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Neurobiology of Sleep and Circadian Rhythms

Circadian dysregulation in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects over one million individuals in the US alone. PD is characterized by a plethora of motor and non-motor manifestations, resulting from a progressive degeneration of dopaminergic neurons and disbalance of several other neurotransmitters. A growing body of evidence points to significant alterations of the circadian system in PD. This is not surprising given the pivotal role that dopamine plays in circadian regulation as well as the role of circadian influences in dopamine metabolism. In this review we present basic and clinical investigations that examined the function of the circadian system in PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting over one million people in the United States (Dorsey et al., 2007; Alves et al., 2008). Motor hallmarks required to establish the diagnosis of PD include tremor, bradykinesia, and rigidity. These symptoms emerge due to progressive dopaminergic loss within the nigro-striatal system. Non-motor manifestations of PD are common and represent some of the most disabling dopa-resistant symptoms of PD. These symptoms encompass sleep disturbances, autonomic dysfunction, mood and psychiatric disturbances, and reflect ongoing neurodegeneration outside the basal ganglia systems. Both motor and non-motor manifestations of PD demonstrate strong diurnal oscillations (Pathak and Senard, 2006; Piccini et al., 1991). This raises a possibility that the circadian system drives some changes of biological rhythms in PD. Circadian dysregulation has indeed emerged as an important etiology of sleep disruption in the most common neurodegenerative disorders, including PD, Huntington's (HD) and Alzheimer's (AD) diseases (Videnovic et al., 2014a, 2014b). Of note, circadian and sleep misalignment likely influence the neurodegenerative process itself (Ju et al., 2014; Mamelak, 1997; Morton et al., 2005). A good example of bidirectional relationship between sleep/circadian function and neurodegeneration is AD, where amyloid accumulation disrupts sleep and disrupted sleep increases the risk of accumulation of amyloid and development of dementia (Ju et al., 2014). The role of the circadian system in PD has not been systematically studied to date. In this manuscript we review the current understanding of circadian function in experimental models of PD and in the clinical expression of this disorder.

2. Dopamine and circadian system

Since dopaminergic neurotransmission lies at the core of PD-related disorders, it is relevant to acknowledge diurnal and circadian variation in dopamine content and metabolism. indeed, diurnal variation in dopamine and some of its metabolites has been reported for many years (Kafka et al., 1986). Changes in dopamine content could be directly related to rhythms in its synthesizing enzymes (tyrosine hydroxylase (TH)) and transporters (DAT), whose activity exhibit temporal changes both in basal ganglia and cortical structures (Sleipness et al., 2007). Indeed, rhythmic dopaminergic activity can be controlled by the circadian clock and, in turn, might also regulate the activity of the clock itself (Mendoza and Challet, 2014; Sleipness et al., 2007). In addition, dopamine might be relevant in the modulation of circadian retinal input (Witkovsky, 2004), and also as a developmental signal for the appearance of fetal and presumably neonatal rhythms (Seron-Ferre et al., 2001).

We have recently reported that striatal dopamine levels exhibit daily rhythms with nocturnal peaks in mice (Agostino et al., 2011a), as had been previously demonstrated in rats (Castaneda et al., 2004; Hood et al., 2010). Moreover, functional arrhythmocity induced by bright constant light (Bussi et al., 2014) or SCN lesions (Sleipness et al., 2007) disrupted dopamine and TH rhythms and reward-related behaviors such as interval timing. Clock genes also exhibit periodic

variations in striatal structures (Bussi et al., 2014; Li et al., 2009; Natsubori et al., 2014), and could be related to rhythms in the expression of dopamine-related genes (Shumay et al., 2012). Dopamine type 3 receptors also show 24-h fluctuations which are regulated by the canonical molecular clock (Ikeda et al., 2013).

Indeed, circadian rhythms in dopaminergic function could be the molecular correlate of cycles in reward, motivation and/or timing behavior (reviewed in (Agostino et al., 2011b; Golombek et al., 2014; Parekh et al., 2015). Dopamine along with iron metabolism also seem to underlie circadian fluctuations in symptoms associated with restless legs syndrome, a movement disorder of sleep frequently associated with PD (Baier and Trenkwalder, 2007).

Dopaminergic influence has been implied at several levels within the circadian system. In retina, dopamine is involved in light adaptation and rhythmic expression of malanopsin and clock genes. Dopamine also modulates light input to the SCN from retina (Witkovsky, 2004). While clock genes regulate dopaminergic transmission in the ventral tegmental area, dopamine regulates clock gene expression in the dorsal striatum (Hood et al., 2010; Roybal et al., 2007). Dopaminergic activity can also be considered an output of the SCN. In summary, dopamine exhibits a two-way interaction with the circadian system at several levels.

3. Circadian system in PD – lessons from animal models

PD-related animal models have advanced our understanding of the disease process overall, and opened possibilities for exploring novel treatments and insight in the molecular and physiological mechanisms underlying PD-specific neurodegeneration. Studied that centered on alterations of circadian rhythmicity and applications of potential circadian-based interventions in animal models of PD are scarce. While non-specific, age-related circadian disruption has been reported in different PD animal models, especially rodents (Brown et al., 2011; Mattis and Sehgal, 2016), these studies did not necessarily offer specific insights into the origin and scope of PD effects on biological rhythms and vice versa.

