https://doi.org/10.14802/jmd.23216 / J Mov Disord 2024;17(1):1-14
pISSN 2005-940X / eISSN 2093-4939

REVIEW ARTICLE

Fighting Against the Clock: Circadian Disruption and Parkinson's Disease

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ABSTRACT

Circadian disruption is being increasingly recognized as a critical factor in the development and progression of Parkinson's disease (PD). This review aims to provide an in-depth overview of the relationship between circadian disruption and PD by exploring the molecular, cellular, and behavioral aspects of this interaction. This review will include a comprehensive understanding of how the clock gene system and transcription–translation feedback loops function and how they are diminished in PD. The article also discusses the role of clock genes in the regulation of circadian rhythms, as well as the impact of clock gene dysregulation on mitochondrial function, oxidative stress, and neuroinflammation, including the microbiota-gut-brain axis, which have all been proposed as being crucial mechanisms in the pathophysiology of PD. Finally, this review highlights potential therapeutic strategies targeting the clock gene system and circadian rhythm for the treatment of PD.

Keywords Circadian clocks; Parkinson disease; Circadian rhythm; Gastrointestinal microbiome; Feedback.

INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disorder that has been traditionally characterized by its debilitating motor symptoms. However, recent research has provided information on significant nonmotor manifestations, among which circadian disruption emerges as a critical but underappreciated dimension.[1] The circadian clock, which is an intrinsic time-keeping system orchestrating physiological processes, appears to be altered and perturbed in PD. This scenario correspondingly contributes to sleep disturbances, cognitive decline, and possible exacerbation of motor symptoms.[2] This article explores the molecular and cellular underpinnings of this disruption by highlighting the roles of proteins, genes, and neurotransmitters at the intersection of circadian rhythms and PD pathology. Emerging evidence also links the gut microbiota-brain axis with circadian regulation and PD, thus suggesting a potentially transformative approach to our understanding of the etiology and progression of this disorder.[3,4] This new research direction emphasizes the implications of diagnostic strategies and therapeutic interventions; moreover, it advocates for a greater focus on the identification of reliable biomarkers, the development of personalized medicine, and the use of precision therapeutics from a holistic perspective of circadian disruption in PD. We believe that by integrating circadian health into the PD management framework, we can enhance our current therapeutic strategies and improve the quality of life of those individuals living with PD.

Received: October 19, 2023 **Revised:** November 7, 2023 **Accepted:** November 20, 2023
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CIRCADIAN RHYTHM

Circadian rhythm regulation

Circadian rhythms are inherent timekeeping systems that govern a wide array of physiological processes, thus ensuring that they occur at biologically advantageous times. Spanning approximately 24 hours, these rhythms have evolved to align with the Earth's rotation, thereby synchronizing the internal processes of an organism with the external environment. This internal timer is controlled by genes and synchronized by environmental signals, such as light and nutrition, to regulate physiological activities in every cell structure.[5] Indeed, the 2017 Nobel Prize in Physiology and Medicine, which was awarded to Rosbash, Hall, and Young, recognized their groundbreaking work on the molecular dynamics of this circadian rhythm and the relevance of circadian synchronization to health.[5-11]

A central idea of the orchestration of these rhythms in mammals is the suprachiasmatic nucleus (SCN), which is a dense cluster of neurons located in the anterior hypothalamus. The autonomy of the rhythmicity of the SCN is remarkable but not impervious to external cues. Such environmental signals, which are aptly known as "zeitgebers" (a German lexicon translating to "time givers"), rely predominantly on ambient light. The SCN receives direct input from the eyes through a pathway known as the retinohypothalamic tract. Specialized photoreceptive retinal ganglion cells containing pigment melanopsin absorb light and relay this information to the SCN. Neurons within the SCN exhibit rhythmic firing patterns, and these patterns are instrumental in conveying time-of-day information to various regions of the brain and peripheral tissues.[12,13] These patterns are supported by secondary input from structures such as the intergeniculate leaflet and brainstem.[14]

Without the influence of light, SCN neurons autonomously generate an intrinsic circadian rhythm, which produces an approximate 24-hour cycle. Harmonized output of the SCN is transmitted to peripheral molecular oscillators, thus extending its temporal influence throughout the organism.[15] Although these peripheral clocks possess innate rhythmic capabilities, their temporal alignment is orchestrated by the SCN via various modulatory pathways, including endocrine signaling, autonomic output, thermoregulatory changes, physical activity, and dietary patterns.[16-19] For example, rhythmic hormonal cascades originating from the hypothalamus and pituitary are driven by the SCN. Additionally, hormones such as melatonin, serotonin (5-HT), and glucocorticoids subsequently modulate circadian gene expression, thus establishing a pivotal feedback loop for circadian synchronization.[20,21] These hormonal mechanisms involve the secretion of specific neuropeptides and the intricate modulation of the hypothalamic–pituitary–adrenal axis, which subsequently influence the secretion of melatonin from the pineal gland, as well as secretion of glucocorticoids and catecholamines from the adrenal gland.[22,23]

