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REVIEWS

# Circadian Regulation and Its Disorders in Parkinson's Disease Patients. Part 2: Experimental Models, alpha-Synuclein, and Melatonin

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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, melatonin, α-synuclein

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## EXPERIMENTAL PARKINSON'S DISEASE (PD) MODELS DEMONSTRATE CIRCADIAN RHYTHM DISORDERS

Because of the large number of factors involved in the pathogenesis of PD (such as age, medical therapy, depression, anxiety, cognitive impairments, etc.), in clinical trials it is still impossible to distinguish those of them that affect the sleep—wakefulness cycle regulation at dopaminergic neurodegeneration. Similar studies were performed in animal models, in particular, using the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) or the neurotoxin 6-oxydopamine, which lead to a selective destruction of the dopaminergic system.

Seven Californian drug addicts with severe symptoms of Parkinson's disease (discovered in 1983) were examined. On the basis of the results of these studies, the MPTP model was created. These young subjects practiced intravenous injections of crude meperedine, a synthetic analogue of heroin containing high concentrations of MPTP, a by-product of heroin synthesis. Thorough studies performed in subsequent years showed that MPTP, due to its high lipophilicity, easily passes through the barrier and penetrates into astrocytes, where it is converted into the 1-methyl-4-phenyl-pyridin ion ($MPP^+$) by type B monoamine oxidase (MAO-B). This ion binds to dopamine transporter and thus gets into the mitochondria of dopamine-containing neurons. In mitochondria, it inhibits complex-1 (bound to NADH ubiquinone oxidoreductase) of the mitochondrial electron transfer chain and thus uncouples oxidative phosphorylation. This, in turn, leads to disruption of adenosine triphosphate (ATP) production, increase in the extracellular calcium levels, and generation of free radicals/reactive oxygen species. The latter interact with cellular proteins, nucleic acids, lipids, and other molecules and cause cellular damage and, ultimately, the death of neurons (i.e., dopamine neurotoxicity symptoms) [1].

MPTP toxicity in different species of mammals varies widely and depends primarily on the level of MAO-B in the brain. This level is high in carnivorous and primates, low in rodents, and almost zero in rats (which determines their high resistance to disinfestation procedures). For this reason, the relative doses of the toxin required to form the parkinsonian phenotype in cats and monkeys are 15 times lower than in mice. In rats, it is practically impossible to induce parkinsonism symptoms in chronic experiments with systemic MPTP administration [2].

Nevertheless, a model of Parkinson's disease, which is generally accepted today and which was validated by the International Society of Psychopharmacologists, was developed in black mice of the C57BL/6 strain. In this model, black C57BL/6 mice are systemically injected with the neurotoxin MPTP which selectively destroys the dopaminergic system. The effect of this toxin depends on the dose and injection regimen. For this reason, the results of different studies of the effect of MPTP-induced destructions on the circadian rhythms in mice are contradictory. The authors of [3] detected no disturbances in circadian rhythms in mice after MPTP administration but observed severe destruction of dopaminergic neurons (approximately 50%) [3]. The authors of another study showed that MPTP affected the circadian rhythm of locomotor activity, lengthening the period of free locomotor activity (running in a wheel) compared to the control mice [4]. This was accompanied by a reduction in the number of dopaminergic neurons in the substantia nigra (SN) by 43%. It was also shown that MPTP-induced destructions caused changes in the architecture and efficiency of sleep in mice (in particular, increase or reduction in REM sleep) [5–9].

Simulation of dopaminergic system pathology is also widely used in other rodents and predators. For example, injections of the toxin oxydopamine-6 in rats lead to the loss of large amounts of dopaminergic neurons and disrupt both behavioral rhythms and clock gene expression rhythms [10]. In cats, MPTP injections reduce the REM sleep duration [11].

In the PD models in lower primates, caused by the destruction of the dopaminergic system with MPTP, an increased daytime sleepiness and sleep fragmentation were detected [12, 13]. In addition, MPTP was shown to significantly enhance the tonic muscle activity during REM sleep, which is indicative of a phenomenon similar to the REM sleep behavior disorder (RBD) [14]. Similarly to PD patients, dysregulation of REM sleep and increased daytime sleepiness occur before the motor symptoms [12, 14–16].

