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REVIEWS

Circadian Regulation and Its Disorders in Parkinson's Disease Patients. Part 1: The Role of Dopamine in Circadian Dysfunction

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Abstract—Circadian disturbances related to Parkinson's disease are reviewed, and possible pathogenetic mechanisms are discussed. The role of dopaminergic system degeneration in the development of circadian dysfunction is emphasized. The accumulation of α-synuclein in the suprachiasmatic nucleus is considered as a possible mechanism of circadian dysfunction unrelated to dopamine deficiency. Data on the disbalance of dopamine and melatonin levels in Parkinson's disease patients and its role in disturbances of circadian rhythms of physiological processes are analyzed.

Keywords: Parkinson's disease, experimental models, circadian regulation, sleep–wakefulness, dopaminergic system, α-synuclein, melatonin

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The classic triad of progressive clinical manifestations (symptoms) of Parkinson's disease (PD) includes rest tremor, rigidity, and bradykinesia. Parkinson's disease patients are characterized by a progressive loss of dopaminergic neurons and the formation of Lewy bodies in the pars compacta of the substantia nigra (SN). The main motor symptoms of PD first occur when approximately 60% of SN neurons are lost, and the dopamine content in the striatum drops by 80%. Earlier, PD was considered primarily as a motor disorder, but today it is clear that this is a multisystem disease affecting many brain structures [1–5]. Not only SN but also other brain regions (namely, the locus coeruleus, the dorsal motor nucleus of the vagus, and the pedunculopontine nucleus) are affected in PD [6]. Degeneration of these regions, apparently, begins before the SN degeneration [7] and is responsible for many non-motor symptoms of PD. Some researchers showed that the non-motor PD symptoms contribute more significantly to the deterioration of life than the motor symptoms [4, 5, 8–10]. The most well-known non-motor PD symptoms are the cognitive impairments that accompany PD and develop into dementia in 30–40% patients, depression in 40% of patients, as well as anxiety, apathy, and personality changes [4, 5, 11, 12]. In addition, there are other common non-motor PD symptoms, such as metabolic disorders, smell disorders, cardiovascular and gastrointestinal dysfunctions, and sleep–wakefulness disorders [4, 5, 10, 13–19].

Many of PD Symptoms Indicate Underlying Circadian Dysfunction

A number of known non-motor PD symptoms have a diurnal timing component, indicating that circadian dysfunction underlies these symptoms. Clinical fluctuations of PD symptoms include diurnal changes in the level of motor activity [5, 20–22], autonomic functions [23–26], sleep–wakefulness cycle [16, 17, 19, 27–30], visual functions [31], and the dopaminergic therapy efficiency [20, 32]. These observations testify to circadian rhythm disorders in PD. Various types of sleep and wakefulness disorders in PD are most illustrative.

The majority (60 to 98%, according to different authors) patients with PD have sleep disorders. As was shown by some studies, these symptoms usually occur at the beginning or even before the onset of the disease [33–37]. Sleep disorders in PD are diverse and include insomnia, parasomnias, and daytime sleepiness [16, 17]. One of the most common sleep disorders accompanying PD is the REM sleep behavior disorder (RBD) parasomnia, or behavioral disorders during REM sleep[1]. Observed in 40–50% of patients with PD, RBD is characterized by vivid dreams accompanied by active and sometimes violent behavior associ-

[1] The terms non-rapid eye movement sleep and rapid eye movement sleep have about ten pairs of synonyms (slow-wave/fast-wave, orthodox/paradoxical, telencephalic/rhombencephalic, quiet/activated, synchronized/desynchronized sleep, etc.). There is no unified, generally accepted English terminology yet. Here, we use the term rapid eye movement (REM) sleep.

ated with the dreams experienced at the moment. Patients with PD also experience increased daytime sleepiness. Sleep disorders may be observed many years before the appearance of the first motor symptoms of the disease. This is especially characteristic of the RBD parasomnia and hypersomnia, which usually precede the motor symptoms of PD, thereby serving as early markers of the premotor phase of PD [16, 17].

Sleep disorders in patients with PD are caused by different factors, including the motor and non-motor PD symptoms, the "switching off" phenomena observed after weakening the effect of doses of the drugs that used for the treatment of motor symptoms, and dysfunctions of the brain stem centers that control sleep [34, 38, 39]. Dopaminergic drugs—the main therapeutics used in PD—can themselves disturb the sleep–wakefulness cycle [40, 41].