Upon further investigation into the cellular architecture of the SCN, most of its neurons are GABAergic. Those neurons that reside in the ventrolateral core divisions of the SCN predominantly express neurotransmitters and neuropeptides, such as vasoactive intestinal polypeptide (VIP), calretinin, gastrin-related peptide, and neurotensin. In contrast, the divisions of the dorsomedial shell are enriched in neurons expressing arginine vasopressin (AVP), angiotensin II, prokineticin-2, and met-enkephalin.[24] A unique characteristic of SCN neurons is their intercellular coupling, which promotes autonomous circadian oscillations in both neuronal activity and gene expression. The VIP produced by ventrolateral core neurons plays a key role in this intercellular synchronization, whereby it influences other neuropeptides, such as AVP and gastrin-releasing peptide (GRP) (Figure 1). This intricate synchronization is crucial, and VIP knockout studies have demonstrated marked desynchronization of SCN activities.[25-27]

Recent studies have provided information on a subset of VIP-positive SCN neurons that display activity during dark periods, which is in contrast to the predominant pattern of SCN neuronal activity. These neurons have been postulated to play a pivotal role in modulating sleep patterns between activity bouts in nocturnal murines, either by inhibiting activity and fostering quiescence or via direct effects of sleep promotion.[26,28] This finding not only underscores the role of the SCN in maintaining 24-hour rhythms but also suggests its involvement in fine-tuning intricate features of the sleep–wake cycle.

Molecular and cellular mechanisms

The regulation of circadian rhythms at the molecular level is governed by a transcriptional/translational feedback loop (TTFL).[29] Every major tissue in the mammalian body has rhythmic gene expression, and a substantial proportion of mammalian genes (ranging from 10% in rodents to more than 50% in primates [including humans]) exhibit rhythmic fluctuations that are tailored to specific tissue environments.[30-32] A key concept of this oscillation is the intricate feedback mechanism involving core circadian genes and their protein products. The synchronization of these rhythms across various tissues ensures the coordinated functioning of the body's systems.[24,33] At the molecular level, circadian rhythms are maintained by a series of clock genes that are regulated by a TTFL (Figure 2).[34]

Positive regulators

The *CLOCK* (circadian locomotor output cycles kaput) and *BMAL1* (brain and muscle ARNT-like 1) genes encode proteins

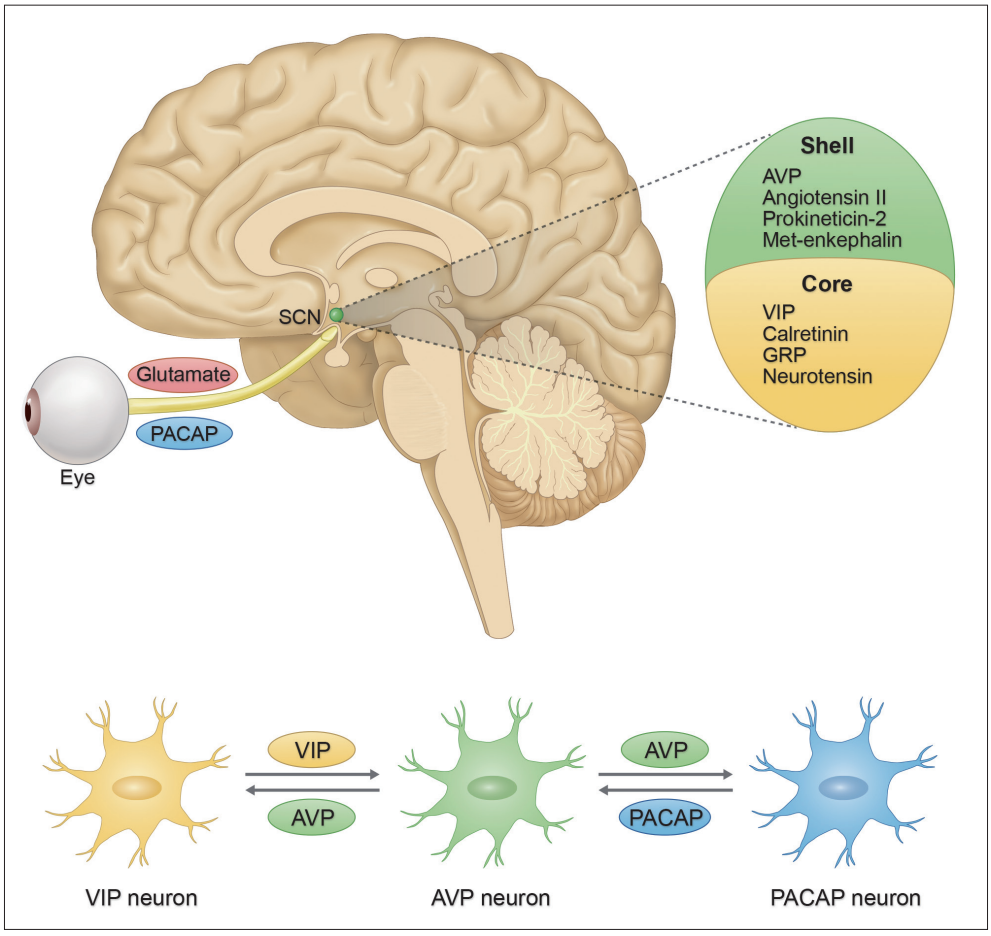

Figure 1. Molecular cartography of suprachiasmatic nucleus interactions. SCN, suprachiasmatic nucleus; PACAP, pituitary adenylate cyclase-activating polypeptide; AVP, arginine vasopressin; VIP, vasoactive intestinal polypeptide; GRP, gastrin-releasing peptide.

