

REVIEW ARTICLE

THE ROLE OF CIRCADIAN REGULATION OF GHRELIN LEVELS IN PARKINSON'S DISEASE (LITERATURE REVIEW)

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ABSTRACT

The paper is aimed at the analysis of the role of the circadian regulation of ghrelin levels in patients with Parkinson's disease.

Based on the literature data, patients with Parkinson's disease have clinical fluctuations in the symptoms of the disease, manifested by the diurnal changes in motor activity, autonomic functions, sleep-wake cycle, visual function, and the efficacy of dopaminergic therapy. Biological rhythms are controlled by central and peripheral oscillators which links with dopaminergic neurotransmission – core of the pathogenesis of Parkinson's disease. Circadian system is altered in Parkinson's disease due to that ghrelin fluctuations may be changed. Ghrelin is potential food-entrainable oscillator because it is linked with clock genes expression. In Parkinson's disease this hormone may induce eating behavior changing and as a result metabolic disorder.

The "hunger hormone" ghrelin can be a biomarker of the Parkinson's disease, and the study of its role in the pathogenesis, as well as its dependence on the period of the day, intake of levodopa medications to improve the effectiveness of treatment is promising.

KEY WORDS: circadian rhythms, clock genes, ghrelin, Parkinson's disease, dopaminergic system

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease accompanied by the motor and nonmotor disorders, which often precede the onset of motor symptoms by 15-20 years.

The complex lesion of dopaminergic systems is associated not only with the onset of motor disruptions, but also with a wide range of autonomous, sensory, affective, cognitive manifestations that can occur at the preclinical stage of the disease, sometimes long before the manifestation of classical motor disorders. The incidence and severity of nonmotor disorders correlate with the duration of PD and the severity of motor disruptions [1]. A number of known nonmotor symptoms of PD have a diurnal component, which indicates that they are based on circadian dysfunction. Clinical fluctuations in symptoms of the disease involve diurnal changes in motor activity, autonomic functions, sleep-wake cycles, visual function, and the effectiveness of dopaminergic therapy [2-10]. The observations indicate circadian rhythm disorder in PD. The most significant are the different types of sleep and activity disorders in PD.

PD patients often experienced rhythm disruption and other physiological disorders, which also indicate circadian dysfunction. It is known that PD causes disorder of autonomic regulation of the cardiovascular system, which is closely related to the sympathetic cardiac denervation due to the loss of postganglionic sympathetic fibers of the cardiac nerves [11-13]. PD also causes circadian disruptions in the autonomic nervous system.

Circadian disruptions in the autonomic nervous system regulation lead to alterations of blood pressure and heart rate of patients with PD. In particular, daily monitoring of patients' blood pressure

showed inversion of the circadian rhythm of arterial blood pressure, afternoon hypotension and nocturnal hypertension [1,6,11].

Another example of the autonomic nervous system dysregulation in patients with PD can be the symptoms of urinary disorders: nocturia, frequent urination and urinary incontinence can be [28-30]. Control of urination is provided primarily by dopaminergic mechanisms, and their dysfunction can lead to bladder hyperactivity [1,2,7].

Among the nonmotor symptoms caused by disruption of the circadian rhythms are metabolic disorders, manifested by changes in basal metabolism, body weight, nutritional imbalance, are notable/ But it is unclear about the role of circadian regulation of "hunger hormone" ghrelin in patients with PD.

THE AIM

The paper is aimed at the analysis of the impact of the circadian system on the ghrelin levels in Parkinson's disease.

REVIEW AND DISCUSSION

Currently, much of the evidence correlate sleep disturbances, reduced sleep duration, sleep fragmentation and excessive daytime sleepiness with disruption of temporary sleep-wake pattern, which often occurs due to circadian dysfunction [11-13]. Consequently, it can be stated that circadian disorders contribute to the development of insomnia and hypersomnia in PD. Melatonin is the key pacemaker of circadian rhythms, regulated by the central circadian oscillator.

Normally, the central circadian “clock” is located in the suprachiasmatic nucleus (SCN), which sends its projections to the dorsal paraventricular nucleus of the hypothalamus, with its axons descend into the spinal cord in the upper cervical region. Neurons of the paraventricular nucleus promote changes in the balance between the sympathetic and parasympathetic tone of the autonomic nervous system in concordance with the period of the day.

At the cellular level, circadian rhythms are provided by the rhythmic expression of the clock genes *Per1*, *Per2*, *Per3*, *Cry-1*, *Cry-2*, *Clock*, *Bmal1* and others. Their expression is controlled by the transcription-translation feedback loop, which consists of the transcription factors *BMAL1* and *CLOCK*, forming the heterodimer [14-16].