Most animal models of PD have been developed in rodents and centered on deficits in dopaminergic neurotransmission (Jagmag et al., 2015). In addition, non-human primates have provided an adequate model for testing potential therapeutic agents (Johnston et al., 2015). The most widely used models are uni- or bilateral striatal administration of 6-hydroxidopamine (6-OHDA), which mimics some of the motor dysfunctions of the disease, as well as injection of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropuridine (MPTP). The latter induces motor symptoms accompanied by a specific loss of dopaminergic neurons (Burns et al., 1983). Another approach involves genetic manipulation of some of the key molecular regulators related to the development of PD (Crabtree and Zhang, 2012). One of the main experimental paradigms within this group involves the over expression of α-synuclein, the pathognomonic protein for PD-related neurodegeneration. In this model, α-synuclein is over expressed under the control of a Thy-promoter and induces early motor and sensory deficits in mice (Kudo et al., 2011). In another model, mice with alterations in the expression of a key player of dopamine metabolism, the vesicular monoamine transporter 2 (VMAT-2), also show cellular and behavioral changes that resemble some of the clinical features of PD (Taylor et al., 2009). Below we outline investigations that link sleep and circadian function with PD in animal models of this disorder.

3.1. Circadian changes in animal models of PD

Non-motor symptoms in PD animal models have been studied extensively, including sleep changes (McDowell and Chesselet, 2012). MPTP-treated primates exhibit significant disruption of the sleep-wake cycle (Vezoli et al., 2011), in particular related to a deregulation of REM sleep. These changes are more severe compared to those found in

the mouse model (Fifel et al., 2016; Laloux et al., 2008). A similar sleep disruption has been described after MPTP administration in cats (Pungor et al., 1990). Further, MPTP-treated dogs exhibit blunted circadian oscillations in renal parameters, including urine volume, creatinine and several hormones (Hineno et al., 1992). Disruptive MPTP effects on sleep can be reversed by D1 receptor agonist administration (Hyacinthe et al., 2014).

6-OHDA-treated rats exhibit severe sleep deficits, including significant circadian disruption (Gravotta et al., 2011). Indeed, bilateral lesions result in changes in the levels and oscillations of different circadian variables (Ben and Bruguerolle, 2000). The 6-OHDA models exhibit disruptions in circadian rhythms of locomotion, temperature and heart rate, which are at least partially reversible by L-DOPA administration (Boulamery et al., 2010). It is interesting to note that optic enucleation increases the severity of PD-like symptoms in 6-OHDA lesioned rats, suggesting the importance of visual and circadian connections in PD (Willis et al., 2008).

Circadian changes have been documented in rotenone-induced neurodegeneration in rats, including alterations in serotonergic transmission and circadian expression of clock genes; both parameters partially recover with melatonin administration (Mattam and Jagota, 2015). Interactions between melatonin and dopamine are complex and not fully elucidated. While melatonin appears to have neuroprotective effects on the nigrostriatal dopaminergic system through its antioxidant properties and effects on mitochondrial activity, inhibition of dopamine release by melatonin in several brain areas has been demonstrated. It has been proposed that melatonin and dopamine may act as mutually inhibitory signals for night and day, respectively (Zisapel, 2001).

Circadian alterations have been reported in several other animal models of PD. Alterations in the glutamatergic transmission in the striatum also induce PD-like motor symptoms. The glutamate transporter 3 knockout mice exhibit diurnal hyperactivity and changes in circadian dopamine metabolism (Divito et al., 2015). Dopaminergic deficits induced by genetic deficiency of the vesicular monoamine transporter 2 (VMAT2) in mice are accompanied by a premature decrease in sleep latency and reduced amplitude of the sleep-wake cycle, as well as in dampened circadian rhythms in general (Taylor et al., 2009).

α-synuclein transgenic mice exhibit fragmented rhythms of locomotor activity, as well as changes in firing rate in the suprachiasmatic nuclei (SCN), the site of the mammalian main circadian clock (Kudo et al., 2011). This fragmentation seems to be dependent on the photoperiodic conditions in which the animals were housed, and progresses with age. Adult transgenic mice exhibited diurnal wakefulness and increased hyperactivity pattern (McDowell et al., 2014). Another mouse model of PD involves inactivation of a mitochondrial transcription factor, MitoPark that induces dopaminergic degeneration. In this model deficits in locomotion and, more specifically, diurnal patterns of rest/activity were reported (Fifel and Cooper, 2014).

It is important to note that the central circadian pacemaker, the SCN, also exhibits significant changes in animal models of PD. As indicated by Willison et al. (Fliers et al., 1985), oscillations in the suprachiasmatic nuclei are disrupted in α-synuclein transgenic mice quite early in the development of the disease. An intriguing consequence of this observation is that circadian synchronization and treatments that increase circadian rhythm amplitude have to be explored further as these approaches may be beneficial for the management of PD.

Collectively, these basic investigations provide a support for alterations of circadian system in PD. Further studies that will employ carefully designed experiments will be needed to advance out understanding the anatomical and pathophysiological signatures of circadian disruption associated with PD.

