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REVIEW ARTICLES

The Neurochemistry of the Sleep–Wakefulness Cycle and Parkinson's Disease

V. M. Kovalzon[1] and I. M. Zavalko

Severtsov Institute of Ecology and Evolution, Russian Academy of Sciences, Moscow, Russia

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Abstract—Parkinson's disease (PD) is one of the most socially relevant illnesses. Sleep disturbances in PD are common and manifold; they are present, according to different data, in 45–98% of all patients and include insomnia, parasomnia, hypersomnia, and other symptoms. Many of these symptoms appear several years before the development of movement disorders and may be regarded as early predictors of PD. We review the possible roles of the dopaminergic, orexin/hypocretinergic, and melaninergic cerebral structures in the development of PD sleep disorders, such as excessive daytime sleepiness, rapid eye movement sleep behavior disorders (RBD), and restless legs syndrome.

Keywords: sleep disorders, Parkinson's disease, excessive daytime sleepiness, REM sleep behavior disorders (RBD), restless legs syndrome

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INTRODUCTION

Parkinson's disease (PD) is a socially important disease. Analysis of its biological bases (along with Alzheimer's disease, depression, and stroke) is an important task of modern fundamental neuroscience. This was specially stressed by the President of the Russian Academy of Sciences during the scientific session "The Brain," which took place in December 2009 [1]. PD is associated with very slow (during tens of years) undeviating degeneration of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNpc), which project to nuclei of the striatum; the causes of this degeneration are still unknown. The process has no symptoms (presumably, due to the activation of compensatory mechanisms) and only at the late stage of the disease, when less than half of the initial number of DA neurons exist and the level of dopamine released by these neurons in the striatum falls by four times, do motor and, later, cognitive disturbances occur. However, starting treatment at this period is too late and the history of worldwide medicine has no patients who were healed. Modern medicine can only alleviate the symptoms and, in some cases, slow the development of the disease; hence, the creation of adequate experimental models and the search for early markers are current paramount tasks [2, 3].

During recent years, the above traditional viewpoint on PD as a disease of the motor system that is predominantly related to complete or, at least, substantial selective damage to the DA nigrostriatal system has been revised [4–6]. It has been shown that some unknown factor (presumably, exotoxic, bacterial, or viral) begins deleterious activity in the brain after penetration into the body starting from the rostral and caudal parts. Disruptions gradually move from the rhinencephalon and the medulla oblongata to the brain's geometric center and embrace all non-myelinated or weakly myelinated nerve cells and their outgrowths (cells and outgrowths that are protected by a thick myelin sheath remain undamaged) "on their path." During movement to the SNpc and two other rostral areas of the midbrain that contain DA neurons, the ventral tegmental area (VTA) and the ventral periaqueductal gray (vPAG), many neuronal assemblies become more or less damaged, not only in the rhinencephalon and medulla oblongata but also in the pontine tegmentum and rostral part of the midbrain (SNpc, VTA, and vPAG) and then in the hypothalamus and structures of the forebrain (Fig. 1). The early period of the disease already has different non-motor symptoms, such as disturbances of smell and the sleep–wakefulness cycle. Thus, according to the modern viewpoint, degradation of the nigrostriatal system and concomitant motor disturbances are not the only and perhaps even not the major characteristics of PD but rather are the final and the most dramatic part of a long-term process of neurodegeneration [7, 8].

In this article, we tried to answer the following questions: which *sleep disorders* are the most typical of PD? What are their possible mechanisms? Can some of them serve as early predictors of PD? Therefore, we reviewed studies that were performed predominantly in this century that were related to disturbances in the

[1] Corresponding author; address: Leninskii pr. 33, Moscow, 119071 Russia, phone: (495) 954-15-11, e-mail: kovalzon@sevin.ru.

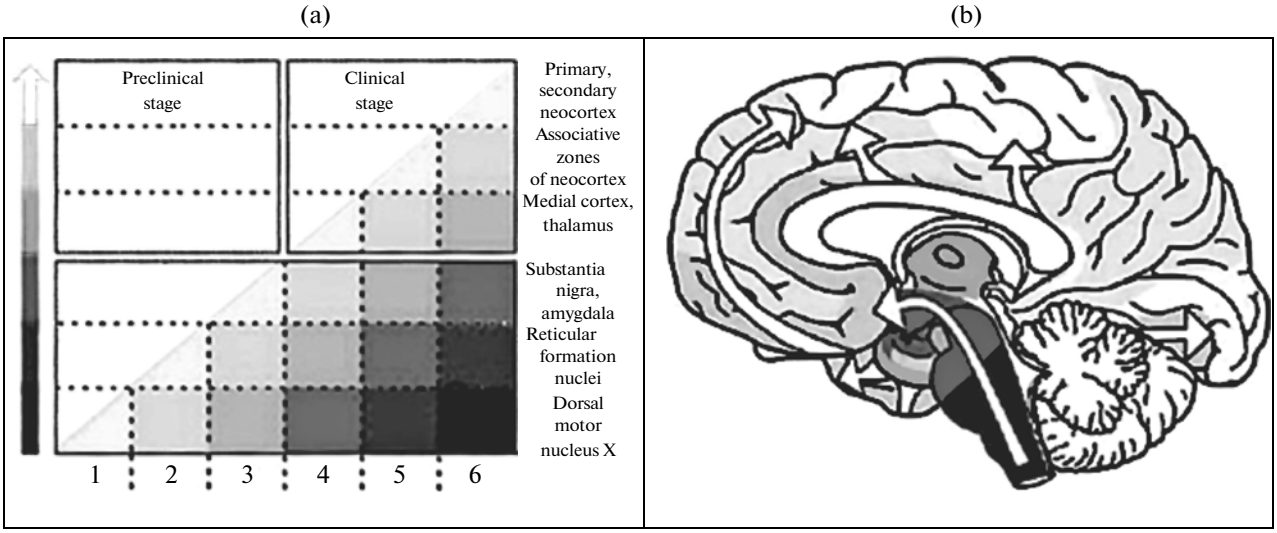

Fig. 1. Preclinical and clinical stages of PD. (a) Preclinical stages are characterized by the appearance of Lewy bodies/neurites in the brain. Further progression of neuropathological changes occurs during clinical stages. Intensity of staining (from bright grey to black) of squares under the diagonal line shows growth of lesion severity in the sensitive brain areas (right). (b) Arrows show spreading of pathological process. Shades of grey correspond to panel (a). Reprinted with permission from [7, 9].

sleep–wakefulness cycle that appear and progress during the development of Parkinson's disease, as well as possible neurochemical and neurophysiological causes of these disturbances, which were found in experimental models. Discussion of some aspects of these disturbances, in particular, the roles of the orexinergic and melaninergic systems, has almost been avoided in the Russian literature.