that dimerize, thus forming the *CLOCK-BMAL1* complex. This complex binds to enhancer box elements on the promoters of target genes, thus stimulating the transcription of downstream clock genes, especially *Period* (*PER1*, *PER2*, and *PER3*) and *Cryptochrome* (*CRY1* and *CRY2*) genes.[34,35]

Negative regulators

As the PER and CRY proteins accumulate in the cytoplasm, they form complexes and translocate to the nucleus. Herein, they function as negative regulators by inhibiting the activity of the *CLOCK-BMAL1* complex. This results in decreased transcription of the *PER* and *CRY* genes, thus creating the negative feedback loop that defines the rhythm.[35-37]

Posttranslational modifications

The maintenance of a precise 24-hour cycle requires posttranslational modifications to fine-tune protein stability and function, with phosphorylation playing a pivotal role.[38] Kinases such as CK1δ/ε (casein kinase 1 delta/epsilon) phosphorylate PER proteins, thereby marking them for degradation. Moreover, phosphatases remove phosphate groups, thus stabilizing proteins. The interplay between kinases and phosphatases ensures timely protein degradation, which is crucial for the precision of the rhythm.[38,39]

Beyond the core TTFL, auxiliary feedback loops provide additional layers of regulation. For example, the *CLOCK-BMAL1* complex also activates the transcription of the genes *Rev-Erbα* and retinoic acid receptor-related orphan receptor alpha (*RORα*). Rev-Erbα protein acts as a repressor by inhibiting *BMAL1* transcription, whereas *RORα* enhances *BMAL1* transcription by binding to ROR-responsive elements on the *BMAL1* promoter. This loop intersects with the core TTFL, thus providing stability and robustness.[40,41]

Recent studies have provided more information on the interaction between cellular metabolism and the circadian clock. Nicotinamide adenine dinucleotide (NAD+) levels, which vary with the circadian rhythm, influence the activity of sirtuin 1 (SIRT1), which is an NAD-dependent deacetylase sirtuin-1. Importantly,

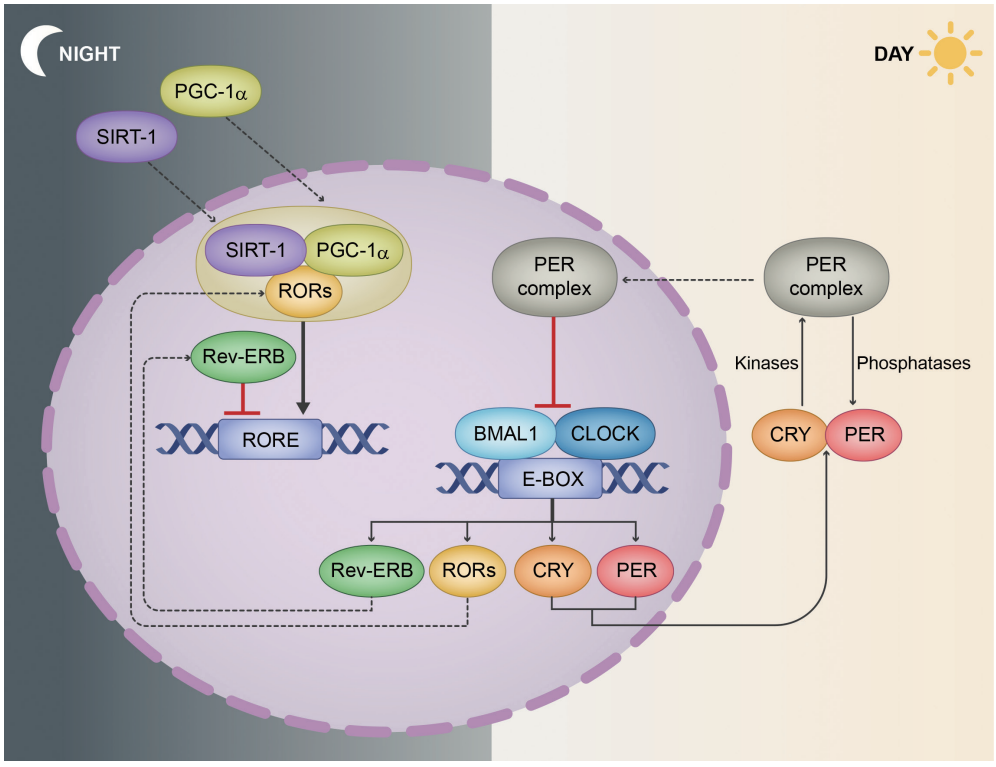

Figure 2. Regulatory mechanisms of the circadian clock: core and auxiliary feedback loops and metabolic interactions. SIRT-1, sirtuin 1 also known as NAD-dependent deacetylase sirtuin-1; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; RORs, retinoic acid-related orphan receptors; Rev-ERB, nuclear receptor subfamily 1 group D derived from "*Rev-ERBA*," which was later truncated to "Rev-Erb"; RORE, ROR response elements; CRY, cryptochrome proteins; PER, period proteins; *BMAL1*, brain and muscle ARNT-like 1; *CLOCK*, circadian locomotor output cycles kaput; E-BOX, enhancer box; *PER* complex, period proteins complex; NAD, nicotinamide adenine dinucleotide.

