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PARKINSON'S DISEASE AND CIRCADIAN RHYTHM DISRUPTION

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily associated with motor symptoms such as bradykinesia, rigidity, and tremor. However, it is increasingly recognized that non-motor symptoms—including sleep disturbances, mood disorders, cognitive impairment, and autonomic dysfunction are equally impactful and often precede the onset of motor signs. Mounting evidence highlights a strong bidirectional link between PD and circadian rhythm disruption. Circadian dysregulation is not only a consequence of PD-related neurodegeneration but also a potential contributing factor to its onset and progression. Central mechanisms underlying this interplay include dopamine (DA) dysregulation, microglial activation, and α-synuclein aggregation, all modulated by core circadian clock genes such as BMAL1, CLOCK, and REV-ERBα. Disruption of these genes impairs DA synthesis, promotes oxidative stress and inflammation, and accelerates neurodegeneration. Circadian dysfunction in PD also affects the suprachiasmatic nucleus and peripheral clocks, disrupting physiological rhythms governing sleep-wake cycles, thermoregulation, blood pressure, mood, gastrointestinal function, and urination. Notably, sleep disorders—particularly REM sleep behavior disorder (RBD), insomnia, and excessive daytime sleepiness, affect over 90% of PD patients and often appear in prodromal stages, offering a valuable opportunity for early diagnosis. RBD is considered one of the most specific predictors of future neurodegeneration, frequently preceding motor symptoms by more than a decade. Understanding the circadian regulation of DA transmission, immune function, and metabolic activity offers novel therapeutic avenues. Interventions aimed at restoring circadian rhythms, such as light therapy, melatonin supplementation, and pharmacological targeting of clock genes, have shown potential in alleviating both motor and non-motor symptoms and may modify disease progression. This growing recognition of the circadian system's role in PD pathophysiology underscores the need for further research and integration of chronobiological strategies into personalized treatment plans.

KEYWORDS: circadian rhythm, dopaminergic neurons, neurodegenerative diseases, Parkinson disease, sleep wake disorders

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder affecting over 1% of the population over 60.[1] It is characterized by the loss of dopaminergic neurons in the nigrostriatal pathway, especially substantia nigra pars compacta (SNpc), and intraneuronal α-synuclein (α-syn) inclusions called Lewy bodies. It is primarily known for motor disturbances like pill-rolling tremors, rigidity, bradykinesia, gait impairment, and postural instability.[1] PD also displays many non-motor symptoms like neuropsychiatric disorders, autonomic dysfunction, sensory deficits, and sleep disturbances.[2] They often appear years or even decades before motor symptoms and clinical diagnosis. They could prove to be a potential marker for early discovery and treatment of PD, leading to slower progression and better prognosis.[1]

Circadian rhythm, also known as the "biological clock," is an intrinsic 24-hour timekeeping mechanism responsible for our body's physiological adaptation to day and nighttime. It dictates the daily rhythmicity of hormonal levels, body temperature, rest-activity behavior, feeding, and many other physiological processes (Figure 1).[1,3] Circadian rhythms originate from interconnected molecular oscillators in the brain and peripheral tissues, which synchronize with environmental and behavioral cycles to facilitate sleep during nighttime. There are central and peripheral parts of the mechanism. The suprachiasmatic nucleus (SCN) in the hypothalamus is the primary central circadian pacemaker, containing around 50,000 neurons. It comprises core and shell subnuclei, which are regulated by the neurotransmitter γ-Aminobutyric acid (GABA). It is synchronized with zeitgebers and external environmental cues like temperature and light from the retina (directly via the retinohypothalamic tract or through retinogeniculate pathways), enabling it to adjust to daily and seasonal changes (Figure 2).[3] The SNC regulates peripheral parts of the circadian system, such as the heart, skin, liver, or kidneys, through the autonomic nervous system or endocrine hormone signaling. This rhythm can frequently be disrupted by changes in work and social schedules, exposure to light, changes in living environments, food intake, metabolites, body temperature, and physical activity. The disruption is detrimental to the timing of sleep and our physical and mental well-being.[1,4,5]