Increased daytime sleepiness and sleep fragmentation, possibly, indicate circadian dysfunction. Indeed, parkinsonism caused by MPTP administration in lower primates is associated not only with sleep disorders but also with changes in other circadian rhythms of behavior and physiological processes such as secretion of melatonin and prolactin [17] and rhythms of temperature and locomotor activity [18]. Hence, dopamine deficiency entails an overall circadian system disruption. A recent study [19] has shown that MPTP-induced destruction of the dopaminergic system leads to a decrease in amplitude, increase in fragmentation, and reduction in stability of the circadian rhythm of locomotor activity in animals kept in a light/dark regime. Under conditions of constant illumination, severe disturbances of rhythm and even its complete disorganization are observed, but the amplitude and phase of secretion of melatonin and cortisol remain unchanged. The authors concluded that after the dopaminergic system destruction the central "clock" in the suprachiasmatic nucleus (SCN) is retained. However, in the absence of stimulatory and inhibitory effects of light and dark the clock cannot ensure the down-regulating effects on the clock genes of the striatum and the dopaminergic functions which control the locomotor behavior.

Another way to assess the role of the dopaminergic system in the sleep–wakefulness cycle regulation is the study of sleep and circadian rhythms in genetically modified animals lacking specific dopamine receptors or dopamine transporters. A decrease in the duration of wakefulness with a corresponding increase in the duration of both slow-wave and REM sleep as well as a sharp reduction in the δ-rhythm (0.75–2 Hz) power during slow-wave sleep was shown in D2 knockout mice [20]. In addition, an increase in the number of wakefulness episodes and a decrease in their length were observed, indicating the instability of wakefulness. The authors of this study concluded that D2 receptors play an important role in maintaining wakefulness.

Experiments in other models—in mice with deficient expression of the vesicular monoamine transporter (VMAT2) [21, 22] and in mice knockout for the dopamine transporter (DAT-KO mice) [23]—also showed that the disruption of the normal function of dopaminergic cells is associated with the appearance of non-motor symptoms, including sleep disorders and circadian rhythm disturbances.

Thus, different experimental PD models show that the dopaminergic system destruction and the dopamine deficiency lead to disturbances in the rhythms of clock gene expression, sleep–wakefulness, and voluntary locomotor activity.

## PATHOGENIC MECHANISMS OF CIRCADIAN DISORDERS IN PD NOT RELATED TO DOPAMINE DEFICIENCY: ACCUMULATION OF α-SYNUCLEIN

Although the dopaminergic system destruction can lead to circadian dysfunction, the specific pathogenetic mechanisms underlying circadian dysfunction in PD remain poorly understood.

Parkinson's disease, in addition to the degeneration of the nigrostriatal dopaminergic system, can also be accompanied by the destruction of the neuroanatomical parts of the circadian system per se—afferent pathways to the SCN, SCN itself, and the descending peripheral efferents of the SCN. For example, the disturbance of the visual function accompanying PD which is due primarily to the degeneration of dopaminergic retinal networks and dopamine deficiency, is well known [24, 25]. As a result, the transmission of information about changes in illuminance is disturbed, which may affect the circadian rhythm maintenance in PD patients.

Data on the involvement of the hypothalamus in the pathological process in PD are ambiguous [26, 27], and the effect of PD on the structure and function of the SCN is still poorly understood. However, the degeneration of this central pacemaker is considered as another possible mechanism explaining the circadian rhythm disturbances in PD patients [28]. Finally, the disturbances of efferent pathways in SCN may be responsible for the disruption of biological rhythms in PD (in particular, changes in the circadian rhythm of melatonin secretion in PD are known [29–32]).

The mechanisms that determine the circadian fluctuations in PD symptoms are not understood completely as well. These fluctuations may be determined in part by the fluctuations in the metabolism of dopamine, dopamine accumulation per night, or diurnal deactivation of receptors [33, 34].

Despite the fact that PD is primarily the result of degeneration of neurons in the SN which leads to subsequent reduction of the dopaminergic inputs to the striatum, a number of stem nuclei (locus coeruleus, raphe nuclei, dorsal motor vagal nucleus), cortical neurons (in particular, in the cingulate gyrus and entorhinal cortex), Meynert basal nucleus, and preganglionic sympathetic and parasympathetic neurons are also destroyed in this disease. The pathogenetic mechanisms of these diffuse disturbances in different parts of the brain are not understood completely; it was assumed that the accumulation of α-synuclein may play an important role in them [28].