SLEEP AND PARKINSON'S DISEASE

An interesting trait of motor disturbances in PD is their dynamics during and after night sleep and during sleep deprivation. Resting tremors disappear before the onset of sleep and in many cases directly before the disappearance of alpha-rhythm in an EEG and do not occur during sleep. Tremors occur again during arousal, microarousal, large movements, and during changes in sleep stages [9, 10]. They also may occur at the beginning and at the end of paradoxical sleep and during rapid eye movements [10]. Presumably, other motor disturbances during sleep are also altered (bradykinesia and muscle rigidity) but it is not possible to examine them. According to some data, sleep deprivation may result in the improvement of some motor disturbances. After sleep deprivation for one night, Bertolucci et al. noted a decrease in rigidity, bradykinesia, and disturbances in gait for weeks [11]. However, other authors observed improvement of motor symptomatology in almost a half of the patients after normal night sleep [12].

Diverse sleep disturbances are widespread in PD. They are present in 45–98% of patients (according to different data) and include insomnias, parasomnias, hypersomnias, and other disturbances of sleep and wakefulness [13–17]. Up to 60% of all patients have insomnia, 30% have daily sleepiness, and from 15 to 59% have REM behavior disorders (RBD) [16].

Insomnias

Patients with PD are characterized by considerably lower *total sleep time* and *sleep efficiency* (the ratio between sleep time and time spent in bed). The decrease in the total sleep time results from difficulties in falling asleep and early morning awakening but the most widespread disturbance is frequent night awakenings, that result in substantial *fragmentation* of sleep.

Parasomnias

Disturbances in the *sleep structure* result from sleep breathing disorders, which occur more frequently than in the entire population, restless legs syndrome (see below), and periodic limb movements. Disturbances of the rapid-eye movement phase (REM) of sleep include: shortening of its duration and/or a decrease in its frequency; about a third of all patients have nightmares and hallucinations and about a third of all patients have RBDs. RBDs are associated with disturbances of mechanisms that are responsible for muscle atony during REM sleep and the patient, like Jouvet's cat (see below) starts to demonstrate its dreams. This may be frequently accompanied by aggressive behavior, the patient beats with his/her hands and legs, makes sounds, or talks. This is accompanied by the recovery of normal motor control: movements are not retarded and not accompanied by tremor and hypophonia disappears [18]. Although RBDs may occur inde-

Table 1. A simplified scheme for the release of major brain mediators during the wakefulness–sleep cycle

Neurotransmitters	Wakefulness	Slow sleep	REM sleep
Acetylcholine	↑↑	↓→↓↓	↑↑
Glutamate	↑↑	↓→↓↓	↑↑
Noradrenaline	↑↑	↓→↓↓	↓↓
Serotonin	↑↑	↓→↓↓	↓↓
Histamine	↑↑	↓→↓↓	↓↓
Dopamine	= (↑)	= (↓)	↑
GABA	↓↓	↑→↑↑	↓
Orexin/hypocretin*	↑↑	↓	↓↓
MCH**	↓	↓	↑↑

Notes: * orexin (hypocretin), a peptide and CNS mediator that was discovered in 1998.

** MCH, the melanin-concentrating hormone of cold-blooded vertebrates, which was discovered in 1983; in 1985, it was found that it plays the role of a peptide–mediator in the mammalian CNS.

Up arrow, an increase in release; double up arrow, a substantial increase in release; down arrow, a decrease in release; double down arrow, a substantial decrease in release; horizontal arrow right, gradual decrease/increase in release; equal sign, release without changes; arrow in parentheses, data are doubtful.

pendently of PD (idiopathic RBDs), patients with PD and a number of other neurodegenerative diseases (sinucleopatias) have these disturbances more frequently [19, 20]. Moreover, it has been shown that patients with isolated RBDs in the future may develop one of these neurodegenerative diseases, i.e., RBDs may predict PD [21]. In addition, motor disturbances of patients with PD and RBDs progress much faster, as compared to patients with PD without RBDs, and these patients have dementias more frequently [22].

Hypersomnias

Hypersomnias during PD may include excessive daytime sleepiness and "sleep attacks" [23–25]. Approximately one-half of all patients with PD have excessive daytime sleepiness. In addition, patients may suddenly fall asleep during the daytime; this may also occur during activity and is not preceded by daytime sleepiness, these are so-called "sleep attacks." It is still unclear whether "sleep attacks" are manifestations of daytime sleepiness or are a distinct phenomenon. The majority of researchers believe that patients do not remember that they fell asleep during sleepiness due to the amnestic effect of sleep. This is supported by the fact that, despite the preceding sleepiness, patients with "sleep attacks" have high scores according to the Epworth sleepiness scale [24]. It is generally accepted that hypersomnic symptoms and RBDs are early predictors of PD; they sometimes appear several years before and sometimes even tens of years before the appearance of motor disturbances [25].

THE ROLE OF DOPAMINE IN THE REGULATION OF SLEEP AND WAKEFULNESS

What are the causes of sleep disturbances during PD? It is logical to hypothesize that they occur due to disruption of the DA nigrostriatal system. However, the role of dopamine in normal regulation of wakefulness and sleep is ambiguous and for several decades it has remained puzzling. Other aminergic systems of the brain, viz., the noradrenergic (NA) system, whose cells are located in the area of the locus coeruleus (LC), the serotonergic system (5-HT) which is located mainly in the dorsal raphe nuclei (DR), and the histaminergic system (HA), which is located in the tuberomammilary nuclei of the posterior hypothalamus (TMH), have powerful activating (tonic depolarizing) both ascending (to neurons of the neocortex and archipaleocortex) and descending (spinal motoneurons) impacts. The nerve cells of these systems, which are quite active during wakefulness, progressively decrease their impulsation during slow sleep and completely (or almost completely) "become silent" during REM (Table 1). Thus, these three brain systems, along with cholinergic (ACh), glutamatergic (Glu), and the relatively recently discovered orexin/hypocretinergic (Orx/Hcr) systems participate in the maintenance of "neocortical tonus" and muscle tonus during wakefulness [26–30].