4. Clinical implications of circadian function in PD

Circadian rhythms have not been systematically studied in PD patients. Despite this, available literature point to significant modifications of the circadian system in these patients. This is reasonable to expect, given a bi-directional relationship between dopamine metabolism and circadian system physiology. For example, the amplitude of the circadian rhythm of dopamine appears to be highest in the morning around 10am, and that of homovanillic acid in the afternoon, around 2pm (Poceta et al., 2009). These circadian variations may underline sleep-related changes in function, readily observed by clinicians and reported by PD patients (Merello et al., 1997).

4.1. Diurnal clinical fluctuations in PD

Many symptoms and signs associated with PD demonstrate diurnal variations in its intensity and frequency. These symptoms are representative of multi system involvement in PD, and include fluctuations of motor function in PD (Bonuccelli et al., 2000; Nutt et al., 1989; van Hilten et al., 1993; van Hilten et al., 1991), autonomic and sensory functions (Devos et al., 2003; Ejaz et al., 2006; Arias-Vera et al., 2003; Mihci et al., 2006; Pathak and Senard, 2006; Pursiainen et al., 2002), mood and cognitive performance (Suzuki et al., 2007; Whitehead et al., 2008), and sleep and alertness(Comella, 2007; Placidi et al., 2008; Porter et al., 2008; van Hilten et al., 1993; Verbaan et al., 2008). Observed variations may be influenced by circadian oscillations. Although the above discussed fluctuations in various variables may suggest an involvement of the circadian system, one must be cautious not to attribute the fluctuating nature of symptoms/signs of PD completely and directly to circadian disruption, since most studies to date did not employ rigorous circadian experimental protocol that would control for the effects of exogenous stimuli on the endogenous circadian rhythms and symptom manifestation in PD.

Studies that employed actigraphy in the PD population revealed flattening of the diurnal activity rhythms and reduced quiescence during night (Piccini et al., 1991; Placidi et al., 2008). This reduced amplitude of the rest-activity cycle is present in both de novo and more advanced patients, and appears to be independent of the intake of dopaminergic medications (Piccini et al., 1991; Placidi et al., 2008; van Hilten et al., 1994; van Hilten et al., 1993; van Hilten et al., 1993). REM sleep behavior disorder (RBD) is a parasomnia frequently present in the PD population, and characterized by motor and vocal behaviors that are disruptive to sleep and result in sleep fragmentation. While RBD itself may contribute to reduce quiescence during night, it is important to point out that RBD represents a sleep stage under the strong circadian influences that may be implicated in the pathophysiology of RBD. Similar to motor function, prominent changes in 24-hour rhythms of heart rate and blood pressure have been repeatedly reported in PD. These studies report reversal of the normal diurnal rhythm of BP with increased diurnal variability of BP and elevations of overnight BP along with loss of diurnal HR variability and a disappearance of the sympathetic morning peak (Haapaniemi et al., 2001; Kallio et al., 2000; Kallio et al., 2004; Mastrocola et al., 1999). Sensory systems, such as retinal function, also appear to be affected in PD. A good example of this is represented by diurnal changes in contrast sensitivity in PD patients, which may be modulated by circadian signaling of dopamine within the retinal tissues (Struck et al., 1990). Sleep and alertness are commonly disrupted in PD, and this frequently predates emergence of motor symptoms that are currently required to establish PD diagnosis. Sleep fragmentation represents the most common sleep problem in the PD population (Videnovic and Golombek, 2013). The etiology of impaired sleep and alertness in PD is clearly multifactorial and encompasses PD symptoms, medications side effects, autonomic dysfunction, and co-existent primary sleep disorders (Videnovic and Golombek, 2013). The role of circadian disruption has only recently started to emerge as an important etiology of impaired sleep and alertness in PD (Videnovic and Willis, 2016).

Patients with PD frequently report "sleep benefit", described as feeling well after awakening in the morning. They feel as they do not have PD, although they did not take their morning medications (Merello et al., 1997). The underlying mechanisms of sleep benefit have not been well-explored. The pattern of diurnal motor fluctuations and increased dopamine storage in nigral neurons during sleep with subsequent enhanced dopaminergic function have been implicated in sleep benefit (Factor and Weiner, 1998; van Gilst et al., 2013). In a study that assessed circadian influences on sleep benefit employing the Horne-Ostberg morningness-eveningness questionnaire, no differences in circadian phenotype were present between patients with and without sleep benefit (Hogl et al., 1998).