Possible mechanisms of the effect of α-synuclein on circadian regulation can be considered using the mouse model of synucleinopathies as an example. One of the best studied models of PD and other synucleinopathies is the transgenic mouse strain *Thy*1-α*Syn* expressing human α-synuclein controlled by the *Thy*-1 gene promoter [35]. Genetic mutations in the α-synuclein gene or duplication of this gene are closely associated with the PD family forms; polymorphism for this gene determines the risk of PD [36–40]. *Thy*1-α*Syn* transgenic mice exhibit a progressive disturbance of motor and non-motor functions similar to that observed in PD patients, including the impairment of olfaction and cognitive functions and disorders of the autonomic nervous system [41–43]. The study of circadian regulation in these mice showed [44] that they experience severe disorders of the circadian rhythm of locomotor activity: fragmentation, reduced rhythm amplitude due to the lower level of activity at night, and less clear beginning of the activity/rest periods (Fig. 1). Although the duration of the activity period, the circadian rhythm capture by the changes in the light regime, and the expression pattern of the clock gene *Per2* did not differ from the norm, the frequency of spontaneous action potentials in SCN neurons was significantly reduced during the daytime [28, 43].

It is known that the oscillatory clock mechanism of SCN is based on the rhythmic expression of the key clock genes, in particular, the *Per2* gene [44], which, in turn, controls the action potential fluctuations in SCN neurons projecting to other regions of the brain. If the circadian clock in the SCN functions normally, the *Per2* expression level is increased in the daytime and decreased in the dark time of the day; as a result, the pulsation of SCN neurons will be at maximum in the daytime [45]. Since *Thy*1-α*Syn* mice retained a clear rhythm of fluctuations in the *Per2* gene expression in the SCN, it can be concluded that the disturbances in their periodicity were not the result of deficiency in molecular oscillations in the SCN or the pathology of its inputs, and the daytime decrease in the neuronal excitability in SCN is caused by some other factors.

A possible mechanism that mediates the decrease in the neuronal activity of SCN under conditions of α-synuclein overexpression may be the changes in the synaptic transmission. α-Synuclein is a presynaptic protein that regulates the release of synaptic vesicles, and it incorrect expression disrupts the synaptic transmission [46, 47]. Neurons in the nervous networks in the SCN release gamma-aminobutyric acid (GABA) as a neurotransmitter, and the majority of neurons receive a constant inflow of GABA signals [48–50]. Probably, α-synuclein overexpression affecting the synaptic transmission can shift the balance towards enhancement of inhibition in the SCN networks, which ultimately leads to the circadian symptoms in *Thy*1-α*Syn* mice.

An alternative explanation is based on the events that underlie the diurnal rhythms of spontaneous electrical activity of neurons in the SCN, whose depolarization increases in the daytime period. This relatively depolarized resting potential is the result of stimulatory effects implemented by multiple cationic currents [51, 52]. A decrease in the amplitude of these currents may reduce the daytime pulsation of SCN neurons [45, 53, 54]. It was also shown [55] that aging selectively disrupts potassium currents in the SCN which reduces the synchronicity of its cell population.

Although α-synuclein primarily plays a major role in the synapse in the processes of release and recycling of synaptic vesicles, there is evidence of its colocalization in the mitochondrial membrane [56, 57]. It was also shown that the mitochondrial function may be impaired due to incorrect α-synuclein expression [58] and, conversely, the mitochondrial proneurotoxin MPTP leads to α-synuclein accumulation [59].

On the other hand, the circadian system pathology may disrupt the function of mitochondria and induce oxidative stress. In particular, it was shown that a deletion in one of the key clock genes, *BMAL1*, leads to mitochondrial dysfunction, including an increase in the content of reactive oxygen species in peripheral organs [60–62]. Ample data have been accumulated showing that both the generation of reactive oxygen species and the production of cellular antioxidants are controlled by the circadian system [60, 63, 64] and that many parameters of the immune system have circadian oscillations (see, e.g., [65]).