SCN is an important part of the higher hypothalamic “regulatory center”, which translate circadian signals into biological rhythms: activity-rest, sleep-wake, food and drink, secretion of melatonin and corticosteroids, body temperature, and more.

Dopaminergic neurotransmission exists at different levels of the circadian system. In the retina of vertebrates, dopamine concentrations increase during the daytime and decrease at night, obeying circadian regulatory influences [15,16] and the action of light, which stimulates the synthesis, circulation and release of retinal dopamine [12,13,16].

Dopamine is one of the mediators of non-visual reactions to light, in particular, changes in the rhythm of clock gene expression. In both SCN and retinal cells, the molecular oscillator is to be the interconnected translation-transcription cycles of clock genes and their protein products [12, 15-17].

The involvement of dopamine in circadian regulation is not limited to the peripheral parts of the visual system. Dopamine through D1- and D2- receptors is involved in the regulation of clock gene expression in the dorsal striatum [15-18].

Among the rhythms and clock mechanisms, dopamine is primarily related to those ones associated with the reinforcement system. Feeding promotes changes in the motivational state of animals, leading to increasing dopamine and increased expression of the *Period* gene in the forebrain of mice, accompanied by activation of *c-FOS* in dopaminergic and orexinergic neurons, indicating that the influence of feeding rhythm on SCN is mediated by the reward and activation systems [17-19]. With the development of the disease, and then with the beginning of treatment, the lifestyle of patients, their habits and pace of life completely changes. Several clinical studies have established a link between the duration of PD, the severity of motor and nonmotor symptoms and changes in eating behavior of patients.

The main cause of this condition may be a decrease in energy intake and / or increased energy expenditure due to swallowing disorders, gastrointestinal dysfunction, as well as rigidity, tremor and complications from levodopa therapy, which may increase glucose metabolism, leading to increased energy expenditure. Comorbid conditions, antiparkinsonian drugs, movement disorders, bulbar disorders can lead to reduced food intake and contribute to weight loss in PD.

A possible correlation of abdominal obesity with an increased risk for the development of PD has been described. The body mass index of patients affects the progression of PD, since obesity causes the loss of dopamine neuronal cells in the substantia

nigra (SN) in the mice model of PD (Choi et al., 2005), and middle-aged obesity and type 2 diabetes are associated with a higher incidence of PD in humans (Chen et al., 2014).

The control over the regulation of food and energy metabolism depends on the interaction of energy homeostasis, emotional factors. These complex regulations ensure interconnection of neurons of the homeostatic and hedonic systems that receive and integrate multivalued orexigenic and anorexigenic signals from the peripheral tissues regarding the concentration of nutrients in the blood, as well as other parts of the central nervous system. The neuronal “hunger pathway” includes neurons in the arcuate nucleus containing orexigenic peptides. These neurons are projected onto the lateral hypothalamus, called the “hunger center”, which contains populations of neurons that produce orexigenic peptides. Loss of orexin leads to loss of appetite and slow metabolism. Another population of neurons in the arcuate nucleus encodes satiety. These neurons produce numerous anorexigenic peptides, such as α -melanocyte-stimulating hormone. Together with their receptor, these peptides make up the melanocortin system, which plays an important role in energy homeostasis. The interaction of this system with dopamine neurons has been described [17-22]. The availability of multiple, circulating signals by which circadian oscillators in many brain regions might entrain to mealtime has supported a view that food-anticipatory rhythms of behavior are mediated by a broadly distributed system of clocks. The evidence, however, does not rule out the possibility that multiple peripheral and central food-entrained oscillators and feeding-related signals converge on circadian oscillators in a defined location which ultimately set the phase and gate the expression of anticipatory activity rhythms. A candidate location is the dorsal striatum, a core component of the neural system which mediates reward, motivation and action and which contains circadian oscillators entrainable by food and dopaminergic drugs. Systemic metabolic signals, such as ghrelin and leptin may participate in circadian food anticipation to the extent that they modulate dopamine afferents to circadian clocks in this area [23,24].

Peripheral signals of appetite regulation provide bidirectional homeostasis in response to peripheral stimuli that reflect the actual level of nutrition. The feeling of satiety activates gastric distension, intestinal peptides secreted in the postprandial state, metabolites, namely, fatty acids and glucose, and hormones, namely, insulin and leptin. Leptin is a hormone that is synthesized and secreted by the adipose tissue. The level of leptin in blood serum indicates the degree of development of adipose tissue. Elevated leptin reduces food intake. In patients with PD who have lost body weight, the level of leptin is low, which increases in body weight gain [25-27].

Another hormone of the gastrointestinal tract, which directly affects the centers of hunger and satiety of the hypothalamus, is ghrelin. Ghrelin, reduced in PD, is considered a potential biomarker of the disease. It consists of 28 amino acid residues obtained by sequential proteolytic degradation of the protein precursor proghrelin and proghrelin [23,26,27].