4.2. Markers of the circadian system in PD

Endogenous circadian rhythms can be best characterized by analyzing circadian markers. Melatonin, cortisol and core body temperature are well established markers of endogenous circadian rhythmicity. These circadian markers have been increasingly investigated in PD. Specifically, circadian secretion of melatonin and its relationship with sleep dysfunction associated with PD has been recently examined in several studies. Phase angle of entrainment is defined as the relationship between the timing of the biological clock and the timing of an external time cue. Bolitho et al. demonstrated prolongation of the phase angle of entrainment of melatonin rhythm in the medicated PD patients compared to the PD un-medicated group and controls (Bolitho et al., 2014). These observed changes in the phase angle provide the rationale to suggest uncoupling of circadian and sleep regulation, possibly related to dopaminergic therapy. Two other recent studies did not show alterations in the circadian phase of melatonin secretion (Breen et al., 2014; Videnovic et al., 2014a, 2014b). However, both studies reported decreased amplitude of melatonin secretion. The amplitude of melatonin circadian rhythm was significantly lower in patients with moderate PD compared with age-matched controls (Videnovic et al., 2014a, 2014b). Further, within the PD group, those with excessive daytime sleepiness had significantly lower amplitudes of their melatonin rhythm, compared to those with good alertness. This raises a question related to the role of circadian dysregulation in the pathophysiology of excessive sleepiness, frequently associated with PD. Breen and colleagues examined circadian profiles of melatonin, cortisol, and clock genes in a cohort of 30 patients with early PD and 15 matched controls (Breen et al., 2014). PD patients had elevated cortisol levels and reduced melatonin levels. The significance of all these investigations in part lies in the fact that they employed rigorous circadian experimental designs that controlled well for exogenous signals known to affect endogenous circadian system such as light exposure, feeding schedules, ambient temperature, and physical activity. This is likely the primary reason underlying somewhat different results of these studies from several initial reports that examined melatonin rhythms in PD in 1990s (Fertl et al., 1991; Fertl et al., 1993). These recent observations will need to be better delineated in longitudinal studies employing larger cohorts of PD patients.

Strong oscillatory expression patterns of core clock genes in human blood provide an opportunity to examine circadian regulation from the molecular perspective. Several recent studies examined time-related variations in the expression of several core clock genes patients with PD. Among 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. Expression levels of *Bmal1* patients correlated with PD severity as assessed by the Unified Parkinson Disease Rating Scale (UPDRS) (Cai et al., 2010). This study did not examine daytime expression of clock genes. A lack of time-dependent variation in Bmal1 expression in PD patients was recently confirmed in another study (Breen et al., 2014). These studies have laid out the groundwork for future clinical investigations related to molecular

regulation of circadian timekeeping in PD and other neurodegenerative disorders.

Cortisol rhythm also appears to be impaired in PD. While PD patients exhibit a preserved circadian rhythm of cortisol, the amount of cortsiol secreted is elevated in early PD (Breen et al., 2014). However, somatotrophic, thyrotrophic and lactotrophic axes appear to be intact in early-stage PD (Aziz et al., 2011a, 2011b). Adipokines are endocrine factors released by fat cells and have an important role in feeding, body weight regulation and metabolism. Since patients with PD frequently experience weight loss, a recent study by Aziz et al. focused on the circadian aspects of adipokines in PD, specifically leptin, adiponectin and resistin, and found no differences in the levels between PD patients and controls (Aziz et al., 2011a, 2011b).

4.3. Circadian zeitgebers and PD

Light is the most important and potent synchronizer for the human circadian system (Czeisler et al., 1986; Klerman et al., 1998). Epidemiological studies suggest that higher levels of light exposure are related to a lower risk for PD. Two studies reported increasing incidence of PD, as much as 56%, with higher latitudes, where the yearly net exposure to light is significantly lower (de de Pedro Cuesta, 1987; de de Pedro-Cuesta and Stawiarz, 1991). Activation of the SCN has been hypothesized as one of the mechanisms of bright environmental light effects on mood, sleep and circadian rhythms (McEnany and Lee, 2005; Riemersma-van der Lek et al., 2008). Supplemental exposure to bright light through light therapy (LT) in the PD population, provide an opportunity to indirectly learn about circadian function in PD. To date, several studies have been published on LT in PD (Paus et al., 2007; Willis and Turner, 2007; Willis et al., 2012).

In a case series of 12 PD patients with insomnia and/or depressive symptoms, bright LT of 1000–1500 lux administered for 60–90 minutes prior to the habitual bedtime over a two-week period resulted in improved sleep onset latency, sleep continuity, and mood (Willis and Turner, 2007). Beneficial effects on sleep emerged within two to three days after commencing LT, and lasted for several days after discontinuation. The antidepressant effect was longer lasting, up to several weeks after discontinuation of LT. Bright LT also resulted in improvements in bradykinesia and rigidity symptoms, which led to successful reduction of dopamine replacement therapy in half of the study cohort. 4).

In an open label study, 120 PD patients were prescribed bright LT at the dose of 4000 to 6000 lux for 60 minutes prior to the habitual bedtime, and were followed from a few months to eight years (Willis et al., 2012). Patients with good compliance achieved improvements in mood, anxiety, and tests of motor function. Participants that quit LT early in the treatment period deteriorated over time, while those who remained semi-adherent to LT showed improvements that corresponded with periods of adherence with LT.

In the only controlled LT study in PD, 36 PD patients were randomized to receive bright LT with 7500 lux or placebo LT of 950 lux, for 30 minutes in the morning during two-week period (Paus et al., 2007). Bright LT was associated in significantly improved UPDRS part I and II scores, and modest improvements in mood and daytime sleepiness. The short duration of the study and enrollment of patients with mild depression may explain the modest effects of LT on mood. Beneficial effects of LT on sleepiness were observed in both study groups, which might represent the result of a biological placebo effect, since the intensity of the control lighting condition may have not been fully inert.