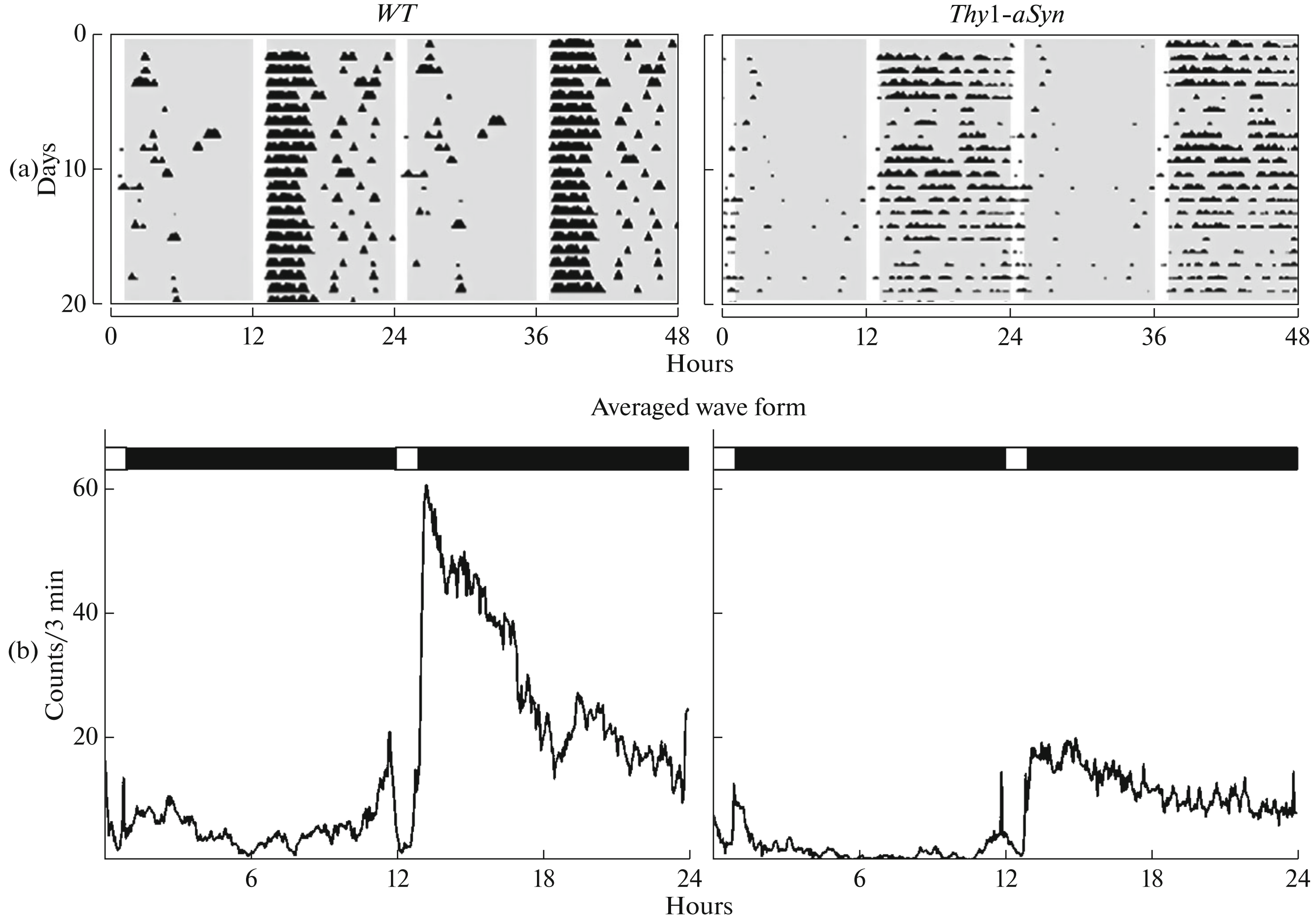

**Fig. 1.** Circadian rhythm disturbance may be the key component of the non-motor symptoms of Parkinson's disease. Data were obtained in the experimental model of transgenic mice overexpressing α-synuclein. (a) A representative plot of the wheel running intensity of the control (WT) and transgenic (*Thy*1-α*Syn*) mice. The abscissa axis shows hours, and the ordinate axis shows days. Animals that were kept under the 12 : 12 LD cycle, shifted to the fragmented photoperiodicity regimen 1 : 11 : 1 : 11 LD. Each horizontal row is a duplicated 24-h record of motor activity day by day (top to bottom). The shaded areas designate the dark periods of the day. (b) Averaged representative curves illustrating the dynamics of motor activity of control and mutant mice. The abscissa axis shows hours, and the ordinate axis shows the number of wheel turns per 3 min. In addition to the sharp decline in the level of activity, the transgenic mice showed disturbed timing of the onset of the periods of increased motor activity relative to switching off the light and an increased fragmentation of these periods. Thus, *Thy*1-α*Syn* transgenic mice overexpressing α-synuclein exhibit a smoothed circadian rhythm of voluntary motor activity [28, 43].

Thus, an enhancement of oxidative stress and inflammatory processes occurring as a result of circadian dysfunction in combination with α-synuclein aggregation can exacerbate the PD pathology. Therefore, the circadian system dysfunction can be considered as a risk factor for PD [28] (Fig. 2).