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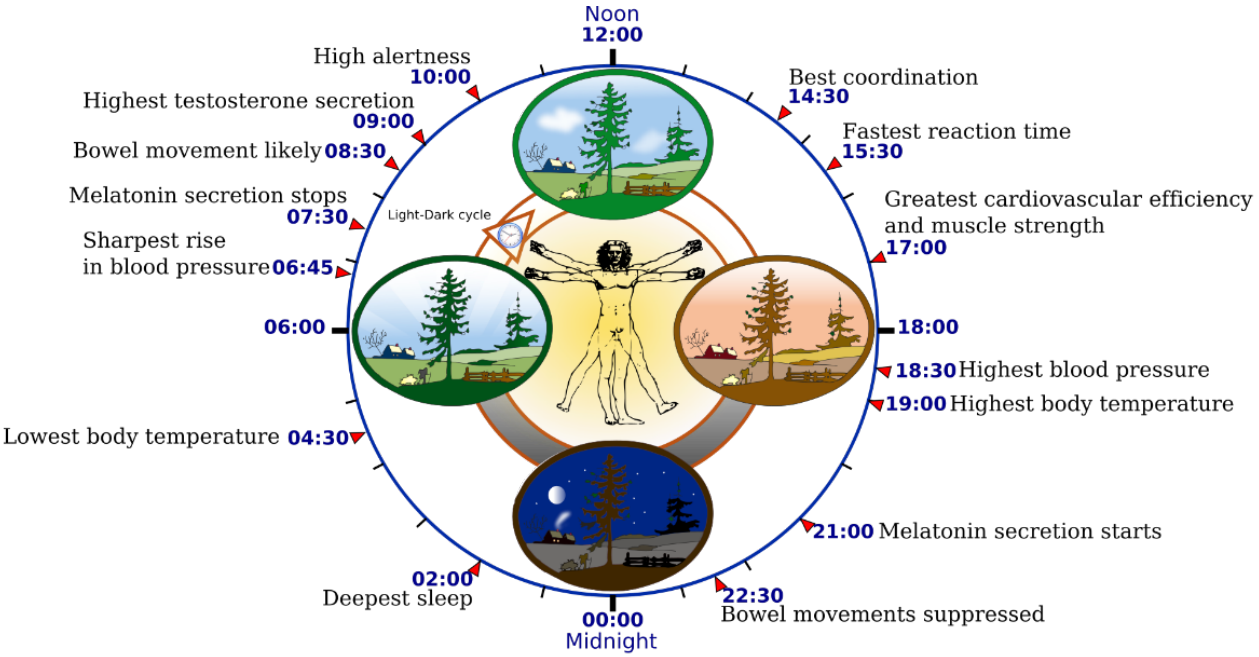

Figure 1. Biological functions follow the 24-hour circadian rhythm in humans.

Source: image ''Overview of biological circadian clock in humans'' by Yassine Mrabet – from Wikimedia Commons, CC 2.5 license. Published May 17th, 2009. Accessed March 10th, 2025.
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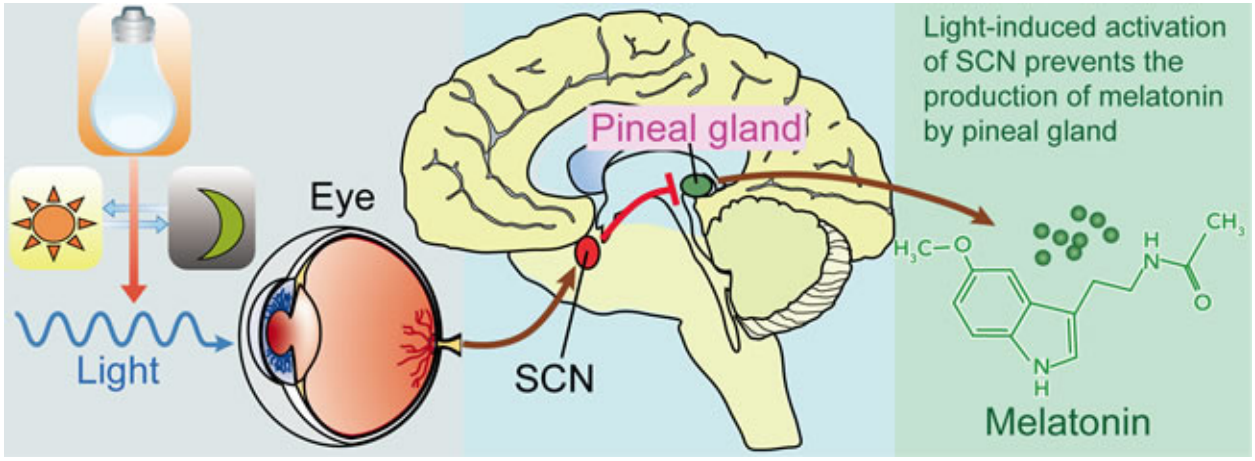

Figure 2. Light-induced activation of the suprachiasmatic nucleus prevents the production of melatonin by the pineal gland.