However, the circadian dysfunction per se, which accompanies PD, may play an important role in sleep–wakefulness cycle disturbances [42]. There is a large amount of evidence that the problems with falling asleep, the reduction in sleep duration, sleep fragmentation, and high daytime sleepiness may be the result of disturbance of temporal structuring of sleep and wakefulness, which often occurs as a result of circadian dysfunction [43–45]. Thus, it can be postulated that circadian disturbances contribute to the development of insomnia and hypersomnia [18].

The pathogenic association of RBD, another common sleep disorder in PD, with the circadian dysfunction is less obvious. Nevertheless, the existence of this association is confirmed by the data that the suprachiasmatic nucleus (SCN) controls the triggering and timing parameters of REM sleep [46], the positive correlation between impaired circadian rhythm of body temperature and the severity of RBD symptoms in PD patients [47], and the frequently observed therapeutic effects of exogenous melatonin in RBD [48–50].

Patients with PD also often show impaired periodicity of other physiological processes, which also indicates the circadian dysfunction.

It is known that PD is accompanied by disturbance of autonomic regulation of the cardiovascular system, which is associated with the sympathetic denervation of the heart due to the loss of postganglionic sympathetic fibers of cardiac nerves [2, 51, 52]. However, PD is also accompanied by the disturbance of the circadian regulation of the autonomic system. Normally, the central circadian "clock" in the SCN sends its projections to the dorsal parvicellular paraventricular hypothalamic nucleus whose axons, as components of the intermediolateral cell column, descend to the spinal cord as a part of intermediolateral cellular column and project, in turn, onto the sympathetic preganglionic neurons in the upper cervical spine. The neurons of the paraventricular nucleus ensure changes in the balance between the sympathetic and parasympathetic tones of the autonomic nervous system in accordance with the time of day. For example, due to these effects, the parasympathetic tone predominates during the night sleep, which is manifested in the reduction of the heart rate and blood pressure [53]. In patients with PD, the circadian regulation of the autonomic nervous system is usually disturbed, which leads to changes in blood pressure and heart rate. In particular, 24-h monitoring of blood pressure in PD patients showed inversion of the circadian rhythm of blood pressure, postprandial hypotension, and high blood pressure and heart rate levels at night [24, 52, 54, 55]. Other authors, who performed Holter electrocardiographic monitoring of PD patients, showed a decrease in the sympathetic activity during the day in these patients as well as the absence of circadian heart rate variability and the disappearance of the morning peak of the sympathetic activity [23].

Another example of autonomic nervous system dysregulation in PD patients may be the symptoms of the urinary system. For example, nocturia, increased urinary frequency, and incontinence are observed in 37–70% patients with PD [56–58]. Urinary control is ensured primarily by dopaminergic mechanisms, and their dysfunction may lead to overactive bladder [59–61]. Thus, at least at the early stages of PD, urination disturbances are associated with the neurodegenerative process underlying this disease (the death of cells of the pars compacta of the substantia nigra), which ultimately leads to the disturbance of urination inhibition mediated by dopamine receptor type 1 (D1). However, some researchers showed that dopaminergic drugs often either ambiguously affect the bladder functions in patients with PD [62, 63] or have no effect at all [64].

It is also known that the volume of urine is influenced by circadian rhythms. SCN is involved in the regulation of the level of antidiuretic hormone, whose secretion increases at night; this, in turn, reduces the amount of urine excreted at night [65, 66]. Disturbances in the diurnal pattern of this hormone in patients with PD were detected [67]. Therefore, nocturia can also be caused by circadian dysfunction, which often accompanies PD.

PD is also accompanied by changes in the circadian rhythm of the body temperature: PD patients with comorbid depression are characterized by disturbed rhythm of the body core temperature and lower amplitude of its fluctuations [68]. In addition, it was shown that disturbances of the circadian rhythm of the body core temperature in patients with PD are positively correlated with the severity of RBD symptoms [47]. Changes in the circadian regulation of the body

temperature in PD are confirmed by the data obtained in an experimental model of parkinsonism: after central injections of 6-oxydopamine to rats, a significant reduction in the mesor[2] and a shift to advancing the temperature fluctuation phase were observed [69].