There are numerous data demonstrating that clear circadian rhythms are an essential component of a good health. Many studies have shown that disturbances in the circadian system cause a cluster of symptoms, including the cognitive deficit and memory problems [66, 67], metabolic disorders [68, 69], cardiovascular disorders [70, 71], gastrointestinal diseases [72, 73], and an increased risk of certain types of cancer [74]. Many of these symptoms were described in PD patients. It may be concluded that circadian dysfunction is not only a symptom of PD but also a deep (and, maybe, even a pathogenetic), component of the disease.

## THE LEVEL OF MELATONIN AND DISTURBANCES IN CIRCADIAN REGULATION IN PD

The most important biological marker of the circadian system is melatonin, a hormone that is synthesized primarily in the pineal and plays an important role, in particular, in the regulation of sleep and seasonal biorhythms [75]. The synthesis of melatonin increases at the dark period of nychthemeron and is inhibited in the daytime.

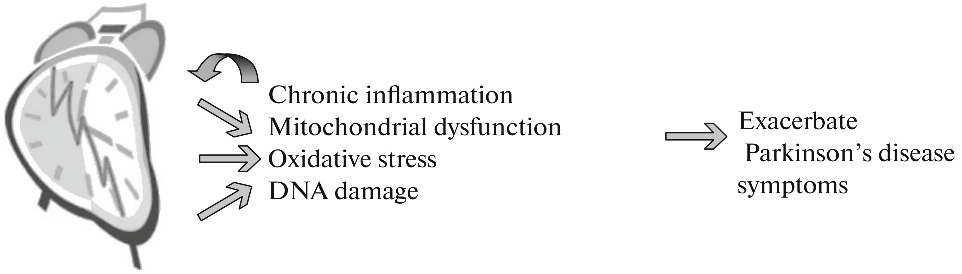

**Fig. 2.** Potential mechanism by which circadian dysfunction can exacerbate PD symptoms. The molecular clock of the body regulates the mitochondrial function, the generation and decay of reactive oxygen species, the DNA repair, and immune responses. Disturbances in the biological clock contribute to the development of chronic inflammatory processes, mitochondrial function disturbance, and DNA damage. All these processes are assumed to be involved in the development of Parkinson's disease symptoms and age-related changes in the brain. Circadian dysfunction caused by genetic factors or perturbations in the environment can accelerate the development of disorders in PD [28].

The study of the secretion of this hormone in PD showed, first of all, changes in the circadian rhythm of fluctuations in the melatonin concentration. In particular, the amplitude of the rhythm of melatonin secretion in PD patients decreases [29, 30]. The comparison of the treated (with levodopa and/or dopamine agonists) and untreated (newly diagnosed with PD) patients indicates a trend to phase advance in melatonin fluctuations in the treated patients [29, 31, 32]. In particular, according to [32], the usual bedtime and the time of the beginning of twilight melatonin secretion was not significantly different between the treated and untreated patients. However, the phase angle between the rhythms determined as the difference between the bedtime and the beginning of melatonin release was more than twice higher in the patients who received dopaminergic therapy compared to the untreated patients. According to the authors, the discordance of circadian regulation and sleep regulation in PD is caused by the use of dopaminergic drugs rather than the disease process itself.

The effect of PD on the overall level of secreted melatonin was also studied. Patients with the newly diagnosed PD were characterized by a decrease in the circulating melatonin level compared to the healthy age-matching subjects [76]. In another study, the patients who received dopaminergic drugs also had a lower melatonin concentration compared to the control group [30]. In addition, the effect of dopaminergic therapy on the melatonin level was revealed. In particular, the amount of circulating melatonin in the treated patients was higher compared to the untreated ones [32]. An increased daytime secretion of melatonin in the PD patients with the motor side effects of levodopa compared to the patients without the side effects and the untreated patients was detected [31]. In the study [77], PD patients treated with dopaminergic drugs had elevated levels of melatonin in the morning, and the melatonin level was positively correlated with the stage of the disease and did not depend on the dose of dopaminergic drugs. However, it should be noted that the intensity of illumination, which is known to affect the level of melatonin, was controlled only in the single study [32].

The increased melatonin secretion in response to dopaminergic therapy can be explained by taking into account the data on the involvement of dopamine in the regulation of secretion of the pineal gland. In particular, the receptor D4 whose expression is dependent on the light intensity and obeys circadian fluctuations was identified in the pineal of rats [78]. Moreover, the secretion of serotonin and melatonin from the pineal gland is controlled by heteromerization of adrenergic and dopaminergic receptors, which also obeys the circadian rhythm. Using $\alpha_1$B-D4 and $\beta_1$-D4 heteromeric receptors, dopamine inhibits the adrenergic receptor and blocks the synthesis of melatonin induced by adrenergic receptor ligands. This inhibition is not observed in the daytime, when D4 is not expressed. The identified heteromerization between the adrenergic and dopaminergic D4 receptors is a neurohumoral feedback mechanism by which the dopaminergic regulation of circadian inputs is realized [79].