Source: Ma Z, Yang Y, Fan C, et al. Melatonin as a potential anticarcinogen for non-small-cell lung cancer. *Oncotarget*. 2016; 7(29): 46768-46784. doi: 10.18632/oncotarget.8776.
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MOLECULAR MECHANISMS OF THE CIRCADIAN RHYTHM AND THE IMPACT OF ITS DISRUPTION

Circadian rhythm is created by the core transcription-translation feedback loop (TTFL) of the central clock genes in SCN. During the day, CLOCK and BMAL1 form heterodimers and act as transcriptional activators. They bind to the regulatory elements (E-boxes) of promoter regions of many genes, up-regulating their expression, including PER1/2 and CRY1/2. When night comes, levels of PER and CRY increase, and they also form their own heterodimers and transport to the nucleus, where they act as suppressors and inhibit CLOCK/BMAL1-induced transcription. TTFL is also strengthened with BMAL1 transcription mediated by nuclear receptors RORα/β/γ and REV-ERBα/β through positive and negative

feedback mechanisms.[1,5] This is the basis of the circadian expression of up to 20% of the genome (variable depending on the cell type).[1] TTFL of the circadian rhythm clock genes is depicted below in Figure 3.

Circadian disruption has been identified as a risk factor and driving force of three progressive PD neurodegeneration culprits: dopamine depletion, intraneuronal α-syn accumulation, and microglial activation. The mechanisms of these interactions are discussed below, and the role of circadian function restoration as a promising neuroprotective strategy for PD is also highlighted.[5]

CIRCADIAN RHYTHM DISTURBANCE-REGULATED DOPAMINE DEPLETION

Dopamine (DA) levels can be a significant indicator of the prodromal PD stage because its symptoms appear when there is already a substantial depletion of dopaminergic neurons in the striatum. Circadian rhythm genes can control DA production. The CLOCK gene regulates tyrosine hydroxylase (TH), a key component of DA synthesis. Its product binds to the promoter regions related to DA and controls the expression of TH, D1 receptors, and active transporters of DA, influencing DA metabolism.[5,6] A 2021 study noted lower melatonin levels in the blood and lower expression of BMAL1 and other circadian genes in PD patients. Reduced BMAL1 expression contributes to oxidative stress, spontaneous loss of TH, and finally, dopaminergic neuron degeneration, especially in the SNpc, where they are the most vulnerable. This confirms BMAL1's neuroprotective role in maintaining mitochondrial function and reducing oxidative stress.[7,8] Circadian gene REV-ERBα inhibits TH expression and, therefore, restricts the production of DA. It can be a significant causative factor for PD's non-motor symptoms, like mental health disorders. Blocking REV-ERBα has been found to reduce depressive and anxiety-like symptoms in PD.[5,9]

CIRCADIAN RHYTHM DISTURBANCE-REGULATED MICROGLIAL ACTIVATION

Microglia are the brain's central immunological cells. Their overactivation and subsequent neuroinflammation characterize PD. They follow their circadian rhythm, which regulates inflammatory responses like phagocytosis, cytokine release, and metabolic and nutritional support.[10,11] Microglial overactivation can also indicate prodromal PD, preceding and potentially contributing to dopaminergic neuron loss.[12] In studies conducted on mice, BMAL1 deletion causes increased microglial activation, consequently raising their inflammatory response.[13,14] REV-ERBα was also shown to modulate microglia, and its absence also increased their activity. Therefore, this gene's activation was studied as a potential target for PD treatment.[15,16]

CIRCADIAN RHYTHM DISTURBANCE-REGULATED ALPHA-SYNUCLEIN ACCUMULATION

Alpha-synuclein is an amyloid protein that forms toxic intraneuronal folded aggregates called Lewy bodies, which drive neuronal death and neurodegeneration in PD.[17] Once deposited, they are very hard to decompose. Increased α-syn expression in SCN disrupts circadian rhythms by reducing