Actigraphic studies showed a decrease in the maximum activity and a lower amplitude of fluctuations in the activity–rest cycle in PD patients compared to the healthy elderly subjects [21, 22, 70]. An increased level of motor activity and a shortened period of immobility during the night lead to flattening the diurnal pattern of motor activity in PD [21, 22, 71]. In addition, patients with PD have a more fragmented pattern of activity with sharp transitions from high- to low-activity periods, which is ultimately manifested in a barely predictable activity–rest rhythm [70]. The facts that motor symptoms in PD change in the afternoon and evening and that this deterioration can be observed both in stable patients and in patients with the dose-effect exhaustion symptoms also indicate the circadian dysfunction [20, 32]. Moreover, the ability of the motor symptoms of PD to respond to dopaminergic therapy decreases during the day, despite the absence of significant changes in the pharmacokinetics of levodopa [20].

Similarly to the disturbances of motor and autonomic functions, circadian fluctuations of the visual function (in particular, the contrast sensitivity [31]), which are probably due to the depletion of retinal dopamine, have also been found in PD. The disturbance of the expression rhythm of *Bmal*1 and *Bmal*2 clock genes in the blood cells of patients with PD was also shown [72, 73].

Thus, there is a large amount of data pointing to a disturbance in the periodicity of various physiological processes (sleep–wakefulness, activity–rest, the balance of the sympathetic and parasympathetic systems, visual contrast sensitivity, etc.) in PD. The circadian dysfunction may underlie the changes in the temporal structure of physiological rhythms.

Circadian System

The circadian system of humans and other mammals consists of a network of oscillators that are located in different parts of the body. These oscillators are autonomous in terms of their rhythmic properties and regulated by the central "clock," which is located in the SCN [74]. At the cellular level, circadian rhythms are set by a rhythmic expression of clock genes *Per1*, *Per2*, *Per3*, *Cry-1*, *Cry-2*, *Clock, Bmal1*, etc. Their expression is controlled by the transcription–translation feedback loop consisting of the transcription factor BMAL1 and CLOCK, which form a heterodimer. The latter regulates the transcription of many genes, including *Per* and *Cry*—genes that suppress their own production by a negative feedback mechanism [75, 76]. SCN neurons receive information on the illumination level from melanopsin-expressing retinal ganglionic cells, integrate the information on the illumination conditions with other timing signals, and finally synchronize their circadian oscillations with the external changes. SCN sends projections to all parts of the nervous and endocrine systems through the hypothalamic relay nuclei, reporting the onset of the time when the external conditions are optimal for the rest of the brain and body. When passing through the hypothalamic-pituitary-adrenal axis and autonomic nervous system, signals from the SCN regulate independent circadian oscillators, which are present in different parts of the body [74, 76].