In the study [32] despite the fact that the treated patients had a significantly longer time elapsed between the beginning of melatonin secretion and the bedtime, they showed no differences in the severity of insomnia and any other deviations in the sleep architecture. Some authors believe that melatonin exhibits somnogenic properties [80]. From this standpoint, the observed separation of these two events in time in the case of increased melatonin secretion seems paradoxical. Accordingly, the existence of certain forms of melatonin resistance in patients with PD was assumed which may supposedly explain the modest success in insomnia therapy in PD patients with the exogenous melatonin [81, 82]. For example, in one of the studies [81], no difference between the effect of 5 and 50 mg of melatonin on the sleep quality and daytime sleepiness in such patients was detected (it should be noted that both doses used were too high to demonstrate the potential somnogenic effect [75]). Data on the reduction in expression of melatonin receptor types 1 and 2 in the striatum and other brain regions that are affected in PD indirectly indicate the development of such resistance [83].

However, to our opinion this is not the main cause. Melatonin is not a "sleep hormone," because it is released at night in diurnal, nocturnal, as well as crepuscular mammals. Its formation requires two factors: (a) the absence of bright lighting and (b) the absence of activity of SCN neurons. In the diurnal (daytime) mammals, including humans, the release of melatonin by the pineal gland, indeed, coincides with the usual sleep hours, which makes attractive the hypothesis of a causal relationship between these two phenomena. It was shown that an increase in the daytime level of systemic melatonin, which was caused by intravenous infusion of tryptophan (melatonin precursor) or 5-methoxypsoralen, which suppressed its degradation, enhanced subjective sleepiness and shortened the latent period of sleep in healthy subjects. Conversely, the suppression of melatonin production by administration of β-blockers destroyed the sleep architecture. In three species of diurnal monkeys (*Macaca mulatta*, *M. nemestrina*, and *M. fascicularis*), evening oral administration of low ("physiological") doses of melatonin decreased the latency and lengthened the night rest period, which can be regarded as a mild somnogenic effect [75].

In humans, the elevation of melatonin levels is not a mandatory signal to falling asleep. In the majority of healthy subjects, the administration of melatonin at "physiological" doses causes only a mild sedative effect enabling the general relaxation and reducing the responsiveness to normal surrounding stimuli which leads to calm wakefulness and gradual falling asleep. Unlike the strong "night" sedatives and hypnotics of the benzodiazepine series melatonin does not cause the sensation of an unbearable fatigue and irresistible thrust to sleep. If this subject is motivated he can easily overcome the "somnogenic" properties of melatonin. Both objective (assessed on the basis of polysomnograms) and subjective (based on the reports of healthy subjects and patients with insomnia) pharmacological characteristics of the "classical" benzodiazepine sedatives and hypnotics, on the one hand, and melatonin, on the other hand, drastically differ [75].

On the basis of the correlation between the subjectively sensed and objectively confirmed increase in evening sleepiness, on the one hand, and the beginning of the increase in the melatonin level in blood, on the other hand, it was assumed that, in humans, melatonin creates the "predisposition to sleep" and inhibits wakefulness mechanisms rather than directly affects the somnogenic structures. Due to the high saturation of the SCN and the adjacent areas of the preoptic area with the high-affinity melatonin receptors, this hormone, along with a number of other physical (bright light) and biochemical (the neurotransmitters glutamic acid and serotonin as well as the neuropeptides neuropeptide tyrosine (NPY) and substance P (SP)) factors, can exert a strong modulating effect on the activity of the main oscillator in mammals including humans. For example, when administered in the morning, melatonin causes a delay in the circadian phase in humans; however, when administered in the evening, it, conversely, causes advanced phase shift. These phase shifts in humans do not exceed 30–60 min per day. Thus, a daily administration of melatonin can help to achieve a forward or backward shift in the activity–rest circadian cycle in humans for several hours [75].

In general, the data on the therapeutic effect of exogenous melatonin regarding the correction of sleep disorders are ambiguous. A number of studies have shown that melatonin decreases the problems with sleep initiation and the nocturnal activity in the elderly [84–86]. The therapeutic effects of exogenous melatonin in RBD were also repeatedly observed [87–89]. However, the hypnotic effect of melatonin was not always confirmed [90]. Furthermore, this effect proved to be limited: it was shown that melatonin improved the subjective estimation of sleep in patients, but the objective improvement in sleep quality was minimal [81, 82]. However, it was assumed that these failures may have been related to the short half-life of melatonin when it is used in inappropriately high doses [91].