SIRT1 can deacetylate *BMAL1*, thus affecting its stability and influencing the pace of the clock.[42-44]

Molecular interactions with light cues

Upon light exposure, the photopigment melanopsin is activated in retinal ganglion cells.[45] This activation influences intracellular signaling pathways that ultimately impact the levels of the PER2 protein, which helps to reset the clock.[46]

The precise coordination of the TTFL ensures that cells can anticipate and prepare for daily changes in their environment. This autonomous cell rhythm, when synchronized across billions of cells, ensures that tissues and organs function in harmony.[34,47] Moreover, several other genes, often termed "clock-controlled genes," are regulated by the circadian rhythm, thus further amplifying the impact of TTFL on cell function. These genes govern a host of processes, ranging from metabolism to DNA repair, which emphasizes the widespread influence of the circadian system.[48,49]

CIRCADIAN DISRUPTION IN PD

PD: beyond motor symptoms

Although it is primarily diagnosed by its core motor features,[50] it is well known that nonmotor symptoms are more prominent and bothersome to the patient's quality of life, especially during the advanced stages of the disease (Table 1). In addition, many nonmotor features have been recognized during the prodromal period of the disease, including REM sleep behavior disorder, excessive daytime sleepiness, hyposmia, constipation, orthostatic hypotension, sexual dysfunction, anxiety, or depression,[51] which are often not declared due to embarrassment or unawareness.[52]

Significantly, there is emerging evidence to suggest that certain sleep-related symptoms in PD are associated with circadian misalignment, which may represent a bidirectional relationship.[53] Two extensive cohort studies have recently indicated a potential link between disturbances in circadian rhythm and a higher likelihood of developing PD. Leng et al.[54] evaluated 2,930 community-dwelling men who were 65 years or older without PD at baseline, and subjects were observed for an 11-year period. Circadian pa-

Table 1. Major motor and nonmotor symptoms of Parkinson's disease

	Domain	Symptom
Motor	Appendicular	Resting tremor
		Rigidity
		Bradykinesia
		Micrographia
		Dyskinesias
	Gait	Postural instability
		Decreased arm swing
		Short step length
		Freezing of gait
	Oral	Hypophonia
		Dysphagia
Nonmotor	Psychiatric	Depression
		Anxiety
		Apathy
		Hallucination/delusion
		Dementia
		Obsessional disorder
	Sleep	Periodic limb movement in sleep
		REM sleep behavior disorder
		Excessive daytime sleepiness
		Insomnia
		Vivid dreaming
	Autonomics	Orthostatic hypotension
		Sexual dysfunction
		Bladder dysfunction
	Gastrointestinal	Constipation
		Nausea/vomiting
		Dyspepsia
	Sensory	Hyposmia
		Paraesthesia
		Pain
	Other	Fatigue
		Weight loss
		Blurred vision

rameters generated by wrist actigraphy-extended cosinor analysis (specifically, amplitude, mesor, and robustness) were found to be potent indicators of PD risk. Individuals in the lowest quartile for these circadian measures demonstrated an approximately threefold elevated risk of developing PD compared to those in the highest quartile.[54] Another expansive cohort study included 72,242 UK Biobank participants aged 37–73 years, wherein subjects were monitored for a median duration of 6.1 years. Circadian relative amplitude, which was derived from 7-day accelerometry data, served as a key measure to assess circadian rhythm disturbance. The study found that people with diminished relative amplitude exhibited increased risks in a range of neurological and psychiatric conditions, with risk ratios of 1.33 for PD in their fully adjusted models.[55] These findings highlight the substantial role of circadian disruption as a common risk factor for PD and underscore the prognostic significance of prodromal circadian markers concerning the onset of PD. Little is known about whether this disruption of the circadian system may impact mitochondrial dysfunction,[56] oxidative stress,[57] and neuroinflammation,[58] which are all considered to be potential contributors to the neuropathology of PD.

Behavioral and clinical evidence

Sleep disturbance affects 60% to 98% of patients with PD, especially in the more advanced stages of the disease.[59] In addition to sleep disturbance, diurnal changes in other motor and nonmotor symptoms, such as the disruption of the rest-activity cycle, variation in blood pressure or cardiac rhythms, impaired sleep and alertness, and oscillations in mood, have also been associated with disease progression.[60]

Compared to healthy subjects, previous studies have suggested the relevance of PD and disruption of circadian rhythm via activity measurements.[61,62] Surprisingly, actigraphy recording rest-activity in PD has not demonstrated that lower activity and amplitude correlate with more advanced disease. However, such studies have also demonstrated a phase advance in PD, thus indicating a disturbance in circadian activity rhythm.[63,64] Moreover, diurnal variation in cardiovascular systems (reflected by increased blood pressure variability, reverse dip, and awakening hypotension) has also been reported in PD.[65] This clinical and preclinical evidence supports the assertion that circadian rhythm dysregulation may be a driver of the pathogenesis of PD.[66]