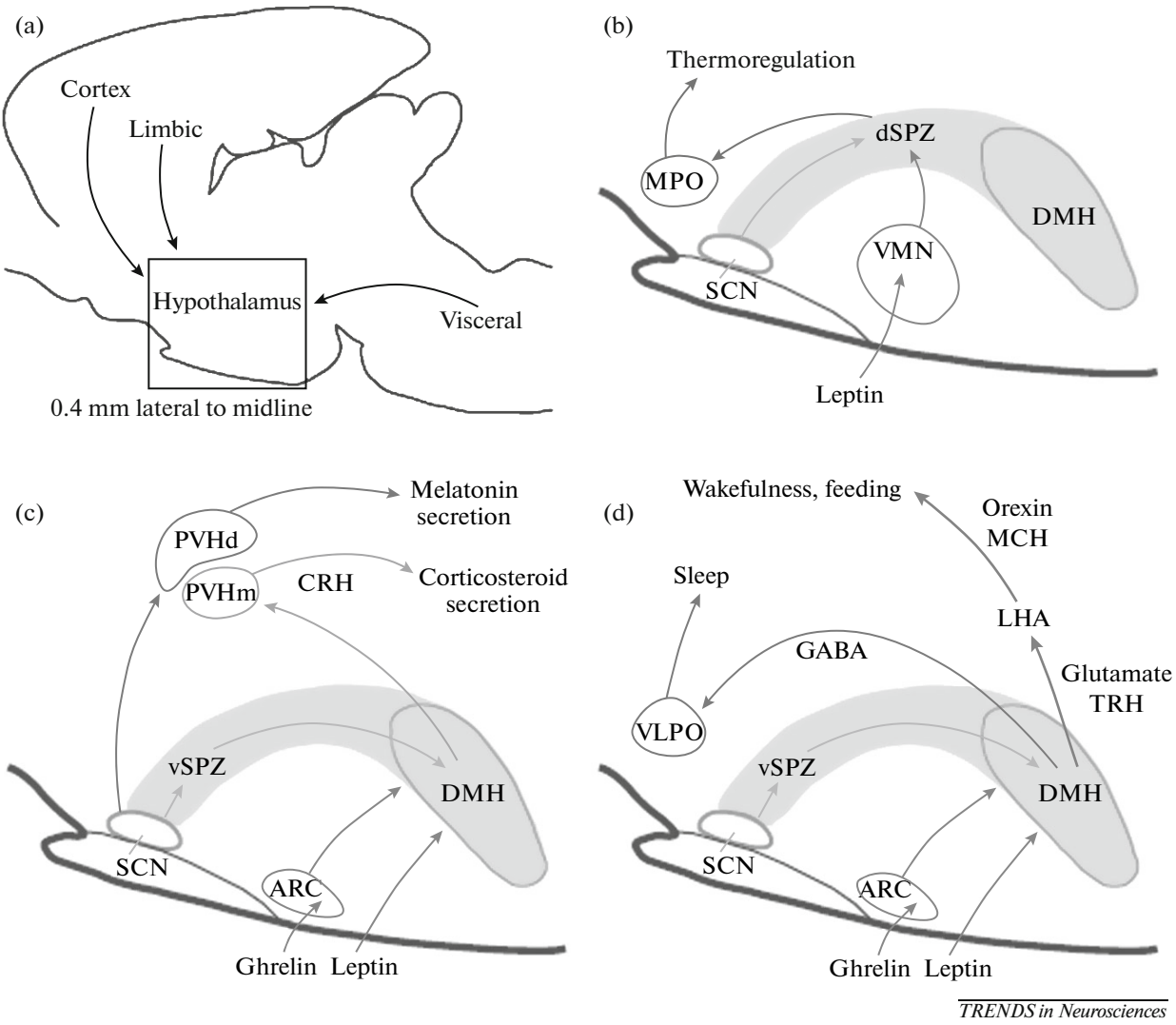
Some SCN projections are particularly relevant to the pathogenesis of PD: there is evidence that SCN regulates the level of neural activity in the main subcortical centers that maintain wakefulness, including the locus coeruleus and the raphe nuclei, in which the frequency of impulses during the active period of the animal increases [77, 78].

SCN is an important component of the higher hypothalamic "regulatory center," which converts circadian signals to biological rhythms: activity–rest, sleep–wakefulness, eating and drinking, secretion of melatonin and corticosteroids, body temperature, etc. (Fig. 1).

The hypothalamus receives three types of impulses that affect the formation of circadian rhythmicity: (1) the so-called cognitive influx from the infralimbic, prelimbic, and insular cortex, which is associated with the general regulation of behavior; (2) emotional impulses from the limbic system, including the hippocampus and amygdala; and (3) visceral impulses from the nucleus of the solitary tract and the parabrachial nucleus (Fig. 1a).

Having relatively weak direct projections to the wakefulness and sleep regulation centers, SCN send the main stream of impulses to the adjacent hypothalamic region, which is called the subparaventricular zone. Neurons of this zone, which is divided into the dorsal and ventral parts, perform a peculiar role of "amplifiers" of SCN signals. Through the ventromedial nucleus, which contains receptors for leptin, the neurons of the dorsal subparaventricular zone also receive information on the level of this polypeptide ("saturation factor," which is secreted by adipose tissue) in blood. The integrated signals are sent to the medial preoptic nucleus, which contains thermosensitive neurons and controls the body temperature rhythm (Fig. 1b). The ventral part of the subparaventricular zone transfers enhanced circadian signals from the SCN to the main element of the "regulatory center"—the dorsomedial nucleus of the hypothalamus. The dorsomedial nucleus also contains receptors for

[2] Mesor is the level of the mean values of parameters of a studied process (mean value of the desired signal). It makes it possible to assess the daily-average value of the index since it allows ignoring the random deviations.



Hypothalamic "supreme command center" of the brain (for explanations, see the text [79]).

leptin; in addition, through the arcuate nucleus it receives information on the blood content of polypeptide ghrelin—the "starvation factor" secreted by gastric mucosa.