The side effect profile in these clinical PD LT studies is consistent with other light therapy studies, including transient headache, eye itching, sleepiness (Terman and Terman, 1999; Terman and Terman, 2005). These studies demonstrate beneficial effects of bright LT on sleep, mood and non-motor function in PD. Differences in timing of LT in studies performed to date may explain its variable effects on specific outcomes. Due to limitations of these studies, mainly their relatively small size, short duration, and suboptimal design, further studies designed to test the efficacy of LT, and its mechanisms of action, in treating motor and non-motor symptoms in patients with PD are warranted.

5. Future directions

Increasing evidence from basic and clinical investigations points to disruption of circadian function in PD. This is likely reflective of the neurodegenerative process of PD that affects sleep-wake regulatory centers and its connections with the circadian circuitry. Further, dopaminergic deficits that represent a neurochemical hallmark of PD, negatively affect circadian function since dopamine represents a major regulator of the circadian system.

Future research efforts in this field will need to center on the systematic study of circadian system in PD by employing longitudinal assessments and carefully designed study protocols that will allow for proper characterization of endogenous circadian signaling in the PD population. Such studies may examine the role of dopamine in the regulation of circadian system, provide the characterization of the circadian system/function from physiological, molecular and behavioral perspectives throughout the course of PD but also in pre-manifest PD, and develop circadian-based interventions for PD. Limitations of conducting such circadian studies in PD patients are substantial, given the burden of PD symptoms and frailty of PD patients. Therefore, it will be critical to establish a collaborative research programs between clinical investigators and basic/translational neuroscientists in order to advance our understanding of circadian regulation in PD through exploration of animal models of PD-relevant neurodegeneration.

As any novel research area, circadian research in PD provides very exciting and promising direction with potential to improve PD burden and better understand the biology of the disease. One of the key questions is whether there is a bi-directional relationship between PD and circadian health. Does circadian function itself affects the biology of PD? Answer to this question may position circadian system as a novel target in PD with direct potential for development of circadian based intervention for PD.

Conflicts of interest

References

Agostino, P.V., Do Nascimento, M., Bussi, I.L., et al., 2011a. Circadian modulation of interval timing in mice. Brain Res. 1370, 154–163.

Agostino, P.V., Golombek, D.A., Meck, W.H., 2011b. Unwinding the molecular basis of interval and circadian timing. Front. Integr. Neurosci. 5, 64.

Alves, G., Forsaa, E.B., Pedersen, K.F., et al., 2008. Epidemiology of Parkinson's disease. J. Neurol. 255 (Suppl 5), 18–32.

Arias-Vera, J.R., Mansoor, G.A., White, W.B., 2003. Abnormalities in blood pressure regulation in a patient with Parkinson's disease. Am. J. Hypertens. 16 (7), 612–613.

Aziz, N.A., Pijl, H., Frolich, M., et al., 2011a. Diurnal secretion profiles of growth hormone, thyrotrophin and prolactin in Parkinson's disease. J. Neuroendocrinol. 23 (6), 519–524.

Aziz, N.A., Pijl, H., Flilich, M., et al., 2011b. Leptin, adiponectin, and resistin secretion and diurnal rhythmicity are unaltered in Parkinson's disease. Mov. Disord. 26 (4), 760–761.

Baier, P.C., Trenkwalder, C., 2007. Circadian variation in restless legs syndrome. Sleep Med. 8 (6), 645–650.

Ben, V., Bruguerolle, B., 2000. Effects of bilateral striatal 6-OHDA lesions on circadian rhythms in the rat: a radiotelemetric study. Life Sci. 67 (13), 1549–1558.

Bolitho, S.J., Naismith, S.L., Rajaratnam, S.M., et al., 2014. Disturbances in melatonin secretion and circadian sleep-wake regulation in Parkinson disease. Sleep Med. 15 (3), 342–347.

Bonuccelli, U., Del Dotto, P., Lucetti, C., et al., 2000. Diurnal motor variations to repeated doses of levodopa in Parkinson's disease. Clin. Neuropharmacol. 23 (1), 28–33.

Boulamery, A., Simon, N., Vidal, J., et al., 2010. Effects of L-Dopa on circadian rhythms of 6-OHDA striatal lesioned rats: a radiotelemetric study. Chronobiol. Int. 27 (2), 251–264.

Breen, D.P., Vuono, R., Nawarathna, U., et al., 2014. Sleep and circadian rhythm regulation in early Parkinson disease. JAMA Neurol. 71 (5), 589–595.

Brown, S.A., Schmitt, K., Eckert, A., 2011. Aging and circadian disruption: causes and effects. Aging 3 (8), 813–817.

Burns, R.S., Chiueh, C.C., Markey, S.P., et al., 1983. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc. Natl. Acad. Sci. USA 80 (14), 4546–4550.

Bussi, I.L., Levin, G., Golombek, D.A., et al., 2014. Involvement of dopamine signaling in the circadian modulation of interval timing. Eur. J. Neurosci. 40 (1), 2299–2310.

Cai, Y., Liu, S., Sothern, R.B., et al., 2010. Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson's disease. Eur. J. Neurol. 17 (4), 550–554.

Castaneda, T.R., de Prado, B.M., Prieto, D., et al., 2004. Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light. J. Pineal Res. 36 (3), 177–185.

Comella, C.L., 2007. Sleep disorders in Parkinson's disease: an overview. Mov. Disord. 22 (S17), S367–S373.