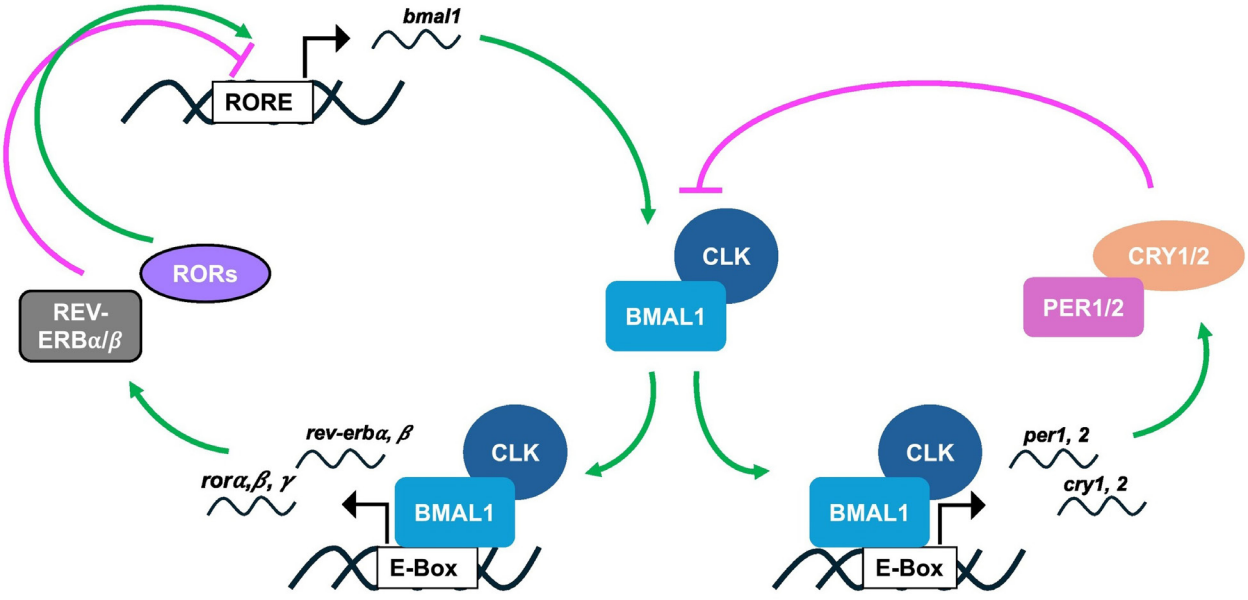

Figure 3. Molecular interactions that create the basis of circadian rhythm transcriptional-translational feedback loops.

Source: Duret LC, Nagoshi E. The intertwined relationship between circadian dysfunction and Parkinson's disease. *Trends Neurosci*. 2025; 48(1): 62-76. doi:10.1016/j.tins.2024.10.006.
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neuronal activity. A proposed explanation is a reduced number of synapses in SCN due to α-syn's disrupted role as a modulatory protein for releasing synaptic vesicles.[18,19] High levels of α-syn can lead to a decreased inhibitory GABA effect (the main neurotransmitter in SCN), contributing to circadian disruption among reduced synapses.[20] Synuclein Alpha gene (SNCA) mutations have been associated with sporadic and dominant PD instances.[21] One example is the A53T mutation of SNCA, which is often linked to autosomal dominant hereditary PD. It leads to lower motor activity in mice and reduced BMAL1 expression, a key factor for circadian disruption. Furthermore, decreased stability of SNCA mRNA contributes to α-syn accumulation. [21,22]
(Figure 4)

ROLE OF DOPAMINE IN CIRCADIAN RHYTHM AND WAKEFULNESS

DA neurotransmission is deeply integrated into the circadian system, influencing photic input, circadian gene regulation, and behavioral rhythms. Its signaling activity and metabolism also follow a circadian rhythmic pattern.

The retina plays a crucial role as a circadian zeitgeber through light detection. DA is involved in retinal light adaptation and regulation of retinal sensitivity via dopaminergic amacrine cells, which express circadian clock genes (PER, CRY, CLOCK, BMAL1). Furthermore, it regulates the rhythmic expression of photopigment melanopsin in intrinsically photosensitive retinal ganglion cells, essential for circadian synchronization.[3] In a 2018 study examining post-mortem retinas, it was confirmed that PD patients had melanopsin-containing retinal ganglion cell degeneration.[23] They showed decreased density and substantial structural damage (e.g., fewer dendritic branches and synaptic contacts, simplified architecture of the melanopsin-expressing networks).[23] DA modulates second messenger systems (cAMP) via D4 receptors, influencing photoreceptor sensitivity. This can manifest as impaired visual contrast sensitivity—the inability to distinguish a visual object from its background, commonly found in PD. Contrast sensitivity has also shown circadian variation in PD patients.[1,24,25]

In the SCN, dopaminergic D1 receptors are present but function differently depending on the developmental stage. They exist in both adults and fetuses, but their phase-resetting effects are only seen prenatally, and they do not influence photic entrainment or melatonin-driven circadian pathways in adults.[26–29] The CLOCK gene, a key regulator of circadian rhythms, directly affects dopaminergic activity in the ventral tegmental area (VTA). Clock gene mutations lead to altered DA signaling, causing mood-related changes and heightened sensitivity to stimulants like cocaine.[26,30] DA also influences circadian TTFL by modulating DA synthesis and transport genes. Circadian clock machinery can bind to E Box elements in promoter regions and regulate the activity of the tyrosine hydroxylase (TH), D1A receptor, and dopamine active transporter (DAT). In turn, via interaction with D1 and D2 receptors, DA influences the expression of those clock genes in the dorsal striatum and the nucleus accumbens (regulating the circadian rhythms of behavior and addiction).[3,26,31,32] Haloperidol treatment has been shown to upregulate the expression of clock genes that regulate the transcriptional feedback loop underlying circadian rhythms, both in live models and in cultured SCN cells.[33]