The dorsomedial nucleus generates regulatory activating and inhibitory impulses and sends them in three directions: (1) activatory effects to the medial parvicellular paraventricular nucleus, which controls the corticotropin-releasing factor *(corticoliberin=CRF)* containing neurons and, therefore, the release of stress hormones corticotropin and corticosteroids (Fig. 1c); (2) to the "sleep center"—the GABAergic ventrolateral preoptic nucleus (through the inhibitory neurotransmitter GABA; Fig. 1d); and (3) to the lateral hypothalamus, the orexinergic and melaninergic systems regulating the rhythms of wakefulness, REM sleep, and, possibly, food consumption (through the activatory neurotransmitters thyrotropin and glutamate; Fig. 1d) [79].

This complex, three-step system of integration of circadian rhythms is required to achieve a high degree of flexibility and lability in the realization of this rhythm. Humans and many other mammals do not need subordinating strictly their behavior to innate circadian rhythms. Conversely, within certain limits, they are able to rearrange their biorhythms, subordinate them to behavior, and optimize in accordance with changing environmental conditions. Circadian clock controls the temporal patterning of molecular, cellular, and physiological processes throughout the body, and potential disturbance of this "timing" system in PD can cause many pathological symptoms [75].

The Role of Dopamine in Circadian Regulation

Dopaminergic neurotransmission is present at different levels of the circadian system. In the vertebrate

retina, the dopamine concentration increases during the day and decreases at night, being exposed to circadian regulatory effects [80] and the action of light, which stimulates the synthesis, turnover, and release of the retinal dopamine [81, 82].

The retinal dopamine plays the key role in the regulation of numerous processes mediating the light adaptation of the visual function [81]. In particular, by acting through type 4 dopamine receptors (D4), dopamine modulates the rhythms of the second messenger cyclic adenosine monophosphate (cAMP) in the retina. In addition, it plays an important role in the circadian modulation of the conductivity of gap junctions between rods and cones, thereby mediating the diurnal oscillations in the retina contrast sensitivity. Dopaminergic transmission through D1 receptors modulates the gap junctions between the horizontal cells. This signaling pathway is essential for maintaining a high spatial resolution of the retina. However, the disturbance of transmission through D1 receptors does not affect the circadian regulation of light adaptation of electroretinogram: the effect of dopamine, mediated by D1 receptors, requires the light-induced release of dopamine, whereas the regulation of contacts between photoreceptors, which is ensured by D4 receptors, is a circadian-regulated process [83, 84].

Dopamine is a mediator of non-visual responses to light, in particular, the changes in the clock gene expression rhythm. Similarly to the SCN, the molecular oscillator in the retinal cells is representative of interrelated transcription–translation cycles of the clock genes and their protein products [85]. The expression rhythms of these genes can be altered under exposure to light, which makes it possible to adjust the circadian clock to the changes in external illumination and adapt retinal tissues for optimal response to light [86]. This basic clock mechanism of the retina is captured by illumination oscillations primarily through the dopaminergic transmission. Studies in mice showed that the stimulation of retinal D1 receptors with dopamine agonists acts similarly to light, enhancing the expression of the *Per2* clock gene and thereby affecting the circadian clock phase. The effect of light on the *Per2* gene phase is attenuated by D1 receptor antagonists [87]. Dopamine, which acts through type 2 receptors (D2), enhances *Per1* expression in the mouse retina [88] and regulates the rhythmic expression of melanopsin, a photopigment of photosensitive ganglionic cells, which play an important role in the light adjustment of the circadian clock [89].

In addition, dopamine is an essential efferent of the circadian clock regulating many functional changes in retinal neurons and their networks, which determines the "daytime" or "nighttime" state of the retinal function (e.g., electroretinogram amplitude, melatonin secretion by photoreceptors, and domination of information from the cones or rods in the visual system) [85, 90, 91].

In addition to the light adjustment of the circadian clock, the eye mediates a non-visual response to light such as an acute suppression of pineal melatonin and suppression of locomotor activity — the so-called light masking of circadian rhythms [92] in nocturnal animals, which is required for limiting their activity period to the dark time of day. Nervous transmission mediated by D2 receptors is an essential component of the light masking mechanism [93].

The involvement of dopamine in the circadian regulation is not limited to the peripheral parts of the visual system. It was shown that D1 receptors are present in the SCN [94, 95] and that the rhythmic expression of the *mPer1* clock gene in the mouse SCN is affected by haloperidol, a nonselective antagonist of dopaminergic receptors [96].