Crabtree, D.M., Zhang, J., 2012. Genetically engineered mouse models of Parkinson's disease. Brain Res. Bull. 88 (1), 13–32.

Czeisler, C.A., Allan, J.S., Strogatz, S.H., et al., 1986. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science 233 (4764), 667–671.

Devos, D., Kroumova, M., Bordet, R., et al., 2003. Heart rate variability and Parkinson's disease severity. J. Neural Transm. 110 (9), 997–1011.

Divito, C.B., Steece-Collier, K., Case, D.T., et al., 2015. Loss of VGLUT3 produces circadian-dependent hyperdopaminergia and ameliorates motor dysfunction and L-dopa-mediated dyskinesias in a model of Parkinson's disease. J. Neurosci. 35 (45), 14983–14999.

Dorsey, E.R., Constantinescu, R., Thompson, J.P., et al., 2007. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 68 (5), 384–386.

Ejaz, A.A., Sekhon, I.S., Munjal, S., 2006. Characteristic findings on 24-h ambulatory blood pressure monitoring in a series of patients with Parkinson's disease. Eur. J. Intern. Med. 17 (6), 417–420.

Factor, S.A., Weiner, W.J., 1998. Sleep benefit' in Parkinson's disease. Neurology 50, 1514e5.

Fertl, E., Auff, E., Doppelbauer, A., et al., 1991. Circadian secretion pattern of melatonin in Parkinson's disease. J. Neural Transm. Park Dis. Dement. Sect. 3 (1), 41–47.

Fertl, E., Auff, E., Doppelbauer, A., et al., 1993. 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. 5 (3), 227–234.

Fifel, K., Cooper, H.M., 2014. Loss of dopamine disrupts circadian rhythms in a mouse model of Parkinson's disease. Neurobiol. Dis. 71, 359–369.

Fifel, K., Piggins, H., Deboer, T., 2016. Modeling sleep alterations in Parkinson's disease: how close are we to valid translational animal models? Sleep. Med. Rev. 25, 95–111.

Fliers, E., Swaab, D.F., Pool, C.W., et al., 1985. The vasopressin and oxytocin neurons in the human supraoptic and paraventricular nucleus; changes with aging and in senile dementia. Brain Res. 342 (1), 45–53.

Golombek, D.A., Bussi, I.L., Agostino, P.V., 2014. Minutes, days and years: molecular interactions among different scales of biological timing. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1637), 20120465.

Gravotta, L., Gavrilla, L.A., Hood, S., et al., 2011. Global depletion of dopamine using intracerebroventricular 6-hydroxydopamine injection disrupts normal circadian wheel-running patterns and PERIOD2 expression in the rat forebrain. J. Mol. Neurosci. 45 (2), 162–171.

Haapaniemi, T.H., Pursiainen, V., Korpelainen, T., et al., 2001. Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. J Neurol. Neurosurg. Psychiatry 70 (3), 305–310.

Hineno, T., Mizobuchi, M., Hiratani, K., et al., 1992. Disappearance of circadian rhythms in Parkinson's disease model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in dogs. Brain Res. 580 (1-2), 92–99.

Hogl, B.E., Gomez-Arevalo, G., Garcia, S., et al., 1998. A clinical, pharmacologic, and polysomnographic study of sleep benefit in Parkinson's disease. Neurology 50, 1332e9.

Hood, S., Cassidy, P., Cossette, M.P., et al., 2010. 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. 30 (42), 14046–14058.

Hyacinthe, C., Barraud, Q., Bezard, E., et al., 2014. D1 receptor agonist improves sleep-wake parameters in experimental parkinsonism. Neurobiol. Dis. 63, 20–24.

Ikeda, E., Matsunaga, N., Kakimoto, K., et al., 2013. Molecular mechanism regulating 24-hour rhythm of dopamine D3 receptor expression in mouse ventral striatum. Mol. Pharmacol. 83 (5), 959–967.

Jagmag, S.A., Tripathi, N., Shukla, D., et al., 2015. Evaluation of Models of Parkinson's Disease. Front. Neurosci. 9, 503.

Johnston, T.M., Fox, S.H., et al., 2015. Symptomatic models of Parkinson's disease and L-dopa-induced dyskinesia in non-human primates. Curr. Top. Behav. Neurosci. 22, 221–235.

Ju, Y.E., Lucey, B.P., B, P, Holtzman, D.M., et al., 2014. Sleep and Alzheimer disease pathology–a bidirectional relationship. Nat. Rev. Neurol. 10 (2), 115–119.

Kafka, M.S., Benedito, M.A., Roth, R.H., et al., 1986. Circadian rhythms in catecholamine metabolites and cyclic nucleotide production. Chronobiol. Int. 3 (2), 101–115.

Kallio, M., Haapaniemi, T., Turkka, J., et al., 2000. Heart rate variability in patients with untreated Parkinson's disease. Eur. J. Neurol. 7 (6), 667–672.

Kallio, M., Suominen, K., Haapaniemi, T., et al., 2004. Nocturnal cardiac autonomic regulation in Parkinson's disease. Clin. Auton. Res. 14 (2), 119–124.

Klerman, E.B., Rimmer, D.W., D.J., et al., 1998. Nonphotic entrainment of the human circadian pacemaker. Am. J. Physiol. 274 (4 Pt 2), R991–R996.