DA is considered wake-promoting, with stimulants like amphetamines enhancing wakefulness by increasing DA release and blocking its reuptake. Dopaminergic D1 and D2 receptors play a role in sleep-wake balance, with some evidence suggesting DA's involvement in sleep fragmentation and hypersomnolence. Consequently, DA depletion in PD affects the sleep-wake cycle, with patients often experiencing circadian rhythm misalignment, REM sleep disturbances, excessive daytime sleepiness, fragmented sleep-wake cycles, and increased slow-wave sleep during wakefulness (hallmark of hypersomnolence).[26] Agonists used in DA replacement therapy can either improve sleep in PD or lead to paradoxical effects like sudden sleep attacks, worsening the symptoms. This happens because D1 receptor activation promotes wakefulness, but D2 activation's impact on sleep is dose-dependent: low dose (e.g., pramipexole) increases deep sleep, but high doses lead to wakefulness. L-DOPA primarily promotes motor function and does not help with sleep disturbances. Deep Brain Stimulation can improve nocturnal sleep, but its effects on circadian rhythms are still unclear.[26]
(Figure 5)

CIRCADIAN DISRUPTION OF SLEEP IN PD

Sleep disorders are the most prevalent among non-motor PD symptoms, which are experienced by over 98% of the patients.[34] They include REM sleep behavior disorder (RBD), insomnia, excessive daytime sleepiness (EDS), restless leg syndrome (RLS), etc.

REM SLEEP BEHAVIOR DISORDER

RBD is a sleep disorder in which individuals lose the normal muscle paralysis (atonia) of REM sleep, leading to dream enactment behaviors such as talking, shouting, kicking, punching, or even falling out of bed. The content of the dreams is mostly violent, and patients will remember it if they are woken during the RBD episode. Parasomnia is very rare because REM's postural atonia persists during RBD, which is characterized by simple motor actions and usually results in the patient falling and waking up on the floor.[35] The prevalence of RBD in the general population is lower than 0.05%, while it is around 47% in PD.[36,37] This suggests a high correlation and PD as a significant risk factor. It is a potentially excellent indicator of prodromal PD or other neurodegenerative synucleinopathies (e.g., dementia with Lewy bodies) because over 80% of idiopathic RBDs develop them.[38] The average latency before developing motor symptoms is about 12 to 14 years.[39,40] Those who have both RBD and EDS have a higher risk of developing PD.[41] There have been attempts to determine the origin of RBD because of its PD prodromal trait and the potential to explain how and why PD develops. A malfunction of the pathway that connects the ventromedial medulla and nucleus subcoeruleus could