Disruption of DA neurons of the vPAG in rats results in an increase in the duration of slow and paradoxical sleep due to a decrease in the total time of wakefulness [31], which suggests that they are related to the system of wakefulness maintenance. Moreover, mice with a knocked out dopamine transporter, which had an elevated level of extracellular dopamine, had

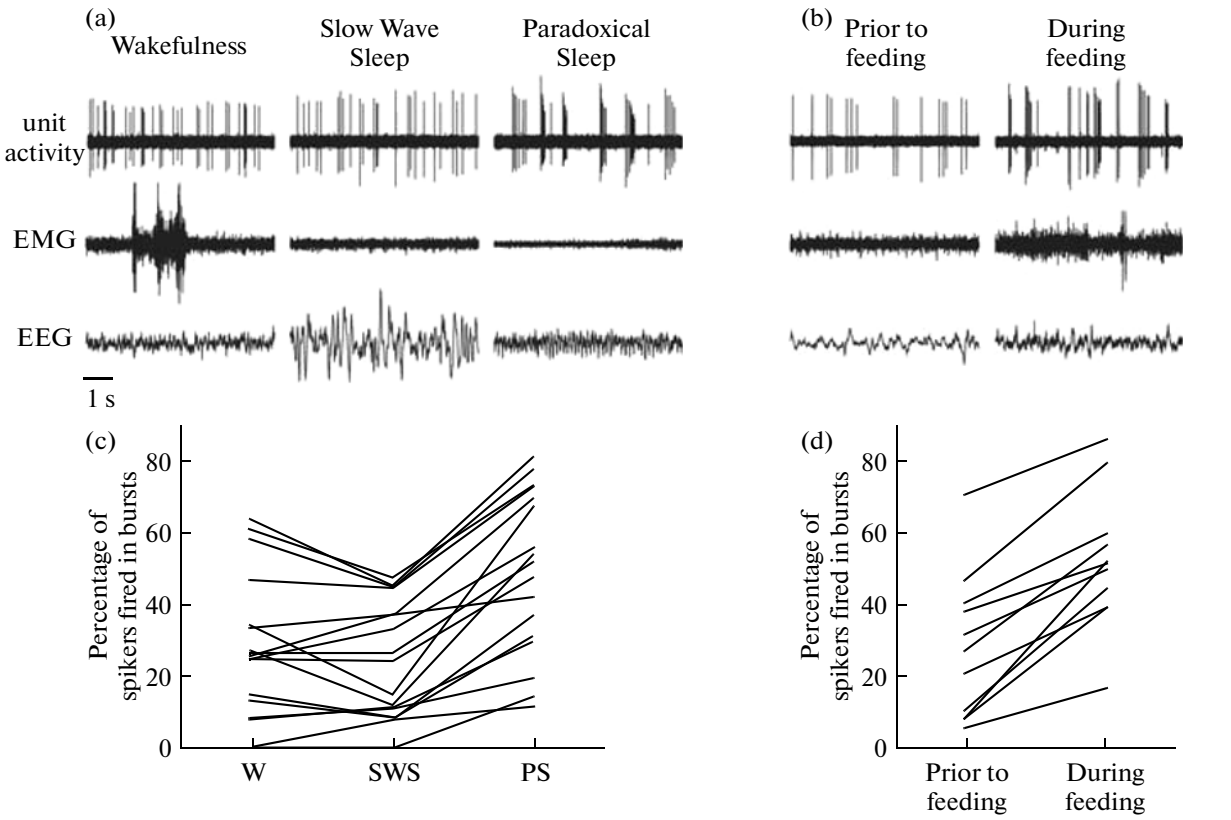

Fig. 2. DA neurons in the ventral tegmental area transit to the "burst" mode of discharges during REM sleep (a, c) and during the consumption of tasty food by rats (b, d). Upper panels: discharges of single neurons (unit activity); one neuron during the wakefulness–sleep cycle (W, wakefulness; SWS, slow wave sleep; PS, paradoxical sleep); another neuron, prior to feeding and during feeding. EMG, electromyogram; EEG, electroencephalogram. Wakefulness is characterized by pronounced EMG activity and low amplitude desynchronized EEG; SWS is characterized by lowered EMG activity and high voltage slow EEG waves; PS is characterized by the disappearance of muscle tone on an EMG and pronounced theta-rhythm on an EEG. Time division, 1 s. DA neurons switch from irregular discharges with seldom duplets during calm wakefulness and SWS to a "burst" pattern during PS and feeding. Each burst consists of several spikes with progressively decreasing amplitudes. It also can be seen that phasic activation of EMG during wakefulness does not affect impulsation. Bottom panels: abundance of burst activity as a percentage of spikes fired in bursts in 17 neurons that were recorded during the wakefulness–sleep cycle. The number of bursts increased during PS and feeding in the entire population of DA neurons. There are no significant differences between neuronal activity in W and SWS. Reprinted with permission from [38].

increased durations of wakefulness and decreased durations of slow wave sleep (by about one-fifth) during the daytime (non-active period) as compared to heterozygous and control (wild-type) animals [32].

Early studies in rats and cats did not reveal considerable changes in the activity of DA neurons located in the SNpc/VTA during the sleep–wakefulness cycle [33–36]. Hence, it has been believed for a long time that, in contrast to the afore-mentioned brain aminergic systems, the DA neurons of the nigrostriatal system are not involved in the regulation of sleep and wakefulness. However, it was found later that the concentration of extracellular dopamine in the locations of the projection of nigrostriatal neurons oscillates during the wakefulness–sleep cycle, decreases during slow wave sleep as compared to wakefulness, and increases during REM sleep [37]. It is unclear why dopamine release is altered in the striatum despite constant spiking frequency of neurons that synthesize it? More detailed analysis of characteristics of DA neurons of VTA has revealed considerable differences in the spiking pattern during REM sleep as compared to calm wakefulness and slow sleep [38]. The frequency of impulsations such as "flashes" and "bursts" increases during REM sleep and the amplitude of spikes progressively decreases in each "flash" (Fig. 2a, c). Analogous changes in the spiking pattern of DA neurons of the VTA (an increase in the frequency of "bursts") were observed during the transition from calm wakefulness to emotionally motivated behavior with positive reinforcement (for example, eating tasty food by rats; Fig. 2b, d). These "flashes" are accompanied by a massive release of dopamine in the synaptic clefts and extracellular space [39].