Kudo, T., Loh, D.H., Truong, D., et al., 2011. Circadian dysfunction in a mouse model of Parkinson's disease. Exp. Neurol. 232 (1), 66–75.

Laloux, C., Derambure, P., Houdayer, E., et al., 2008. Effect of dopaminergic substances on sleep/wakefulness in saline – and MPTP-treated mice. J. Sleep Res. 17 (1), 101–110.

Li, S.X., Liu, L.J., Jiang, W.G., et al., 2009. Morphine withdrawal produces circadian rhythm alterations of clock genes in mesolimbic brain areas and peripheral blood mononuclear cells in rats. J. Neurochem. 109 (6), 1668–1679.

Mamelak, M., 1997. Neurodegeneration, sleep, and cerebral energy metabolism: a testable hypothesis. J. Geriatr. Psychiatry Neurol. 10 (1), 29–32.

Mastrocola, C., Vanacore, N., Giovani, A., et al., 1999. Twenty-four-hour heart rate variability to assess autonomic function in Parkinson's disease. Acta Neurol. Scand. 99 (4), 245–247.

Mattam, U., Jagota, A., 2015. Daily rhythms of serotonin metabolism and the expression of clock genes in suprachiasmatic nucleus of rotenone-induced Parkinson's disease male Wistar rat model and effect of melatonin administration. Biogerontology 16 (1), 109–123.

Mattis, J., Sehgal, A., 2016. Circadian rhythms, sleep, and disorders of aging. Trends Endocrinol. Metab. 27 (4), 192–203.

McDowell, K., Chesselet, M.F., 2012. Animal models of the non-motor features of Parkinson's disease. Neurobiol. Dis. 46 (3), 597–606.

McDowell, K.A., Shin, D., Roos, K.P., et al., 2014. Sleep dysfunction and EEG alterations in mice overexpressing alpha-synuclein. J. Parkinsons Dis. 4 (3), 531–539.

McEnany, G.W., Lee, K.A., 2005. Effects of light therapy on sleep, mood, and temperature in women with nonseasonal major depression. Issues Ment. Health Nurs. 26 (7), 781–794.

Mendoza, J., Challet, E., 2014. Circadian insights into dopamine mechanisms. Neuroscience 282, 230–242.

Merello, M., Hughes, A., Colosimo, C., et al., 1997. Sleep benefit in Parkinson's disease. Mov. Disord. 12, 506e8.

Mihci, E., Kardelen, F., Dora, B., et al., 2006. Orthostatic heart rate variability analysis in idiopathic Parkinson's disease. Acta Neurol. Scand. 113 (5), 288–293.

Morton, A.J., Wood, N.I., Hastings, M., H., et al., 2005. Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. J. Neurosci. 25 (1), 157–163.

Natsubori, A., Honma, K., Honma, S., 2014. Dual regulation of clock gene Per2 expression in discrete brain areas by the circadian pacemaker and methamphetamine-induced oscillator in rats. Eur. J. Neurosci. 39 (2), 229–240.

Nutt, J.G., Woodward, W.E., Carter, J.H., et al., 1989. Influence of fluctuations of plasma large neutral amino acids with normal diets on the clinical response to levodopa. J. Neurol. Neurosurg. Psychiatry 52 (4), 481–487.

Parekh, P.K., Ozburn, A.R., McClung, C.A., 2015. Circadian clock genes: effects on dopamine, reward and addiction. Alcohol 49 (4), 341–349.

Pathak, A., Senard, J.M., 2006. Blood pressure disorders during Parkinson's disease: epidemiology, pathophysiology and management. Expert Rev. Neurother. 6 (8), 1173–1180.

Paus, S., Schmitz-Hubsch, T., Wullner, M., et al., 2007. Bright light therapy in Parkinson's disease: a pilot study. Mov. Disord. 22 (10), 1495–1498.

de Pedro Cuesta, J., 1987. Studies on the prevalence of paralysis agitans by tracer methodology. Acta Neurol. Scand. (Suppl. 112), 1–106.

de Pedro-Cuesta, J., Stawiarz, L., 1991. Parkinson's disease incidence: magnitude, comparability, time trends. Acta Neurol. Scand. 84 (5), 382–388.

Piccini, P., Del Dotto, P., Pardini, C., et al., 1991. Diurnal worsening in Parkinson patients treated with levodopa. Rev. Neurol. 61 (4), 219–224.

Placidi, F., Izzi, F., Romigi, A., et al., 2008. Sleep-wake cycle and effects of cabergoline monotherapy in de novo Parkinson's disease patients. An ambulatory polysomnographic study. J. Neurol. 255 (7), 1032–1037.

Poceta, J.S., Parsons, L., Engelland, S., et al., 2009. Circadian rhythm of CSF monoamines and hypocretin-1 in restless legs syndrome and Parkinson's disease. Sleep Med. 10 (1), 129–133.

Porter, B., Macfarlane, R., Walker, R., 2008. The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease. Eur. J. Neurol. 15 (1), 50–54.

Pungor, K., Papp, M., Kekesi, K., et al., 1990. A novel effect of MPTP: the selective suppression of paradoxical sleep in cats. Brain Res. 525 (2), 310–314.