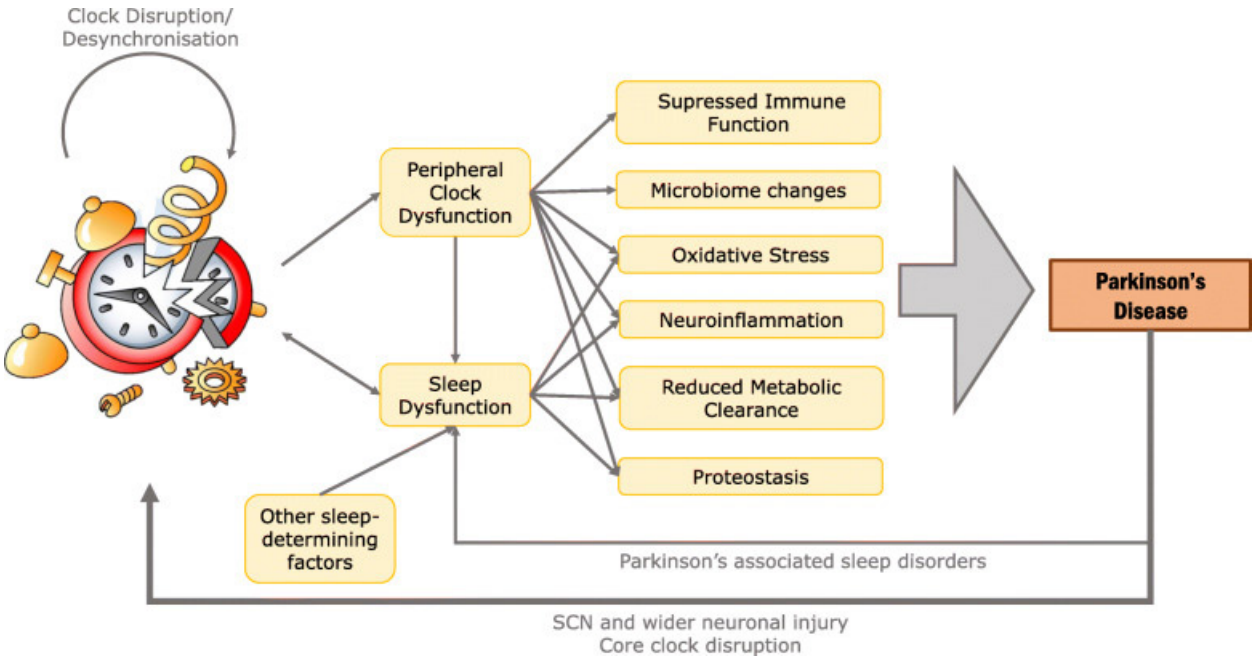

Figure 4. Potential mechanisms of interplay between circadian dysfunction and Parkinson's disease.

Source: Hunt J, Coulson EJ, Rajnarayanan R, Oster H, Videnovic A, Rawashdeh O. Sleep and circadian rhythms in Parkinson's disease and preclinical models. *Mol Neurodegener*. 2022; 17(1): 2. doi:10.1186/s13024-021-00504-w
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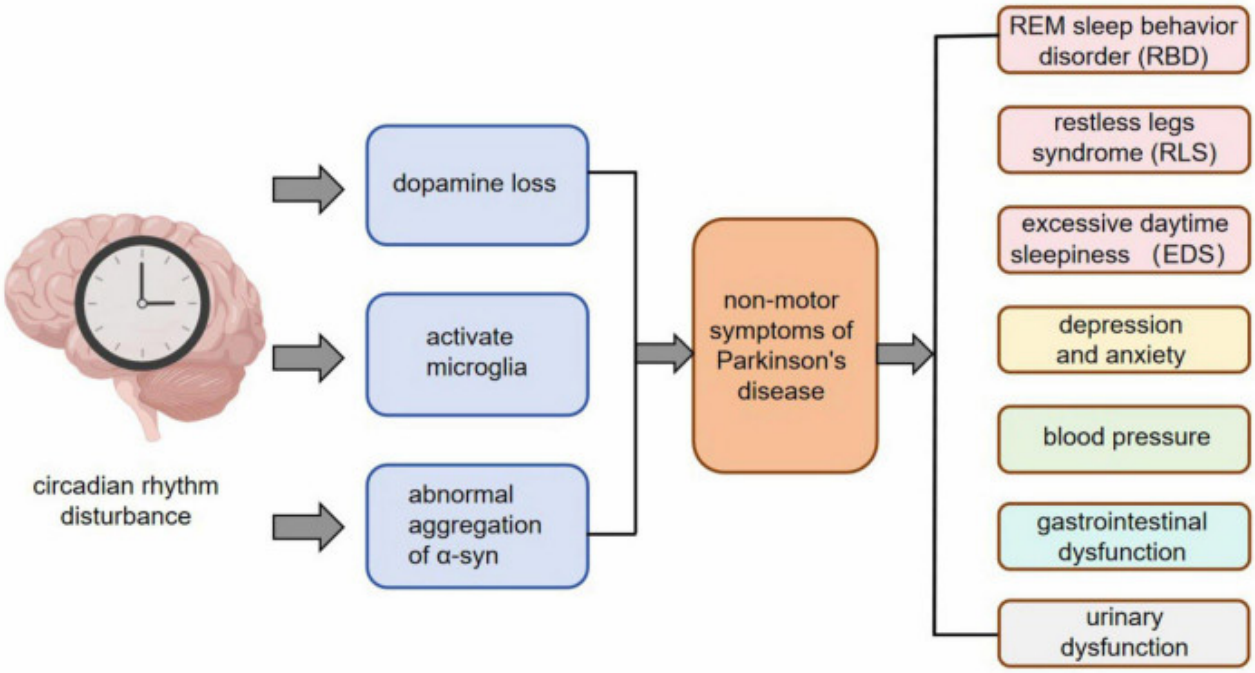

Figure 5. Possible pathophysiology of non-motor PD symptoms due to circadian rhythm disturbance.