Immunohistochemical study of the expression of c-Fos by DA neurons in the rat brain showed that VTA neurons, in contrast to SNpc neurons, increase their activity during recovery REM sleep after a 2-day REM

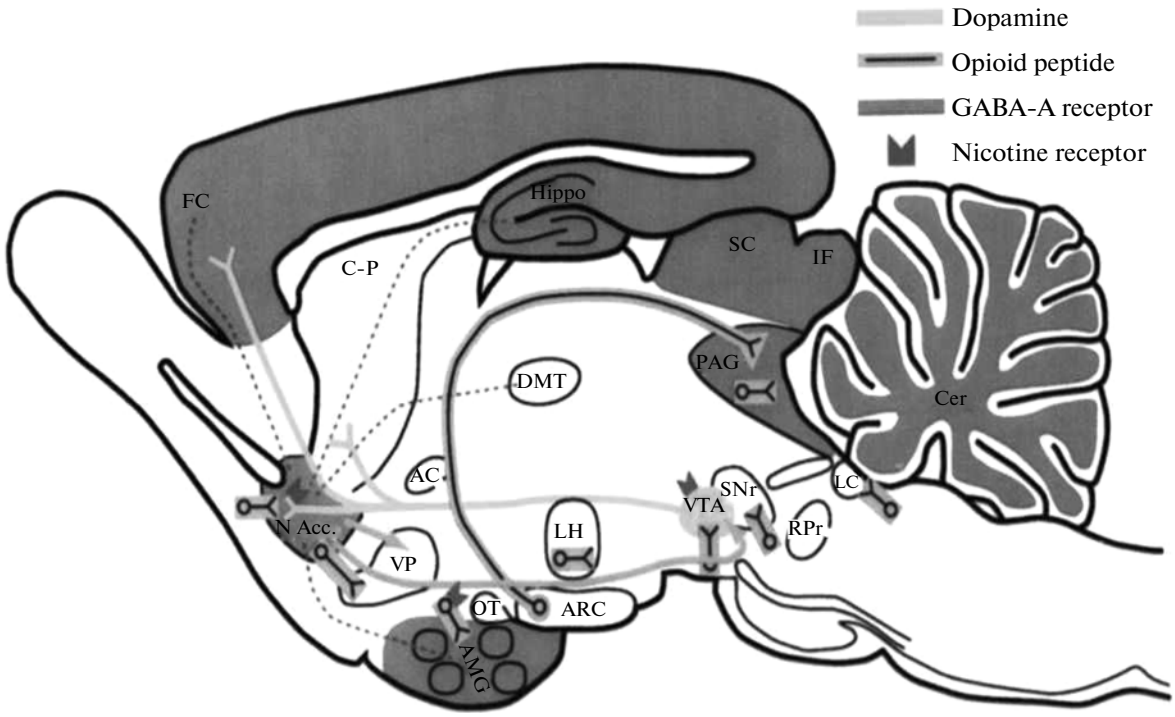

Fig. 3. The dopaminergic system of the ventral tegmentum and its projections in a parasagittal slice of the rat brain (SNr = SNpc). Figure by Dr. Timothy Roehrs, 2007. Reprinted with the author's permission.

sleep deprivation by the method of "small platforms" [40]. However, a recent study by French authors did not reveal changes in Fos-expression in areas A9 and A10 (SNpc/VTA and vPAG) during recovery sleep after a 3-day deprivation of REM sleep or 3-day wakefulness in a sensorially enriched environment. Only a small increase in the activity of DA neurons located in the caudal part of the hypothalamus (A11) was found. In addition, the number of Fos-immunopositive DA-containing cells increased in the zona incerta (A13) [41]. However, the authors noted, referring to [42], that the c-Fos technique is not a reliable marker of neuronal activation [43].

What is the role of an elevated DA level during REM sleep? British neuropsychologist Mark Solms generalized his observations of patients with various neurological disturbances and noted that suppression of REM sleep in many patients with disruptions of the brainstem *is not accompanied* by the disappearance of subjectively experienced dreams. In contrast, no reports on dreams were observed in patients with lesions in an area that seems to have no relation to the regulation of REM sleep, viz., the ventromesial frontal white matter [44]. This area includes the projection DA pathway from the VAT/SNpc to the nucleus accumbens (NAcc) and further, to the frontal cortex (FC, Fig. 3). This area is damaged during the frontal leucotomy and this results in the disappearance of hallucinations and delirium, as well as dreams.

In addition to neurosurgical evidences, we also have psychopharmacological evidence of the important role of the DA system in the emergence of dreams. It is well known that schizophrenic symptomatology is associated with excess production of brain dopamine (along with a decrease in glutamate, noradrenaline, and serotonin) and is treated by suppression of DA transmission using haloperidol and other antipsychotics that suppress dreams. Conversely, insufficiency of DA transmission, which is typical of PD and induces motor disturbances, results in complete cessation of patient reports about dreams [45]. Treatment of PD with dopaminergic drugs (levodopa and others) results, according to patient reports, in drastic activation of the experiencing of dreams [46].

Thus, according to Solms, REM sleep and dreams are associated phenomena that in the norm occur simultaneously but they are not identical phenomena. This is root and branch divergence with the classical hypothesis of Jouvet, which was developed in the 1960s; he presented it not only in the scientific and popular literature but in fiction as well [47, 48]. If REM sleep is related to the activation of rhombencephalon and hypothalamic structures, which use glutamate, acetylcholine, GABA, and MCH as neuromediators, then the material basis of sophisticated psychological phenomenon such as the perception of emotionally saturated dreams includes activation of DA structures of the midbrain and frontal brain, according to Solms [44].

In summary, the involvement of DA neurons in the regulation of the sleep–wakefulness cycle consists in the maintenance of emotional manifestations of wakefulness and REM sleep. Therefore, the DA insufficiency that gradually develops during PD-induced neurodegeneration should be seen as an increase in sleepiness and a weakening of the expression of dreams. In addition, it may indirectly (via enhancement of GABAergic inhibition of the cholinergic PPT/LDT "REM sleep center" due to activation of the substantia nigra pars reticulata) induce some decrease in the total duration of REM sleep (a decrease in its frequency and/or shortening of its episodes), which is removed by DA drugs [49, 50].

In the end of this section on the role of DA in sleep disturbances in PD, we would like to note that the experimental models of parkinsonism caused by damage of DA neurons in SNpc/VTA have given very contradictory results for symptoms of disturbance of the sleep–wakefulness cycle, which were expected to be similar with the symptoms of PD patients. Thus, partial damage to all the DAergic systems of black C57 *mice*, which was induced by a 5-day daily single systemic injection of a low dose (25 mg/kg) of the neurotoxin MPTP, resulted in only a moderate increase in the duration of REM sleep at certain times of the records [51]. The effects appeared only 20 days after intoxication and disappeared by 40 days despite irreversible damage to DA neurons of the SNpc [52]. It is interesting that a selective pharmacological increase in the synaptic content of dopamine (by a systemic administration of its re-uptake inhibitor) in this model led to suppression of REM sleep, which was more pronounced than in the control mice. Administration of a noradrenaline reuptake inhibitor, viz., the antidepressant desipramine, had a similar effect. However, another antidepressant, the serotonin reuptake inhibitor citalopram, suppressed REM sleep in both experimental and control mice to the same extent. The agonist of muscarinic receptors arecoline caused an increase in the total duration of REM sleep in experimental but not control mice. In general, mice with a disrupted DA system appeared to be much more sensitive to the administration of drugs that modulate aminergic and cholinergic brain systems than control animals [53].