The studies with an oral administration of "physiological" (0.1–0.3 mg) doses of melatonin during the day increasing the plasma melatonin level to 50–120 pg/mL which roughly corresponds to its nighttime level in adult healthy subjects showed only a very small, though significant somnogenic effect. This effect was manifested in strengthening the subjective sleepiness and shortening the latent period of the first and second stages. Evening melatonin administration improved the nocturnal sleep characteristics and shortened latency in patients with insomnia but almost did not alter the sleep structure in healthy subjects [75]. There is evidence that the effect of melatonin is bell-shaped, similarly to the effects of serotonin and dopamine, which at high concentrations cause the "paradoxical" effects.

There is also evidence that melatonin increases motor symptoms in PD patients [92–94] and may exacerbate nightmares and moving activity during sleep [92]. Since the relationship between the elevated levels of melatonin and more severe parkinsonism symptoms in patients [29, 77, 95] and experimental animals were noted, adverse effects of melatonin on motor function were revealed [96, 97]. In view of above, further studies of the effect of exogenous melatonin in PD patients are required.

Interestingly, an epidemiological study based on data from 84794 nurses showed that shift work with night duties reduces (!) the risk of PD development by

50% [98]. Since it was shown that the concentration of circulating melatonin at shift work decreases [99], the lower risk of PD can be, probably, explained by the decrease in the melatonin level due to the prolonged effect of light during night duties.

Light, the main synchronizing factor for the human circadian system, is increasingly widely used to correct various somnological and neuropsychiatric disorders, including the circadian rhythm disorders, seasonal affective disorders, and dementia [100]. A therapeutic effect of light therapy was also found in PD [94, 101–103]. Dopamine is the main neurotransmitter that mediates the input of signals about illumination changes to the retinal circadian clock which sends direct projections to the SCN. Light stimulates the synthesis, turnover, and release of dopamine in the retina [104, 105], so that an exposure to bright light, apparently, makes it possible to compensate for the dopamine deficiency. In addition to the positive effect of bright light on the mood, it was shown to reduce the severity of bradykinesia, rigidity, and dyskinesias [101–103]. The well-known therapeutic effects of REM sleep deprivation on the motor symptoms of PD [106–108] can also be determined by the activating effect of light rather than the deprivation itself [109].

It is known that melatonin and dopamine in the retina are in a reciprocal relationship and play opposite regulatory roles in its adaptation to the day/night conditions. The synthesis of melatonin is suppressed by light, and in the absence of normal amount of light in the environment, the synthesis and secretion of melatonin increase, whereas the level of dopamine decreases [110, 111]. A similar balance between dopamine and melatonin exists in the pineal gland: the concentration of dopamine is increased in daytime, whereas the concentration of melatonin is increased at night [112].

The relationship between the visual impairment and dopaminergic degeneration is also well-known. In particular, disturbances in the visual function in PD such as elongation of evoked potential latencies, reduction in contrast sensitivity, and electroretinogram pattern changes are associated with the retinal dopamine deficiency [113, 114] and correlate with the severity of clinical manifestations of PD [115]. Possibly, the visual deficiency, which develops in PD, is accompanied by a decrease in the effect of light on the retina, which, in turn, leads to an increased daytime melatonin secretion and further disturbs the balance between dopamine and melatonin. Moreover, age-related changes in the visual function due to cataract, macular degeneration, and ganglion cell death can shift this balance, thereby contributing to the development of PD.