Source: Xu K, Zhang Y, Shi Y, et al. Circadian rhythm disruption: a potential trigger in Parkinson's disease pathogenesis. *Front Cell Neurosci*. 2024; 18. doi:10.3389/fncel.2024.1464595
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lead to altered muscle atonia in RBD. Starting caudally in the brainstem and causing sleep disorders, it could expand rostrally and affect SNpc, finally leading to the start of classic PD motor symptoms.[42,43] Nevertheless, RBD proved to have the highest specificity and prediction power for the future diagnosis of PD.[44] Treatment options for RBD involve MLT or clonazepam, for which caution should be taken by medical professionals prescribing it due to its side effects.[44]

INSOMNIA AND EXCESSIVE DAYTIME SLEEPINESS

Insomnia is defined by difficulty falling asleep, lower quality of sleep, and trouble maintaining it despite adequate opportunity to rest. PD patients experiencing insomnia usually have more trouble with waking up early and sleep fragmentation than with the initiation of sleep. It is a pervasive problem in PD, often associated with depression and increasing in prevalence (30-80%) as the illness advances.[45,46] Excessive daytime sleepiness (EDS) is a difficulty in staying alert and awake during the day. It can lead to involuntary incidences of sleep and tiredness. It also rises in PD prevalence (15-76%) as the disease advances, perhaps due to neurodegeneration of wake-promoting areas.[45,47] PD treatment medication is frequently linked as a possible trigger for EDS, which increases in occurrence with higher doses of the drugs.[48] EDS can be screened by the Epworth Sleepiness Scale (ESS) with a positive score of over 10 or the Multiple Sleep Latency Test (MSLT).[49] Insomnia and EDS are strongly tied to MLT levels, markers of circadian dysfunction. In these patients, MLT blood levels have a considerable drop in amplitude and a smaller area under the curve (AUC).[50] Controlling EDS involves detecting all the possible reversible factors, such as PD medication, which should be titrated to an acceptable level for disease control and the side effects of dopaminergic drugs. Other factors, like the progression of PD, cannot be reversed, but treating other sleep disorders can help alleviate the symptoms.[45] Timed light therapy is a promising new method that showed a substantial increase in patient performance on ESS screen tests compared to the control group.[51] Modafinil and sodium oxybate have also been investigated, but there were few test groups and insufficient evidence.[45]

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is an urge for leg movement due to discomfort initiated or intensified by resting (often at night) and eased by activity.[52] Sensations in the legs that cause discomfort are often referred to as pulling, creeping, or itching. RLS always occurs at the beginning of sleep, with symptoms peaking between 11 p.m. and 4 a.m. and being the lowest during the day's first activities (9 a.m. to 3 p.m.).[53] RLS' prevalence in PD is around 14%, slightly higher in those using dopaminergic drugs (14 vs 11%).[54] There is no consensus on the pathophysiology of RLS, but current research shows that DA dysfunction, decreased iron stores, and genetics are important factors.[45,53] One study showed that daylight exposure reduces RLS motor symptoms and MLT secretion, while those who took MLT pills before sleeping had increased motor symptoms.[55] Treatment options include IV iron or DA agonists like rotigotine, pramipexole, or ropinirole.[45]

CIRCADIAN DISRUPTION OF OTHER PHYSIOLOGICAL RHYTHMS

Impaired circadian function in PD is implicated in the dysregulation of the sleep-wake cycle and autonomic, cognitive, psychiatric, and, most notably, motor symptoms. It contributes to fluctuations in motor performance, worsening symptoms in the afternoon or evening, and decreased D receptor sensitivity during the day.[26]

Disrupted circadian thermoregulation often affects body temperature. It can lead to lower body temperature during the day and a lack of temperature drop at night.[1,56]

Autonomic dysfunction can also manifest in altered heart rate variability, as shown on power spectral analyses using 24-hour ambulatory ECG recordings. Multiple actigraphy testing studies showcased patients' lower activity when out of bed and higher activity when in bed. This has also been linked with disease progression, which is associated with lower daytime activity.[57]

Reversal of the normal physiological blood pressure (BP) profile is also frequently found due to autonomic dysfunction. PD patients exhibit a reversal of the circadian blood pressure profile defined by nighttime blood pressure equal to or lower than daytime. Patients experience nocturnal hypertension (non-dipper profile), which can be very detrimental to their cardiovascular health. Postprandial hypotension has also been noted in many PD patients, recorded with a decrease of systolic BP of more than 20 mmHg within 75 min of eating a meal. Even though their mean 24-hour blood pressure is lower (orthostatic hypotension), most patients have daytime BP in the prehypertension or hypertension ranges.[58–61] Non-dipper PD patients more often tend to develop psychiatric symptoms, as discussed below.[62]