Molecular crosstalk between PD and circadian rhythm

Although the exact causes of PD are still unknown, new evidence suggests that disturbances in circadian rhythm and clock gene expression may be involved in PD pathophysiology.[67,68] The intertwined nature of clock genes and TTFL in cellular regulation indicates that their disruption can have systemic effects. In PD, this has been observed through altered neurotransmitter release patterns (especially dopamine), disturbed sleep architecture, metabolic dysregulations, gastrointestinal disturbances, and even immune system abnormalities.[69-73] Clock gene disruptions can lead to misaligned dopamine release patterns, thus providing a window into the complex mechanisms underlying PD symptomatology.[73,74] Dopaminergic neurons, which represent the primary targets in PD, exhibit intrinsic circadian rhythms governed by the TTFL. Dysregulation of these clock genes has been observed in PD patients and animal models of PD (Table 2). McClung et al.[74] found that *CLOCK* mutant mice exhibited in-

Table 2. Summary of key studies providing behavioral or clinical evidence for the linkage between Parkinson's disease and circadian disruption

Study	Behavioral and physiological alternations	
	Presentation	Significance
Sun et al.,[151] 2019	Sleep-awake behavior	Increased α-synuclein in CSF was noted in adults with chronic sleep apnea, supporting poor sleep may be related pathogenesis of Parkinson's disease
Jiang et al.,[152] 2023	Sleep-awake behavior	Poor PD sleepers have severe non-motor symptoms; in addition, the increase of nocturnal arousal may predict the progression of motor symptoms
Brooks et al.,[63] 2020	Rest-activity rhythms	Continuous actigraphy can detect rest-activity disruption in PD, which is associated with motor severity and H&Y stage
Obayashi et al.,[64] 2021	Rest-activity rhythms	PD patients exhibited a phase advance in circadian activity rhythm, along with amplitude reduction
Vallelonga et al.,[65] 2019	Variations in cardiac rhythms or blood pressure	Patients with α-synucleinopathies showed a circadian rhythm disruption characterized by increased BP variability
Shen et al.,[153] 2022	Variations in cardiac rhythms or blood pressure	24-hour ambulatory BP monitoring is an important method to evaluate the BP alterations in PD
Suzuki et al.,[154] 2007	Mood swings	PD patients with depression show an altered circadian rhythm in temperature
Study	**Molecular alternations: clock genes expression from human/animals**	
	Gene/intervention	**Phenotype**
Lee et al.,[155] 2010	*BMAL1*	Alternation in rhythm of locomotor activity, premature aging, risk factor of cancer
Gu et al.,[77] 2015	*BMAL1*	Tremor dominant subtype, contribution not only to circadian dysfunction but also PD pathogenesis
DeBruyne et al.,[156] 2007	*CLOCK*	Circadian disruption presenting in locomotor activity and response to light
Lou et al.,[78] 2018	*CLOCK*	An independent risk factor for motor fluctuations and sleep disturbance in PD
Hua et al.,[157] 2012	*CRY1*	Besides circadian disruption, more prone to depression
Masubuchi et al.,[158] 2005	*PER1*	Fail to adapt to environmental light-dark cycle
Gu et al.,[77] 2015	*PER1*	Postural instability subtype, also contribution to circadian dysfunction and PD pathogenesis
Fu et al.,[159] 2002	*PER2*	Caricadian control and tumor suppressor gene
Lou et al.,[160] 2017	*PER2*	Regulation of psycho-behavioral control, hormone secretion, mood, and sleep
Study	**Molecular alternations: preclinical models from animals**	
	Gene/intervention	**Phenotype**
Tanaka et al.,[161] 2012	MPTP	Lengthen the circadian period of locomotor activity
Hayashi et al.,[104] 2013	MPTP	Alterations of clock genes expression
Choudhury and Daadi,[162] 2018	MPTP	Experience PD-like motor and non-motor symptoms with circadian disruption
Franke et al.,[163] 2016	MPTP	Prodromal stage PD symptoms
Wang et al.,[90] 2018	6-OHDA	Alterations of clock genes expression and antioxidant molecules
Yang et al.,[164] 2021	6-OHDA	Variations in circadian rhythms of blood pressure and body temperature
Mattam and Jagota,[165] 2015	Rotenone	Alterations of clock genes expression
Valadas et al.,[166] 2018	PARK	Sleep fragmentation and circadian dysregulation
Liu et al.,[167] 2022	LRRK2	Lower clock gene expression and disrupted sleep-awake cycle with reduced REM, NREM and total sleep time
McDowell et al.,[168] 2014	α-synuclein	Produce sleep disruption with increased NREM sleep, decreased REM sleep and altered oscillatory EEG activity
Kudo et al.,[169] 2011	α-synuclein	The wheel-running activity shows reduced nighttime activity and increased fragmentation.
Liu et al.,[86] 2023	α-synuclein	Disrupts biorhythms by destabilizing *BMAL1* mRNA through miR-155.
Langley et al.,[170] 2021	MitoPark	Display all-light- or all-dark-induced circadian rhythm dysfunction
Taylor et al.,[171] 2009	VMAT2-Deficient Model	A shorter latency to behavioral sleep

PD, Parkinson's disease; BP, blood pressure; REM, rapid eye movement; NREM, non-rapid eye movement; EEG, electroencephalography.

creased dopamine cell firing in the ventral tegmental area, thus suggesting that clock gene disruptions can directly affect dopaminergic function. Disturbances in the feedback loop within these neurons can also lead to changes in dopamine secretion patterns, thus contributing to the motor symptoms observed in PD.[75,76] These findings suggest a clear link between the clock gene system and the dopaminergic dysfunction observed in PD.