Pursiainen, V., Haapaniemi, T.H., Korpelainen, J.T., et al., 2002. Circadian heart rate variability in Parkinson's disease. J. Neurol. 249 (11), 1535–1540.

Riemersma-van der Lek, R.F., Swaab, D.F., Twisk, J., et al., 2008. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. JAMA 299 (22), 2642–2655.

Roybal, K., Theobold, D., Graham, A., et al., 2007. Mania-like behavior induced by disruption of CLOCK. Proc. Natl. Acad. Sci. USA 104, 6406–6411.

Seron-Ferre, M., Torres-Farfan, C., Forcelledo, M.L., et al., 2001. The development of circadian rhythms in the fetus and neonate. Semin. Perinatol. 25 (6), 363–370.

Shumay, E., Fowler, J.S., Wang, G.J., et al., 2012. Repeat variation in the human PER2 gene as a new genetic marker associated with cocaine addiction and brain dopamine D2 receptor availability. Transl. Psychiatry 2, e86.

Sleipness, E.P., Sorg, B.A., Jansen, H.T., 2007. Diurnal differences in dopamine transporter and tyrosine hydroxylase levels in rat brain: dependence on the suprachiasmatic nucleus. Brain Res. 1129 (1), 34–42.

Struck, L.K., Rodnitzky, R.L., Dobson, J.K., 1990. Circadian fluctuations of contrast sensitivity in Parkinson's disease. Neurology 40 (3 Pt 1), 467–470.

Suzuki, K., Miyamoto, T., Miyamoto, M., et al., 2007. Circadian variation of core body

temperature in Parkinson disease patients with depression: a potential biological marker for depression in Parkinson disease. Neuropsychobiology 56 (4), 172–179.

Taylor, T.N., Caudle, W.M., Shepherd, K.R., et al., 2009. Nonmotor symptoms of Parkinson's disease revealed in an animal model with reduced monoamine storage capacity. J. Neurosci. 29 (25), 8103–8113.

Terman, M., Terman, J.S., 1999. Bright light therapy: side effects and benefits across the symptom spectrum. J. Clin. Psychiatry 60 (11), 799–808.

Terman, M., Terman, J.S., 2005. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectr. 10 (8), 647–663.

van Gilst, M.M., Bloem, B.R., Overeem, S., 2013. "Sleep benefit" in Parkinson's disease: a systematic review. Parkinsonism Relat. Disord. 19 (7), 654–659.

van Hilten, B., Hoff, J.I., Middelkoop, H.A., et al., 1994. Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. Arch. Neurol. 51 (9), 922–928.

van Hilten, J.J., Middelkoop, H.A., Kerkhof, G.A., et al., 1991. A new approach in the assessment of motor activity in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 54 (11), 976–979.

van Hilten, J.J., Hoogland, G., van der Velde, E.A., et al., 1993. Diurnal effects of motor activity and fatigue in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 56 (8), 874–877.

van Hilten, J.J., Kabel, J.F., Middelkoop, H.A., et al., 1993. Assessment of response fluctuations in Parkinson's disease by ambulatory wrist activity monitoring. Acta Neurol. Scand. 87 (3), 171–177.

van Hilten, J.J., Weggeman, M., van der Velde, E.A., et al., 1993. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J. Neural Transm. Park Dis. Dement. Sect. 5 (3), 235–244.

Verbaan, D., van Rooden, S.M., Visser, M., et al., 2008. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. Mov. Disord. 23 (1), 35–41.

Vezoli, J., Fifel, K., Leviel, V., et al., 2011. Early presymptomatic and long-term changes of rest activity cycles and cognitive behavior in a MPTP-monkey model of Parkinson's disease. PLoS One 6 (8), e2395.

Videnovic, A., Golombek, D., 2013. Circadian and sleep disorders in Parkinson's disease. Exp. Neurol. 24, 45–56.

Videnovic, A., Willis, G.L., 2016. Circadian system – a novel diagnostic and therapeutic target in Parkinson's disease? Mov. Disord. 31 (3), 260–269.

Videnovic, A., Lazar, A.S., Barker, R.A., et al., 2014a. "The clock that time us" - circadian rhythms in neurodegenerative disorders. Nat. Rev. Neurol. 10 (12), 683–693.

Videnovic, A., Noble, C., Reid, K.J., et al., 2014b. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 71 (4), 463–469.

Whitehead, D.L., Davies, A.D., Playfer, J.R., et al., 2008. Circadian rest-activity rhythm is altered in Parkinson's disease patients with hallucinations. Mov. Disord. 23 (8), 1137–1145.

Willis, G.L., Turner, E.J., 2007. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. Chronobiol. Int. 24 (3), 521–537.

Willis, G.L., Kelly, A.M., Kennedy, G.A., 2008. Compromised circadian function in Parkinson's disease: enucleation augments disease severity in the unilateral model. Behav. Brain Res. 193 (1), 37–47.

Willis, G.L., Moore, C., Armstrong, S.M., 2012. A historical justification for and retrospective analysis of the systematic application of light therapy in Parkinson's disease. Rev. Neurosci. 23 (2), 199–226.

Witkovsky, P., 2004. Dopamine and retinal function. Doc. Ophthalmol. 108 (1), 17–40.

Zisapel, N., 2001. Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting. Cell Mol. Neurobiol. 21 (6), 605–616.