Up to 70% of circulating ghrelin in humans is synthesized by enteroendocrine P / D1- cells of the gastric mucosa. In addition to the stomach, ghrelin is produced by the cells of the ileum, small intestine and duodenum and in small quantities by the

pancreas, liver, placenta, testicles, hypophysis, lungs, kidneys, thyroid gland, lymphoid organs and immune systems. A small number of ghrelin-producing neurons are also found in the arcuate nuclei of the hypothalamus, which are important structures in realization of the ghrelin effects.

Ghrelin is the only known orexigenic hormone from the periphery that stimulates feeding [20,26,27-29] and activity in humans in the hypothalamus. Currently research demonstrates strong endogenous circadian effect on ghrelin concentrations, with higher fasting and postprandial levels in the biological evening than the biological morning. Postprandial (but not fasting) hunger also showed a consistent circadian variation. The circadian effects on postprandial hunger was blunted following consecutive days of circadian misalignment, with a similar trend for ghrelin. The attenuation in the biological morning/evening differences may be due to blunted, shifted or otherwise disrupted circadian control, and is consistent with evidence from melatonin, cortisol, glucose, and diet-induced thermogenesis [29,30].

The increases in arousal and activity in anticipation of a regularly scheduled meal are believed to depend on a separate food-entrainable oscillator. Since plasma ghrelin levels not only surge prior to mealtime, but are also controlled by the circadian system, this orexigenic peptide imposed itself as a prime candidate output signal of the food-entrainable oscillator, that would be able to provide important metabolic input to the circadian system [31,32].

Some researchers state that endogenous circadian rhythm in hunger with a trough at a circadian phase equivalent to ~8AM and a peak at ~8PM. Potential neuroendocrine mechanism for the circadian rhythm in hunger—a circadian control of ghrelin levels. Ghrelin might mediate the circadian effects on hunger and circadian variation of its level may be mediated by the circadian clock in ghrelin-secreting stomach cells which can be entrained to prior feeding schedules [20,25,26,30-33].

Expression of the clock genes *BMAL1* in total leukocytes is decreased in PD patients. [30,31,33]. *Bmal1* deficiency was previously shown to interfere with circadian rhythm generation, both at the behavioral (locomotor activity) and molecular level (mRNA expression levels of other clock genes in the SCN and transcriptional output genes in the liver). Consistent with these results, the genetic deletion of the core clock gene *Bmal1* not only abolishes the circadian rhythmicity of ghrelin signaling and hence the circadian rhythm of food intake, but also attenuates the absolute mRNA production of ghrelin and *GOAT* [31].

On the other hand, animal studies of mice show that ghrelin may play a role in the circadian system by exerting a direct action on the SCN and that the system as a whole may become sensitive to ghrelin and other feeding-related neuropeptides under conditions of food restriction [34,35]. The plasma level of ghrelin fluctuates diurnally, with a peak in the day and a trough at night. Its level also varies with the feeding time. Circulating ghrelin may act on the circadian system as a potential feedback signal for the SCN. Silver and coworkers have discovered that ghrelin modulates the expression of *Per1* and *Per2* in the stomach. This observation indicates that ghrelin can also

regulate the oscillation of the peripheral circadian rhythm. Ghrelin stimulates appetite through receptors located in the mesolimbic system. It has been proved that the plasma ghrelin is low in PD and paradoxically correlate with the body mass index (BMI) [30,34]. Decrease in postprandial ghrelin level is observed at the early stages of PD, which is not modified by dopamine treatment or acute stimulation. Hypothalamic control of feeding is modulated by the dopaminergic system and both systems are regulated by homeostatic orexigenic and anorexigenic signals, such as ghrelin and leptin [35-37]. Dopamine and the dopamine D2 receptor play the key role in motivated behavior, including eating behavior [38,39]. However, the role of the dopaminergic system in the process of eating behavior is very complex and not fully understood. In Parkinson's disease, ghrelin increases the survival of dopaminergic cells by reducing the activation of microglia and caspases, improving mitochondrial function. Since mitochondrial dysfunction promotes the development of Parkinson's disease, any agent that enhances mitochondrial function may be a potential therapeutic target [40].

CONCLUSIONS

Biological rhythms are controlled by central and peripheral oscillators which links with dopaminergic neurotransmission – core of the pathogenesis of Parkinson's disease. Circadian system is altered in Parkinson's disease due to that ghrelin fluctuations may be changed. It can be possible cause of eating behavior disruption in these patients, but, it is promising to study the role of ghrelin in the pathogenesis of Parkinson's disease, its dependence on the period of the day, intake of levodopa medications to improve the effectiveness of treatment.

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The Authors declare no conflict of interest.

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