The role of *CLOCK* genes in disease risk, phenotype, and prognosis

Several studies have investigated the associations between clock genes and the different phenotypes observed in PD. A case-control study in a Han Chinese population found that the *ARNTL* (*BMAL1*) and *PER1* genes were associated with susceptibility to PD and specific phenotypes. The variant *ARNTL* (rs900147) showed a positive correlation with tremor-dominant (TD) cases, whereas *PER1* (rs2225380) showed a positive correlation with postural instability and gait difficulty (PIGD) cases. The allele frequencies did not significantly differ between TD and PIGD, thus indicating no significant genetic variation between subtypes.[77] These findings suggest that clock genes could actually provide the foundation for the manifestation of specific PD symptoms.

Clock gene variants have also been implicated in the disease phenotype, with the *CLOCK* T3111C variant found to be an independent risk factor for motor fluctuations and sleep disorders in Chinese PD patients.[67,68,78,79] Cai et al.[68] also reported that lower expression of the clock gene *BMAL1* in PD patients during the dark period was associated with disease severity, thus suggesting that the extent of circadian rhythm disruption, as indicated by clock gene expression levels, may also serve as a severity marker in PD.[68]

In summary, these studies indicate that clock genes are associated with susceptibility to PD, specific phenotypes, motor fluctuations, sleep disorders, and disease severity.

Pathophysiological basis of *CLOCK* gene abnormalities in PD

Circadian rhythms regulate the oscillations of tight junction proteins in the blood-brain barrier (BBB); thus, disrupted circadian rhythms can lead to increased permeability of the BBB, altered expression of BBB transporters, and changes in the expression of tight junction proteins in the BBB.[80,81] The breakdown of *BMAL1* has been shown to impair BBB integrity via pericyte dysfunction.[82] These findings suggest that disruption of circadian rhythms can directly affect BBB function, which could contribute to the development of PD.[83]

Beyond the disruptions that occur in the BBB, Willison et al.[84] proposed that circadian dysfunction may even accelerate the underlying pathology of PD by increasing oxidative stress and mitochondrial disruption. Indeed, the decomposition of *BMAL1* expression has been shown to cause terminal synaptic damage, death of dopaminergic neurons, and aggravation of motor dysfunction in the MPTP-induced PD model.[85] Furthermore, it has been reported that the accumulation of α-synuclein can destabilize *BMAL1* mRNA via miR-155, which can affect circadian rhythm.[86] Taken together, these results suggest that there is a bidirectional relationship between disruptions in the circadian clock system and the neuropathology of PD that, if better understood, could have implications for diagnosis and treatment.

The role of *CLOCK* genes beyond circadian rhythm

It has been suggested that clock genes not only regulate circadian rhythms but also play a significant role in neuroprotection through processes such as mitochondrial dysfunction, protein aggregation, neuroinflammation, and oxidative stress pathways (Figure 3).[79,85,87-90]

Clock gene dysregulation and mitochondrial dysfunction

Mitochondrial dysfunction is a prominent feature of the pathophysiology of PD, and emerging evidence suggests a link between clock gene dysregulation and mitochondrial function.

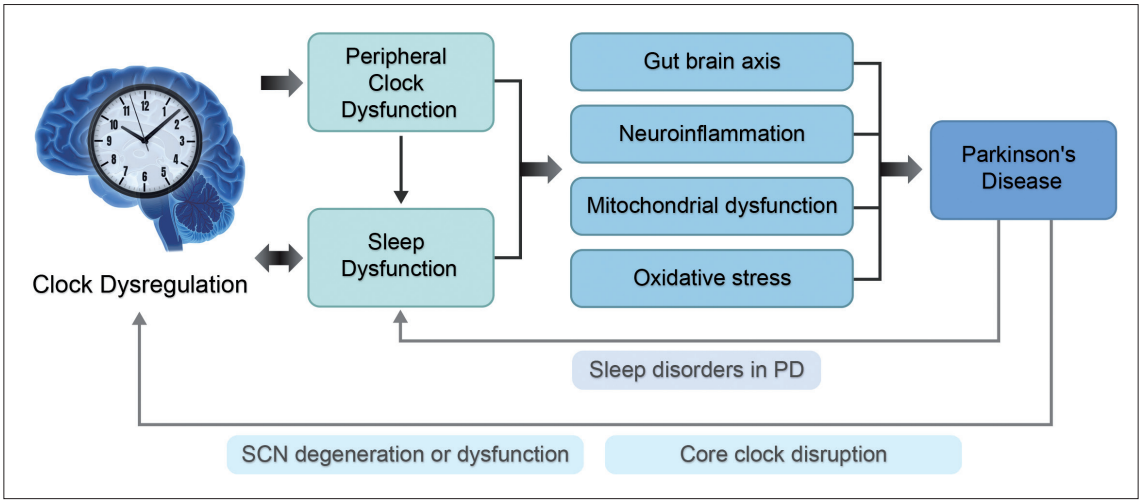

Figure 3. Integrated model of clock gene dysregulation and its multidimensional impact on Parkinson's disease (PD). SCN, suprachiasmatic nucleus.