There is a standpoint according to which various functional disorders in PD are caused primarily by the imbalance between dopamine and melatonin rather than by the dopamine deficiency [109]. According to Fig. 3, melatonin and dopamine in the retina and pineal gland are in reciprocal relationships. During the day, the melatonin level decreases whereas the dopamine level increases (a). Conversely, at night the melatonin level increases whereas the dopamine level decreases (b). However, normally these two systems are functionally coupled (connected by the thin black line in Fig. 3), and their changes in natural conditions are balanced. In PD, the relationship between dopamine and melatonin is disturbed (c), and the dopamine level decreases (at severe symptoms, to 20% of the norm), whereas the melatonin level increases. Long-term dopamine replacement therapy returns the ratio between the levels of dopamine and melatonin to nearly normal values (d). However, long-term dopamine replacement therapy causes an internal compensatory response aimed at restoring the dopamine–melatonin balance which gradually raises the dopamine level above the melatonin level and nullifies the result of treatment (e). A further increase in the melatonin level caused by increasing doses of dopamine-containing drugs throws the entire system into chaos, and the dopamine level continues to increase against the background of the increase in the melatonin level, once again imbalancing the system and causing dyskinesia (f). It was shown that the administration of exogenous melatonin improves the involuntary movements and reduces the severity of dyskinesia induced by an overdose of dopaminergic drugs (g). This is probably due to the return of dopamine and melatonin to the reciprocal functional relationship but at a higher level than in the healthy subjects. This assumption is confirmed by the reports that, although melatonin alleviates dyskinesia it does not improve the symptoms of the disease in general. A functional balance between dopamine and melatonin can be reached most easily using melatonin antagonists (epiphysectomy, bright light, or melatonin receptor blockade) against the background of a slight or moderate increase in the dopamine level (h). The maintenance of this kind of balance between dopamine and melatonin seems to be even more important than the dopamine replacement itself [109].

Dopamine replacement therapy also does not always allows restoring the delicate dynamic balance between the content of dopamine and melatonin, as evidenced by the “on–off” phenomena, which appear in the patients receiving long-term therapy with dopaminergic drugs and are accompanied by an elevated level of melatonin [29]. Given the fact that melatonin can inhibit the release of dopamine in various brain areas (such as the ventral hippocampus, pons, medulla, hypothalamus, and striatum [116]), an imbalance between dopamine and melatonin may exacerbate the disease.

From this standpoint, the therapeutic effect of bright light on PD patients may be due to the restoration of circadian rhythmicity and normalization of the balance between melatonin and dopamine [109,

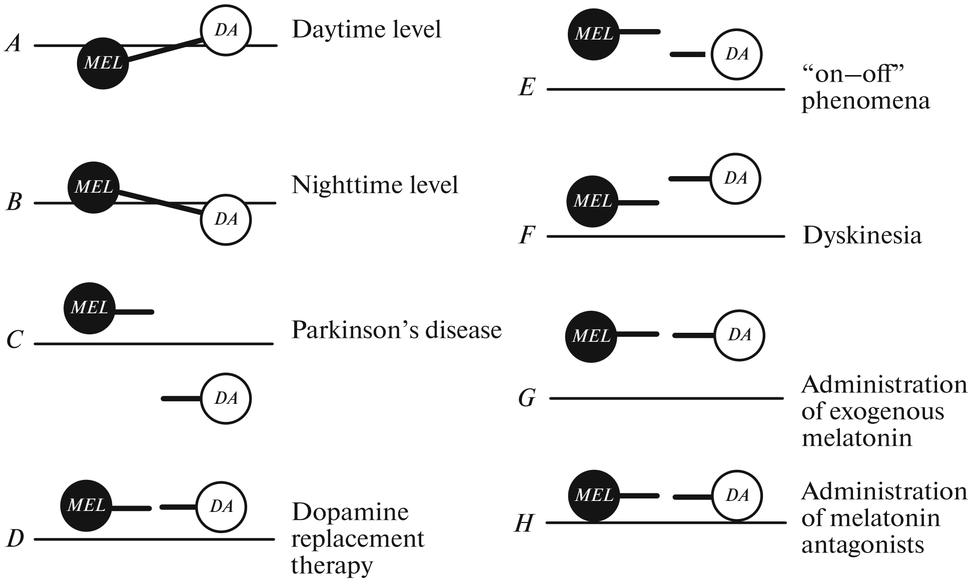

**Fig. 3.** Balance of dopamine (DA) and melatonin (MEL) in normal state and in PD [109] (for explanation, see the text).

117]. This assumption was confirmed by the study of the effect of melatonin on experimental PD symptoms, which showed that a slow injection of melatonin into the brain ventricles enhances the symptoms of parkinsonism, whereas the removal of the epiphysis or keeping animals under constant light conditions caused remission [96]. Thus, a decrease in the bioavailability of endogenous melatonin may alleviate the symptoms of PD. For this reason, melatonin (which exhibited neuroprotective properties in many studies [118]) should be used with caution in PD.

Thus, PD is accompanied by the circadian dysfunction, which significantly impairs the quality of life of patients. Its possible causes include dopamine deficiency, α-synuclein aggregation, imbalance between melatonin and dopamine secretion, as well as the neurodegenerative process in the SCN and its afferents. Studies have shown that the disruption of circadian rhythms observed in PD patients is pathogenetically associated with PD. On the other hand, the disturbance of circadian regulation itself adversely affects all functions of the body and may exacerbate the neurodegenerative processes.

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