Local injection of 0.2 mg of MPTP to the SNpc of Wistar *rats*, which causes a 50% disruption of DA neurons, resulted in alteration of several parameters of the wakefulness–sleep cycle, in particular, to an almost twofold increase in the total duration of slow wave sleep during the dark (active) period on the 2nd and 3rd days after intoxication and to biphasic oscillation of the total duration of REM sleep. On the 1st and 2nd days after toxin administration, a considerable decrease in the total duration of REM sleep occurred during both the dark and light periods of the day; on the 3rd day, it occurred only during the light (inactive) period; on the 4th day, the total duration of REM sleep increased during the light and dark periods, which looked like a "rebound"; on the 5th day, the total duration of REM sleep returned to the norm. Interestingly, a high correlation was found between the total duration of REM sleep during the first day after intoxication and the percentage of lost DA neurons in the SNpc, which was found after immunohistochemical analysis of the brain tissue 5 days after toxin administration [45].

An increase in REM sleep was caused by substantial selective damage to the nigrostriatal system, which was induced by a local administration of the neurotoxin lactacystin into the SN of Wistar rats [54].

Like mice, but in contrast to rats [55], *cats* were also quite sensitive to systemic administration of MPTP [56]. A 5-day daily single intraperitoneal injection of 5 mg/kg of this neurotoxin resulted in selective suppression of REM sleep after the first administration. The effect was maintained for 6–9 days after the end of the injections and was associated with some increase in the total duration of slow wave sleep. This suppression was reversible and recovered along with the recovery of motor activity. Morphological control showed damage of neurons predominantly in the substantia nigra [57].

In experiments with *monkeys* (macaques) systemic toxic doses of MPTP induced irreversible suppression of deep slow wave and REM sleep and disruption of periodicity [58]. A recently performed study on the effects of the systemic administration of MPTP to rhesus macaques confirmed these data. This study showed irreversible disruption of sleep structure, suppression of deep slow wave sleep and the complete disappearance of REM sleep (with subsequent partial recovery) with frequent night awakenings and transient day time sleepiness. Histological analysis confirmed substantial damage of neurons in the SNpc area [59].

In marmosets, systemic doses of MPTP, which induce small motor disturbances, did not influence the structure of the sleep–wakefulness cycle, excluding the appearance of muscle tone during REM sleep, which is an RBD predictor [60].

THE NARCOLEPSY-LIKE THEORY OF SLEEP AND WAKEFULNESS DISTURBANCES IN PD

It seems that the complex of sleep disturbances in PD involves some other systems in addition to DA. As we mentioned above, one of characteristic non-motor symptoms and possible early marker of PD is daytime sleepiness [24, 25, 61]. It is obvious that daytime sleepiness should be determined by preceding disturbance of night sleep; however, not all studies on the correlation between these two phenomena in PD lead to this conclusion. No correlation has been found between the degree of sleepiness (in preliminarily selected patients with excess daytime sleepiness) with the quality of preceding night sleep and the strength of its disturbance (duration of sleep, efficacy of sleep, indices of activation, apnea-hypopnea, and periodic move-

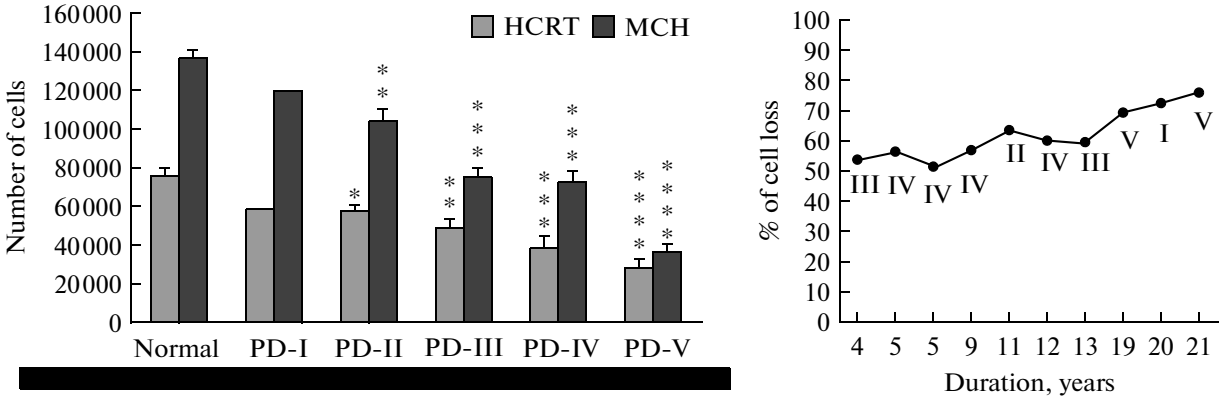

Fig. 4. *Left*: the numbers of orexin/hypocrein (HCRT, grey bars) and MCH (black bars) neurons (Ordinate axis, number of cells) in the hypothalamus of a healthy human (Normal) and patients with Parkinson's disease (PD) of I–V stages (Abscissa axis); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$, significant differences as compared to the norm (Student's *t*-test). It is seen that the number of nerve cells progressively decreases with an increase in the severity of the disease. *Right*: percentage of loss of neuronls (Ordinate axis, % of cell loss) with neuromelanin pigmentation (presumably, dopaminergic) in the hypothalamus of PD patients. Abscissa axis: duration of the disease in years. Roman numerals, stage of disease. It is seen that cell loss is related to disease duration but not severity. Reprinted with permission from [70].

ments of extremities) [62]. Moreover, a paradoxical finding has been made, viz., greater sleepiness during the daytime was associated with a higher sleep duration and sleep efficiency during the preceding night, as well as with a smaller total duration of the stage 1 and a smaller latent period of night sleep [63]. This means that patients that slept better during the night had greater sleepiness (fell asleep faster) during the next day.