The clock gene system regulates mitochondrial dynamics, including processes such as mitochondrial transport, fusion, and fission, as well as mitophagy, which is the selective degradation of damaged mitochondria.[91] Clock genes regulate mitochondrial dynamics, biogenesis, and oxidative phosphorylation via the modulation of key transcription factors, such as PGC-1α and NRF1.[92-94] Thus, dysregulation of clock genes can disrupt mitochondrial homeostasis, thus leading to impaired energy production, increased oxidative stress, and neuronal dysfunction in PD.[89,95]

Clock gene dysregulation and oxidative stress

Oxidative stress, which results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, is believed to be a key contributor to PD pathogenesis.[57] Clock genes play a crucial role in regulating redox homeostasis by modulating the expression of antioxidant enzymes and stress response genes.[70] Disruptions in clock gene expression can lead to increased ROS production and impaired antioxidant defense mechanisms, thus contributing to oxidative stress and neurodegeneration in PD.[90,96,97] Furthermore, dysfunction of the NAD-dependent deacetylase SIRT1, which is regulated by clock genes, is a hallmark of PD. SIRT1 is involved in maintaining cellular redox homeostasis, and its dysfunction may contribute to oxidative stress and neurodegeneration in PD.[43,44,98]

Clock gene dysregulation and neuroinflammation

Neuroinflammation is a salient characteristic of PD, which is highlighted by the pronounced activation of microglia and the subsequent release of proinflammatory cytokines.[99] The immune system is synchronized with the circadian clock to ensure that immune responses are optimally timed to improve their efficacy.[100] Astrocytes possess intrinsic circadian clocks and release cytokines and chemokines, thus modulating the activity of surrounding neurons and glial cells.[101,102] Microglia, which are the resident immune cells of the brain, exhibit circadian patterns in their morphology and phagocytic activity.[103,104] Their role becomes crucial in neurodegenerative diseases where aberrant circadian rhythms can exacerbate disease progression. Within these cells, TTFL modulates several immune responses,[85,105,106] and it is known that *BMAL1* can inhibit the production of proinflammatory cytokines, whereas its disruption leads to heightened inflammatory responses.[107,108] Thus, the targeting of clock genes and their downstream inflammatory pathways may provide novel therapeutic approaches for mitigating neuroinflammation and slowing disease progression in PD.[88]

Clock gene dysregulation and the gut-brain axis

The gut-brain axis refers to the bidirectional communication between the gastrointestinal tract and the central nervous system, and it involves neural, hormonal, and immunological pathways.[109] Recent studies have demonstrated a bidirectional relationship between the gut microbiota and the clock gene system. Disruptions in the gut microbiota, such as dysbiosis or alterations in microbial metabolites, can lead to clock gene dysregulation and circadian rhythm disturbances.[110-112] In contrast, disruptions in circadian rhythm can also lead to gut dysfunction, such as altered gut motility, increased intestinal permeability, and dysregulated immune responses.[113-115] Thus, dysregulation of the gut-brain axis, which is mediated by circadian dysregulation, can further exacerbate neuroinflammation and neurodegeneration in PD.[116]

Clock gene dysregulation and other neurodegenerative disorders

Other neurodegenerative disorders, such as Alzheimer's disease (AD), Huntington's disease, and amyotrophic lateral sclerosis, have been associated with disruptions in circadian rhythms.[55,97,117-121] These disruptions are not only considered manifestations of the diseases but may also directly contribute to their pathogenesis.[122] The role of circadian rhythm abnormalities in these disorders has become increasingly recognized, with evidence suggesting that circadian rhythm disruption and sleep disorders aggravate neurodegeneration; correspondingly, neurodegenerative diseases can disrupt circadian rhythms and sleep.[123]

BIOMARKERS AND DIAGNOSTICS

The early detection of circadian disruption can allow for the identification of prodromal PD, thus allowing for timely disease-modifying interventions. In fact, as highlighted above, it is possible that such strategies may even specifically attempt to restore circadian disruption in an effort to slow the pace of disease progression, which would represent a novel therapeutic strategy for the prevention and management of PD.[54] When considering the importance of circadian disruptions in PD, the future direction and challenge for circadian research in PD should focus on the identification of circadian biomarkers. In addition to traditional measurements of melatonin or cortisol levels,[124,125] new approaches should focus on the evaluation of peripheral clock gene expression.[2,126,127] To date, proteomic studies of pathology related to circadian rhythm disorders have been performed with limited success; moreover, they lack high-quality cohort studies on the onset and course of PD.[128-130] Other chronobiological signatures obtained from wearable devices,