Dopamine, through D1 and D2 receptors, is involved in the regulation of clock gene expression in the dorsal striatum [97, 98]. The *Per2* expression rhythm in the rat dorsal striatum depends on the diurnal activation of D2 receptors. A direct relationship between the extracellular dopamine level and the *Per2* rhythm expression was shown, with the daily peak of the extracellular dopamine rhythm in the dorsal striatum being ahead of the *Per2* peak for 6 h. The depletion of striatal dopamine (by using a toxin for dopaminergic neurons or a D2 receptor blocker) smooths out the rhythm of striatal *Per2*. A daily timely activation of D2 receptors makes it possible to restore the *Per2* rhythm in the striatum even against the background of dopamine deficiency [97]. The authors of another study noted that the agonists of both D1 and D2 receptors affect the expression of *mPer1*, *mClock*, *mNPAS2*, and *mBmal1* clock genes in striatal neurons, both in cell culture and in vivo in mice [98]. Additional information on the role of dopamine in the maintenance of circadian rhythm was obtained in experiments with neurochemical destruction by 6-oxydopamine injections, which disturb normal circadian pattern of behavior and *Per2* expression [99]; therapy with levodopa may partially eliminate these disturbances [100].

A number of data indicate that the clock genes are involved in the dopamine metabolism. For example, increased dopaminergic function in mice mutant for the *clock* gene may underlie the behavioral disorders associated with reward and cocaine addiction [101]. Using the same experimental model, the *Clock* gene (the key element of the molecular circadian oscillator) regulating dopaminergic activity in the ventral tegmental area (*VTA*) and the maniac-like locomotor behavior (hyperactivity, sleep reduction, reduced anxiety, and increased craving for cocaine) associated with it, was shown [102].

Rhythmic changes in dopaminergic neurotransmission were described for different parts of the brain,

including the mesolimbic structures. For example, it has long been known that the level of dopamine, its metabolites, and its receptors in different regions of the brain shows diurnal fluctuations [103], including the striatum, where dopamine metabolism shows a circadian rhythm associated with cyclic variations in the concentrations of the dopamine transporter (DT) and tyrosine hydroxylase (TH) [104]. The authors [105] studied circadian fluctuations in the extracellular dopamine level in the striatum and nucleus accumbens. The destruction of SCN showed that this structure is, at least partially, responsible for the differences in DT and TH expression at night and during the daytime, which are observed in the nucleus accumbens, the medial prefrontal cortex, and the caudate nucleus [106], as well as for the diurnal variations in the cocaine search behavior in rats [107]. It was shown that circadian clock genes directly affect the expression of type A monoamine oxidase (MAO-A, enzyme that degrades catecholamines) and the activity of the mesolimbic dopaminergic rewarding system (including VTA and the ventral striatum/nucleus accumbens). It was found that MAO-A promoter transcription is regulated by the clock components BMAL1, NPAS2, and PER2. Mutation for the *Per2* clock gene in mice results in a decreased expression and activity of MAO-A in the mesolimbic dopaminergic system. In these mice, an increased level of dopamine, impaired neuronal activity in the ventral striatum, and behavioral changes in tests simulating mood disorders in humans were also observed [108, 109].

Among the rhythms and clock mechanisms, primarily those that are involved in the rewarding system are related to dopamine. The authors of [110] studied a case of unlimited access to food; however, provided receiving especially tasty food once a day. In this case changes in the motivational state can affect the circadian clock in the SCN. Receiving tasty food increased the dopamine content and the *Period* gene expression in the forebrain of mice, which was accompanied by c-FOS activation in dopaminergic and orexinergic neurons. These data indicate that the effect of the feeding behavior rhythm on the SCN is mediated by rewarding and arousal systems. The rhythm of receiving tasty food not only captured the behavioral rhythms but also influenced the SCN synchronization with the illumination rhythm, reducing the effect of shifting the *Period* expression phase under the influence of light. The correlations between the limited access to food and the behavior associated with rewarding, on the one hand, and the circadian rhythms of dopamine, on the other hand, were traced [111]. It is, therefore, possible that the important circadian role of dopamine consists in the regulation of periodic processes involved in rewarding-associated behavior.

The mesocorticolimbic dopaminergic system plays an important role in the regulation of sleep and wakefulness, and the dopamine deficiency in PD may be a source of the sleep–wakefulness cycle disorders [16, 17, 112].

There is distinct interaction between dopamine and melatonin, a well-known product of the circadian system that functions as a marker for both diurnal and seasonal variations in physiological parameters and behavior [113]. It is also interesting that the seasonal fluctuations in the dopamine level were also described in humans, although their significance and consequences remains to be established [114].

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