Psychiatric disorders like anxiety and depression are prevalent in PD and other patients with circadian dysfunctions. Anxiety is detected in 50% and depression in 45% of the patients with PD.[63,64] Psychiatric symptoms tend to peak in the afternoon and at night, often being named "nocturnal delirium" or "sunset syndrome."[65] Midbrain ventral tegmental area (VTA) DA neurons form connections with the prefrontal cortex and are considered responsible for psychiatric and cognitive symptoms.[66]

Gastrointestinal (GI) symptoms, like constipation, are believed to follow the circadian clock disruption. GI is the second highest producer of MLT in the body after the epiphysis, and those without symptoms tend to have higher MLT plasma levels.[67,68]

Urinary dysfunction is a consequence of free water and sodium circadian rhythm dysregulation. Typically, only 25% of urine is produced at night, and the rest during the daytime. Arginine vasopressin (AVP) circadian production from the SCN is believed to be the reason. Lower levels of AVP cause decreased free water reabsorption and increased urination.[3,69] According to studies, nocturia was noted in 63% of women and 53% of men with PD.[70] Disrupted AVP diurnal production was also reported. [71]

CONCLUSION

Parkinson's disease (PD) and circadian rhythm disruption are closely linked—circadian disturbances may not only result from PD but also contribute to its progression. Disruption of the biological clock is associated with dopamine dysregulation, microglial activation, and α-synuclein accumulation, worsening motor and non-motor symptoms. These include sleep disorders, blood pressure fluctuations, thermoregulation issues, mood and cognitive impairment, and gastrointestinal and urinary dysfunction. Understanding circadian control of the dopaminergic, immune, and metabolic systems opens new therapeutic possibilities. Interventions like timed light therapy, sleep optimization, and pharmacological targeting of circadian pathways may improve symptoms and slow disease progression. Continued research is needed to refine these approaches and personalize treatment.

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PARKINSONOVA BOLEST I POREMEĆAJ CIRKADIJANOG RITMA

Sažetak

Parkinsonova bolest (PB) je progresivni neurodegenerativni poremećaj koji se primarno povezuje s motoričkim simptomima poput bradikinezije, rigidnosti i tremora. Međutim, sve se više prepoznaje da su nemotorički simptomi—uključujući poremećaje spavanja, promjene raspoloženja, kognitivne poteškoće i autonomnu disfunkciju—jednako značajni i često prethode pojavi motoričkih znakova. Sve više dokaza ukazuje na snažnu dvosmjernu povezanost između PB i poremećaja cirkadijanog ritma. Disregulacija cirkadijanog sustava nije samo posljedica neurodegeneracije povezane s PB-om, već i mogući čimbenik u njenom nastanku i napredovanju. Središnji mehanizmi ove međupovezanosti uključuju disregulaciju dopamina (DA), aktivaciju mikroglije i agregaciju α-sinukleina, a svi su pod utjecajem ključnih cirkadijanih gena kao što su BMAL1, CLOCK i REV-ERBα. Njihovo narušeno djelovanje remeti sintezu dopamina, potiče oksidativni stres i upalu te ubrzava neurodegeneraciju. Cirkadijana disfunkcija u PB-u također utječe na suprahijazmatsku jezgru i periferne "satove", narušavajući fiziološke ritmove povezane sa spavanjem, termoregulacijom, krvnim tlakom, raspoloženjem, funkcijom probavnog sustava i mokrenjem. Poremećaji spavanja—osobito REM poremećaj ponašanja u snu (RPS), nesanica i pretjerana dnevna pospanost—zahvaćaju više od 90 % oboljelih i često se javljaju u prodromalnim fazama bolesti, što pruža vrijednu priliku za ranu dijagnozu. Jedan od najpouzdanijih prediktora buduće neurodegeneracije smatra se RPS, koji često prethodi motoričkim simptomima više od desetljeća. Razumijevanje uloge cirkadijane regulacije dopaminskog prijenosa, imunoloških funkcija i metabolizma otvara nove terapijske mogućnosti. Intervencije poput svjetlosne terapije, nadomjeska melatonina i ciljanog farmakološkog djelovanja na cirkadijane gene pokazale su potencijal u ublažavanju simptoma i usporavanju progresije bolesti. Ova sve veća svijest o ulozi cirkadijanog sustava u patofiziologiji PB-a naglašava potrebu za daljnjim istraživanjima i uvođenjem kronobioloških pristupa u personalizirane terapijske planove.

KLJUČNE RIJEČI: cirkadijani ritam, dopaminergički neuroni, neurodegenerativne bolesti, parkinsonova bolest, poremećaji spavanja i budnosti