Table 3. Comparing different potential therapeutic strategies, their benefits, and drawbacks

Potential therapy for CRD	Benefits	Drawbacks
Physical exercise (Schenkman et al.,[172] 2018)	Improvement in motor symptoms Providing cardiovascular benefits as well May arrest progression of PD	Concern of physical fitness Fear and risks of falling Musculoskeletal injuries
Melatonin supplement (Videnovic et al.,[124] 2014)	Improvement in sleep and poor alertness Beneficial for the sleep-awake cycle Antioxidant activity	Possible side effects, such as, headache, nausea, dizziness, drowsiness
Light therapy (Rutten et al.,[173] 2012; Endo et al.,[135] 2020)	Beneficial in non-motor symptoms, especially in sleep and mood disorder Simple and convenient Low cost No concern of drug adverse effect Potentials to restore circadian rhythm	Still lack of evidence in optimal light exposure, illumination and wavelength
Small chemical modulators (Wang et al.,[147] 2004; Hu et al.,[148] 2015)	Alleviates behavioral impairment Neuroprotective effects of dopaminergic neuron	Lack of evidence in human studies
Chronotherapy (Fifel and Videnovic,[118] 2019; Asadpoordezaki et al.,[133] 2023)	To optimize medication effect Low cost No concern of drug adverse effect Potentials to block the development of non-motor symptoms	Difficult to propose a standard circadian schedule

Combinations may be more effective.
CRD, circadian rhythm disruption; PD, Parkinson's disease.

such as actigraphy devices, combined with advanced bioinformatics tools to assess core body temperature and rhythm of rest-activity, may also offer noninvasive and efficient methods to assess PD onset or progression.[131,132]

THERAPEUTIC POTENTIAL OF CIRCADIAN RHYTHM REGULATION

Along with understanding the role of circadian rhythm disruption in PD and facilitating research on the interplay between neurodegeneration and circadian rhythm disruption, there is a new perspective for therapeutic potential (Table 3).[133] Some simple approaches already exist, such as the effect of high-intensity exercise, which not only improves sleep efficiency but also improves circadian rhythm.[134] Similarly, light therapy has already been explored in PD.[135,136] Despite the low cost, easy accessibility, and excellent safety profile, further studies are needed to clarify the optimal timing, appropriate duration, optimal illumination, and wavelength of the light itself.[135]

The antioxidative capabilities of melatonin[137] and its role in circadian synchronization[138] have positioned it as a potential neuroprotective and chronotherapeutic agent. A recent meta-analysis suggested that melatonin can significantly improve subjective sleep quality and total sleep time in PD with good safety and tolerability.[139] Emerging research has substantiated the efficacy of prolonged release melatonin formulations,[140] as well as melatonin receptor agonists,[141] in enhancing subjective sleep quality among patients diagnosed with PD. However, the endogenous circadian rhythm governing melatonin secretion exhibits inter-individual variability and is susceptible to modulation by external variables, including dietary intake, physical activity, photic stimuli, and even dopaminergic medications.[95,138,142-145] Addressing these confounding factors may potentiate the efficacy of melatonin in the context of individualized therapeutic regimens.

Recent advances in pharmacological research have led to the development of small-molecule modulators designed to target aberrant circadian systems. The CK1δ/ε inhibitor known as CKI-7 has been found to significantly reduce endogenous Aβ peptide,[146] thus indicating its importance in neuroprotective strategies, such as those for AD. Furthermore, other small modulators inhibiting CDKs (cyclin-dependent kinases) or JNK (c-Jun N-terminal kinases) have period-lengthening activities because of their neuroprotective effects on CKIδ in some animal model studies.[147,148] One recent MPTP-induced PD preclinical study demonstrated some preservation of dopaminergic neurons and a partial restoration of striatal dopamine levels by using this approach.[147]

Rev-Erbα is a crucial negative regulator in the circadian clock system that regulates cellular circadian rhythms and energy metabolism and has been associated with the attenuation of neuroinflammation in PD pathology.[149] Thus, the potential therapeutic use of *Rev-Erbα* agonists (such as GSK4112) and antagonists (such as SR8278) to improve circadian dysregulation in neurodegenerative conditions has been suggested and requires further study.[150] Regardless of the agent that is evaluated, future treatments may rely on exploring the efficacy of chronotherapy, whereby medications need to be administered in synchronization with an individual's biological rhythm to optimize their therapeutic effects and to minimize side effects.[118]

CONCLUSION

The role of circadian rhythm is just beginning to be understood in PD. There is clearly an intricate relationship between the clock gene system, the circadian rhythm, and the pathology underlying PD. A better understanding of the clock gene and TTFL disruptions in PD will potentially offer new therapeutic strategies. For example, molecular modulators, gene therapies, and even lifestyle interventions (such as controlled light exposure and diet) need to be explored more fully to realign disrupted circadian rhythms and potentially alter the course of the disease. The modulation of clock gene activity or the realignment of the TTFL can mitigate some of the symptoms or even slow the progression of PD. These insights pave the way for personalized therapeutic interventions and offer hope for better disease management.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

SJGL is supported by an NHMRC Leadership Fellowship (#1195830).

Author Contributions

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