acuna-Castroviejo D. Circadian rhythms of dopamine and dihydroxyphenyl acetic acid in the mouse striatum: effects of pinealectomy and of melatonin treatment. Neuroendocrinology. 2002;75(3):201–8.
77. Weber M, Lauterburg T, Tobler I, Burgunder JM. Circadian patterns of neurotransmitter related gene expression in motor regions of the rat brain. Neurosci Lett. 2004;358(1):17–20.
78. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. The retina in Parkinson's disease. Brain. 2009;132(Pt 5):1128–45.
79. Matzuk MM, Saper CB. Preservation of hypothalamic dopaminergic neurons in Parkinson's disease. Ann Neurol. 1985;18(5):552–5.