If daytime sleepiness during PD is not related to sleep disturbances during a preceding night, then what is its cause? It is logical to hypothesize that daytime sleepiness during PD is "primary." This appears to be quite similar to narcolepsy, because, in general, sleep disturbances in PD are very similar to the disturbances in narcolepsy, especially so-called "narcolepsy without cataplexy" (Table 2). This similarity served as a basis for a hypothesis on a narcolepsy-like (i.e., orexinergic) mechanism of sleepiness during parkinsonism [13, 16, 23]. Narcolepsy is substantially less common than PD, it is an autoimmune disease with unknown etiology whose mechanisms were completely discovered in the 1998–2001 period after description of the orexin/hypocretin system of the brain [26, 64–66]. This mediatory system appears to be completely disrupted in patients with typical form of narcolepsy (i.e., with cataplexy). The level of orexin in the liquor of these patients falls below the level of sensitivity of the method that is used for its measurement and partially decreases in patients with narcolepsy without cataplexy, whose level of orexin is substantially below norm.

After the discovery of the orexin system, it was hypothesized that it is also disrupted in PD [67]. This hypothesis was confirmed only in 2007 when two independent groups in Europe and the USA found considerable degeneration of orexin neurons in the brains of patients with PD during postmortem studies [68–71]. Moreover, Siegel's group [70] showed that PD is also accompanied by disruption of the MCH system of the brain, which is "reciprocal" for the orexin/hypocretin system [72] and remains functional in patients with narcolepsy. The stage of the disease was related to the degree of disruption of orexin and MCH neurons but not DA neurons (Fig. 4). According to some authors, DA neurons only mediate motor disturbances caused by disruption of the orexin system [73]. These revolutionary data were initially opposed by a group of major European neurologists [74] but currently they are generally accepted [75, 76].

DOPAMINERGIC DRUGS AND DAYTIME SLEEPINESS

Although intake of selected doses of dopaminergic drugs by patients with PD results in normalization of night sleep due to suppression of night motor symptomatology (the inability to turn in bed, night rigidity, and night tremors) clinical studies showed that all dopaminergic drugs induce elevated daytime sleepiness.

It is known that there are two subfamilies of DA receptors. The first includes the D1 and D5 receptors and the second subfamily consists of the D2, D3, and D4 receptors. It has been shown that stimulation of D1 receptors enhances wakefulness and suppresses sleep; in contrast, stimulation of D2 has complex effects. Small doses suppress wakefulness and increase the total duration of slow wave and REM sleep due to the predominant activation of DA presynaptic autoreceptors. Large doses have the opposite effect, which is similar to the action of D1 agonists, due to the predominant activation of postsynaptic D2 receptors. Antagonists of both types of receptors increase the total duration of slow wave sleep and suppress wakefulness. According to some data, agonists of D3 recep-

Table 2. A comparison of some of the characteristics of PD and narcolepsy

Characteristics	Parkinson's disease	Narcolepsy
Nature	Neurodegenerative	Autoimmune
Damaging factor	Unknown; presumably, exotoxic, bacterial, or viral nature	Unknown; presumably, preceding streptococcus or viral infection
Distribution	Relatively frequent (150–200 cases per 100000 people)	Rare (in Europe, 20–40 cases per 100000 people)
Location of lesions in the brain	At the beginning of the disease, motor nucleus of the medulla oblongata and olfactory nuclei of the forebrain; later, the DA SNpc/VTA system, hypothalamic nuclei (including orexin/hypocretin and MCH systems) and the brainstem RF of different neurochemical nature; in the final stages, associative zones of the neocortex	Exclusively in the orexin/hypocrein brain system
Degree of damage	DA system, total or subtotal; other systems, including orexin/hypocretin and MCH system, substantial	Orexin/hypocretin system, total or subtotal
Limitations of damage	Cytomophological (presence/absence of a thick myelin sheath)	Neurochemical (synthesis/release orexin/hypocretin)
Age of the usual appearance of the first symptoms	After 40 years	Usually after 20 years but may appear in childhood
Time course of the disease	Continuously progressing until complete disability	Progression is possible during the first 20–30 years. Despite some limitations and difficulties, patient maintains the ability to take care of himself and participate in social life
Lethality	Fatal	Non-fatal
Treatment	Specific treatment is absent. Symptomatic treatment is used. Neuroprotective treatment is developed	Specifics are developed (stage of clinical trials). Symptomatic treatment is used
Disturbances of the sleep–wakefulness cycle		
Cataplexy	Never	Frequent abrupt loss of muscle tone, usually in response to positive or negative emotions. Depending on its presence or absence, narcolepsy is subdivided into narcolepsy with cataplexy and narcolepsy without cataplexy
Cataplexy during awakening and falling asleep ("sleep paralysis")	Never, may be confused with hypo/akinesia of the "off" period	Impossibility of movement during awakening or falling asleep
Daytime sleepiness	Frequently strong. "Sleep attacks", patient may fall asleep even during activity (during driving or cooking)	Strong, leading inescapably to falling asleep (the patient cannot resist their appearance) even during activity (during work or driving)

Table 2. (Contd.)

Characteristics	Parkinson's disease	Narcolepsy
Disturbance of night sleep	Sleep fragmentation. A decrease in total sleep time	Sleep fragmentation
RBD	Frequent	Seldom
Hallucinations	Appear in one third of all cases; appearance is related to treatment with agonists of dopamine receptors; serves as a prognostic characteristic of the development of psychoses	Hypnagogic (during falling asleep) and hypnopompic (during awakening). These have subjects that are different from psychotic hallucinations. Narcolepsy is never associated with psychoses
Results of night polysomnographic recording	Sleep fragmentation, sometimes difficulties in falling asleep	Sleep fragmentation, rapid falling asleep, decreased latency to paradoxical sleep
Results of Multiple Sleep Latency Test	There are patients with development of REM sleep during the first 15 min in two or more cases and decreased latency to sleep	Out of four nap opportunities, a minimum of two start from REM sleep; the mean time to sleep is below 8 minutes

tors have the sleep-promoting effect in humans and laboratory animals [77].

An increase in the extracellular level of dopamine (in knockout mice without the gene for the dopamine reuptake transporter) results in the appearance of hippocampal discharges that are similar to the discharges that occur during so-called "paradoxical sleep without atony" (see below). These discharges disappear after administration of an antagonist of D2 receptors, haloperidol. A considerable decrease in the DA content (the same knockout mice + administration of an inhibitor of dopamine synthesis) completely eliminated the phase of REM sleep and slow wave waves occurred in the hippocampus; this effect was cancelled by D2 agonists and D1 did not influence it [78].

