Neurobiology of Sleep and Circadian Rhythms xx (xxxx) xxxx–xxxx

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/nbscr

Circadian dysregulation in Parkinson's disease

Aleksandar Videnovic[a,*,1], Diego Golombek[b]

[a] Movement Disorders Unit and Division of Sleep Medicine, Massachusetts General Hospital Harvard Medical School, MGH Neurological Clinical Research Institute, 165 Cambridge Street, Suite 600, Boston, MA 02446, United States

[b] Department of Science and Technology, National University of Quilmes/CONICET, R.S. Peña 352, 1876 Bernal, Buenos Aires, Argentina

ARTICLE INFO

Keywords:
Parkinson's
circadian
sleep
dopamine
clock genes

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

* Corresponding author.
E-mail addresses: avidenovic@mgh.harvard.edu (A. Videnovic), dgolombek@unq.edu.ar (D. Golombek).

[1] Dr. Videnovic received research Grant support from the National Institutes of Health (K23 NS072283).

http://dx.doi.org/10.1016/j.nbscr.2016.11.001
Received 31 July 2016; Received in revised form 19 October 2016; Accepted 3 November 2016
Available online xxxx

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 tegemental 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.