It is probable that therapeutic doses of DA drugs correspond to small doses during physiological experiments, i.e., they induce daytime sleepiness; an agonist of D3 receptors, pramipexole, has the strongest effect. Treatment with DA agonists also results in the appearance of sudden daytime sleep ("sleep attacks"). Sudden daytime sleep occurs, as a rule, at a peak of the concentration of these drugs in the blood [25].

It has been hypothesized that some sleep disorders that are traditionally related to PD may be a consequence of not only the disease itself but its pharmacological treatment! In fact, selective agonists of DA receptors of the first type increase the wakefulness time and decrease the time spent sleeping.

Theoretical considerations suggest that a decrease in the dose of DA drugs in combination with treatment with antagonists of adenosine A1 and A2 receptors (for example, caffeine) should result in a decrease in daytime sleepiness without enhancement of motor disorders [23]. The mechanism of the notorious activating actions of food methylxantines (caffeine from coffee, theophylline from tea, and theobromine from cacao) is associated with the blockage of adenosine receptors. This, in its turn, cancels the inhibitory effect of endogenous adenosine, which appears in the intercellular liquid as a result of the normal metabolic activities of neurons and glia, on histaminergic and orexinergic "wakefulness centers." In addition, antagonists of adenosine receptors also have a dopaminomimetic effect on the corticostriatal inputs, which weakens the motor disturbances that are induced by DA insufficiency in PD [23].

REM SLEEP BEHAVIOR DISORDER (RBD) IS A PROMISING EARLY MARKER OF PD

As we mentioned above, RBD is another early parasomnia disorder in PD [13, 79]; it is a phenomenon that to some extent is opposite to narcoleptic cataplexy. The latter disorder is characterized by inadequate *disappearance* of muscle tone (directly from wakefulness but not close to the end of each sleep cycle, during the transition from slow wave sleep to REM sleep). In contrast, RBD is characterized by inadequate *occurrence* of muscle tone and voluntary movements during REM sleep, when they should be suppressed [43].

Locomotor and behavioral activities in REM sleep were found in the middle of the 1960s in experiments with cats with electrolytic disruptions in the area of the locus coeruleus (LC) by the outstanding somnologist Michel Jouvet and his collaborators and called "oneiric behavior" [80]. This phenomenon, viz., motor and behavioral activity in REM sleep, was later studied in detail by Morrison et al. [81–83] in cats and rats and was referred to as "paradoxical sleep without atony." A considerable contribution to studies on this problem was also made by Siegel's laboratory [84]. For 2 decades "paradoxical sleep without atony" did not attract the

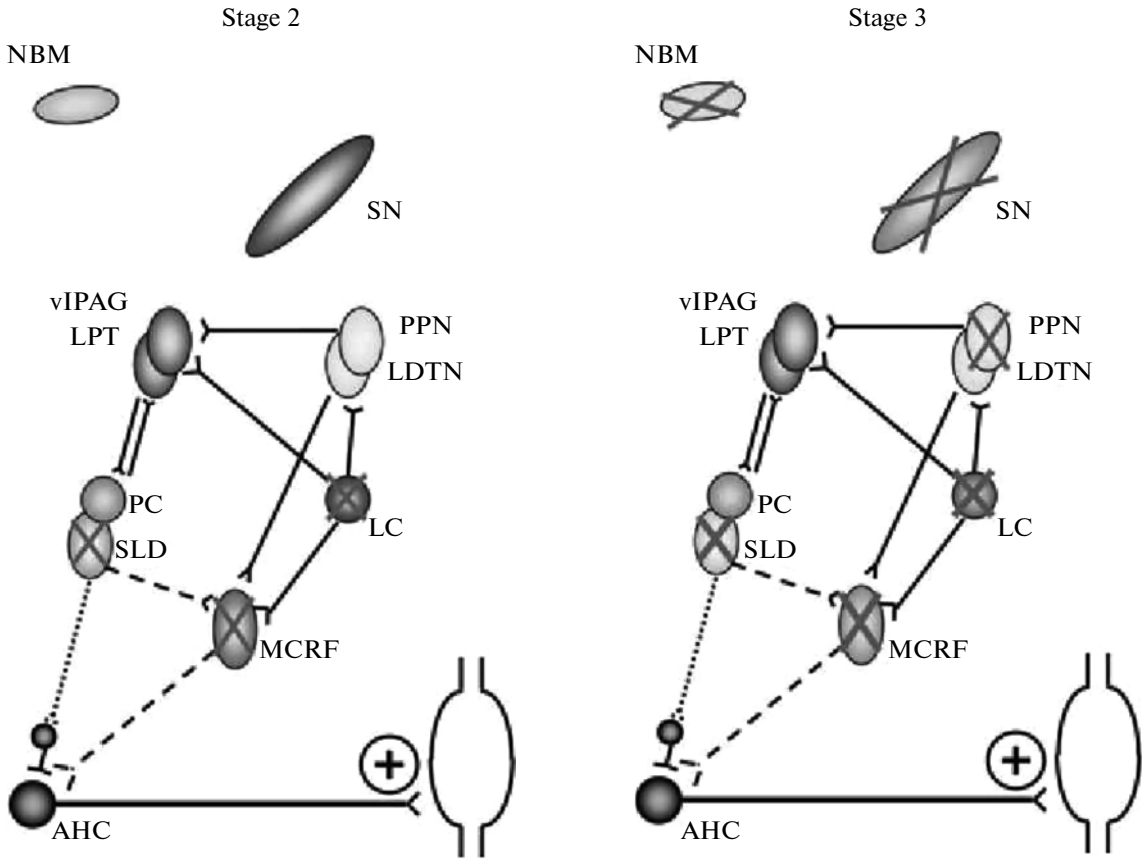

Fig. 5. Schemes of the brainstem nuclei and connections that are related to REM sleep, movements, and cognitive activity. In accordance with six Braak stages (Fig.1), successive development of alpha-synuclein pathology and neurodegeneration begins from the medulla oblongata and olfactory brain and ends in the neocortex. The first stage (not shown) includes lesions of motor nuclei of IX/X nerves, the intermediate reticular zone, and the olfactory bulb. During the second stage (left), the number of Lewy bodies in the structures that are involved in the process at stage 1 increases; caudal raphe nuclei, magnocellular nucleus of reticular formation (MCRF), structures adjacent to the locus coeruleus (peri-LC), and, presumably, sublaterodorsal nucleus (SLD) also become involved. We believe that RBD occurs when damage of the three latter nuclei reaches a certain degree. During stage 3 (right), pathology increases in the structures that are involved in the process at stage 2. It also overwhelms the pedunculopontine nuclei (PPN), substantia nigra (SN), and nucleus basalis of Meynert (NBM). After the achievement of a certain extent of SN damage, some features of parkinsonism appear; after degeneration of the NBM, cognitive disturbances occur. At stages 4–6 (not shown) alpha-synuclein pathology and neurodegeration involves limbic and neocortical structures. This temporal sequence of the development of pathology explains the fact that in many patients with Lewy bodies, RBD precedes parkinsonism and dementia.

Abbreviations: AHC, anterior horn cells; LC, locus coeruleus; LDTN, laterodorsal tegmental nucleus; LPT, lateral pontine tegmentum; MCRF, magnocellular reticular formation; NBM, nucleus basalis of Meynert; PC, precoeruleus; PPN, pedunculopontine nucleus; SLD, sublaterodorsal nucleus; SN, substantia nigra; vlPAG, ventrolateral part of the periaqueductal gray matter. Reprinted with permission [87].

attention of clinicians because it was considered to be a laboratory phenomenon. However, in 1986 Carlos Schenck et al. described this pathology in five elderly men with serious neurological disorders and referred to it as "REM behavioral disorders" (RBD) [13, 85]. After this, dozens of reports were published on various RBDs during brainstem lesions that occurred due to the development of neurodegenerative and autoimmune diseases, strokes, traumas, and tumors. Finally, in 2007, twenty leading specialists, neurologists, and neurophysiologists from the USA and Germany combined their efforts and published a fundamental review that summarized (at that moment) all the knowledge on this problem [86]. The authors analyzed everything that is known on the mechanisms of the generation of REM sleep in the classical model of the cat brain and the considerably better studied model of the rat brain, and tried to extrapolate these data to the human brain, where these mechanisms have been much more poorly studied, for obvious reasons, (Fig. 5) [87].

Pierre-Herve Luppi, one of the authors of the "rat" model of the regulation of REM sleep and a disciple and successor of Michel Jouvet, concluded in a recent review, which was written together with a group of his collaborators, that the development of RBD in this model may have two causes. The first cause is specific disruption of a small group of glutamatergic "PS-on" neurons that are located in the SLD and are responsi-

ble for muscle atony in REM sleep. The second cause is the specific disruption of GABA/glycinergic premotoneurons located in the ventral magnocellular nucleus of the medulla oblongata (this approximately corresponds to the MCRF) [43].

THE RESTLESS LEGS SYNDROME IS A DISEASE THAT IS ASSOCIATED WITH PD; IT PRESUMABLY HAS SIMILAR MECHANISMS

One more interesting disease associated with PD, which is accompanied by disruption of falling asleep and fragmentation of night sleep, is the restless legs syndrome (RLS). This pathology is a sensorimotor disorder. Patients suffer from unpleasant (burning, prickling, and formication) and sometimes painful sensations, which frequently develop in legs but also may involve the hands and body. These sensations frequently occur in the evening and night during relaxed wakefulness or when lying down and decrease or practically disappear during movement [88].

In RLS, the patient has problems with falling asleep, which are associated with the appearance of unpleasant feelings when lying down and the necessity to move their legs or even get up to walk. Even when the patient manages to fall asleep, sleep is defective, because RLS is always accompanied by periodic limb movements disorder. Periodic limb movements are involuntary movements, as a rule, of legs, which vary from movement of the toe to movements of the entire legs, which result in frequent EEG arousals and awakenings.

Why is RLS is associated with the pathology of DA systems? No exact pathology of dopaminergic system in RLS has been found, only indirect data exist. These patients have a hypersensitivity to levodopa, which to a greater extent, as compared to the control group, decreased the level of prolactin and increased the level of growth hormone (which is one of the actions of dopamine) [89]. In RLS, the concentration of DA metabolites is lower than in the control; in addition, the level of metabolites is lower in the evening than in the morning [88]. Of the five genes that are involved in the inheritance of RLS, at least one is related to DA transmission.

RLS frequently occurs during iron insufficiency (including pregnancy) and in a number of neurological pathologies (including PD) [90]. It has been proven that a decrease in the iron level results in RLS and iron insufficiency and may result in the disruption of dopamine metabolism. This is supported by the following facts: iron is irregularly distributed in the brain, predominantly in the DA areas, in particular, in the striatum and substantia nigra; iron is a co-factor of tyrosine hydroxylase (an enzyme that is necessary for dopamine synthesis) and is contained in D2 receptors [88]. An important role of dopamine in the development of RLS is irrefutably supported by the fact that RLS is completely negated by treatment with small doses of agonists of DA receptors.

CONCLUSIONS

PD, unlike any other CNS disease, is characterized by an unusually wide spectrum of sleep disorders, which include both unspecific disorders that are typical of many other diseases (excessive daytime sleepiness, frequent night arousal, and apnoea during sleep) and specific disorders that are typical of this pathology (RBD). Hence, PD, which is a tragedy for patients with this incurable disease with an unknown etiology, is of huge interest for science. PD is a unique experiment that is made by nature itself that reveals the roles of various neurochemical systems of the brain in the regulation of fundamental mechanisms of life, such as the wakefulness–sleep cycle. Accumulation of α-synuclein and loss of DA-containing, orexin-containing, and MCH-containing neurons of the mesencephalon and midbrain result in a decrease in the general level of ascending activation, disruption of the control of the intrinsic rhythmicity of brain function, suppression of REM sleep, and a decrease in its quality [91]. It is very important that some wakefulness–sleep cycle disorders occur long before the appearance of the motor symptoms of PD and, thus, may serve as a reliable early predictor of this disease.

However, despite the considerable number of experimental models, only a few papers have described sleep disorders that are similar to PD and parkinsonism, first of all, suppression of REM sleep and its regulation. This is not surprising, especially if we take the fact into account that current models of PD exclusively include models with neurotoxic, neurosurgical, and neurogenetic disruptions of the DA brain systems, whereas the formation of the pathology involves a number of other neurochemical systems, first of all, the orexinergic and melaninergic systems and possibly the glutamatergic system.

Thus, the presented clinical and experimental data on the disruption of the wakefulness–sleep cycle in PD and on the physiological and biochemical mechanisms that are, presumably, involved in these processes point to the necessity for more detailed studies and the development of new experimental models. In our opinion, recent models of parkinsonism, for example, in mice that were systemically treated with increasing doses of MPTP [92] or transgenic mice with excess expression of human α-synuclein [93] are very promising.

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