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THE ANALYSIS OF THE CHANGE IN GHRELIN LEVEL IN PATIENTS WITH DIFFERENT FORMS OF PARKINSON'S DISEASE

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The aim of our study was to analyze diurnal fluctuations in hunger hormone level in patients with akinetic-rigid and mixed forms of Parkinson's disease. The clinical studies have confirmed changes in the ghrelin level with a tendency to increase in the evening in patients of the control group and insignificant diurnal fluctuations in the level of ghrelin in patients with Parkinson's disease with a tendency to decrease. It has been revealed that in patients with mixed form of the disease, the ghrelin level is lower compared to controls. The human circadian system regulates hunger independently of behavioral factors. There is a large endogenous circadian rhythm of hunger, with a peak in biological evening and a minimum in biological morning. However, the neuroendocrine mechanisms by which the circadian system regulates hunger and appetite remain unclear. Ghrelin, a peptide secreted primarily by the stomach, is the only known circulating orexigenic hormone and a key element in a complex energy balance signaling network. The authors insist that further clinical research is needed to determine the relationship between the intake of antiparkinsonian drugs and the ghrelin level, which can significantly improve the clinical course of this disease.

Key words: Parkinson's disease, ghrelin, circadian rhythms.

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АНАЛІЗ КОЛИВАНЬ РІВНЯ ГРЕЛІНУ У ПАЦІЄНТІВ ІЗ РІЗНИМИ ФОРМАМИ ХВОРОБИ ПАРКІНСОНА

Метою нашого дослідження було вивчити добові коливання рівня гормону голоду у пацієнтів з акінетико-ригідною та змішаною формами хвороби Паркінсона. Проведені клінічні дослідження підтвердили зміни рівня греліну з тенденцією до його збільшення у вечірній час у пацієнтів контрольної групи і незначні добові коливання рівня греліну у пацієнтів із хворобою Паркінсона, з тенденцією до зниження. Виявлено, що у пацієнтів зі змішаною формою захворювання нижчий, порівняно з групою контролю, рівень греліну. Добова система людини регулює відчуття голоду незалежно від поведінкових факторів, Існує великий ендогенний циркадний ритм голоду з піком в біологічний вечір і мінімумом в біологічний ранок. Автори наполягають на тому, що необхідні подальші клінічне дослідження з метою визначення зв'язку прийому протипаркінсонічних препаратів з рівнем греліну, що може істотно поліпшити клінічний перебіг даного захворювання.

Ключові слова: хвороба Паркінсона, грелін, циркадні ритми.

The work is a fragment of the research project "The study of the pathogenetic role of the circadian molecular clock in the development of metabolic diseases and systemic inflammation and the development of treatment methods aimed at these processes", state registration No. 0120U101166, and "Clinical, molecular genetics and neurophysiologic features of the course of the various forms of Parkinson's disease", state registration No. 0119U102848.

Ghrelin is a peptide hormone with a wide spectrum of action in the human body, namely, it participates in the regulation of lipid and energy metabolism, growth, puberty, behavioral reactions, and also has immunomodulatory and anti-inflammatory properties [1, 2, 3]. The ghrelin receptor has two molecular forms: GHSR1A and GHSR1B, though biological activity is associated only with the GHSR1A form. GHSR1A receptors are located mainly in the islets of the pancreas, adrenal glands, thyroid gland, myocardium, as well as in the brain structures [3]. Moreover, the ghrelin systems are involved in the control of motor and emotional behavior in the formation of stress disorders. Corticoliberin-producing neurons of the paraventricular nucleus of the hypothalamus and a number of extrahypothalamic structures of the enlarged amygdala (central amygdala, nucleus accumbens, bed nucleus of stria terminalis and innominate substance), mediating mechanisms of reinforcement and dependence are considered as possible targets for the ghrelin involvement in the stress response [3].

Up to 70% of ghrelin is synthesized by enteroendocrine cells of the mucous membrane of the fundus of the stomach, and in smaller quantities it is produced by the jejunum, small intestine, duodenum, pancreas, liver, placenta, in the testicles, pituitary gland, lungs, kidneys, thyroid gland, immune organs. From the point of view of neurology, special attention is given to ghrelin, which is synthesized in the arcuate nuclei of the hypothalamus, where part of the ghrelin-produced neurons is located. This zone is an important part of the realization of the main effects of ghrelin [6].

Ghrelin acts as a neuroprotector in the degeneration of dopaminergic neurons in Parkinson's disease [6]. However, it is still unknown whether ghrelin can affect the neural stem cells of the midbrain, from which dopaminergic neurons originate. Studies have reported that ghrelin enhances the proliferation of these cells and promotes the differentiation of neurons, especially the differentiation of dopaminergic neurons both *in*

vitro and *ex vivo* [4]. Ghrelin can contribute to the clinical therapy of Parkinson's disease (PD) due to its role in neurogenesis.

Ghrelin has a prokinetic effect on gastrointestinal motility via the vagus and pelvic nerves. The pharmacological potential of ghrelin is limited by its short half-life. Thus, ghrelin receptor agonists (GRLN-R) with enhanced pharmacokinetics have been developed that stimulate defecation and improve impaired transit through the lower gastrointestinal tract in animals and humans [8].

The use of a long-acting, orally active ghrelin agonist may be seen as a promising means of alleviating the non-motor symptoms of PD associated with energy balance in patients with decreased water and food consumption, intestinal atony, and reduced body mass [8].

The concentration of circulating ghrelin is inversely correlated with blood arterial pressure, associated with modulation of the autonomic nervous system, direct vasodilatory activity and renal diuresis [7, 8].

The effects of ghrelin are impaired in the development of Parkinson's disease [11]. With the onset of the disease, the PD patients change their lifestyle and living habits, their mobility and sleep is disturbed, many other non-motor manifestations can appear, leading to a change in circadian rhythms. The study of the diurnal fluctuations in the ghrelin level in patients with neurodegenerative process, as well as the evaluation of the link with the intake of antiparkinsonian drugs is crucial [14].

The purpose of the present paper was to the study of diurnal fluctuations in serum ghrelin level in patients with different forms of Parkinson's disease.

Materials and methods. 51 patients, who received treatment at the Neurological Department of the ME "N.V. Sklifosovsky Poltava Regional Clinical Hospital of Poltava Regional Council" and the Center for patients with Parkinson's disease and other neurodegenerative diseases at the Department of Nervous Diseases with Neurosurgery and Medical Genetics of the Ukrainian Medical Stomatological Academy, have been examined.

The patients have been assigned into groups. Group I (n=16) involved patients diagnosed with Parkinson's disease, akinetic-rigid form; Group II (n=14) involved patients with mixed form of PD. The diagnosis was made according to the criteria of the UK Brain Bank. The severity of the disease was determined according to the Hoehn and Yahr scale. 21 patients without signs of neurodegenerative diseases have been assigned to control group.

All patients, after signing informed consent, underwent a general clinical neurological examination with the assessment of anthropometric parameters: height, weight. Body mass index (BMI) was calculated using the WHO formula (1997). In addition, the patients underwent laboratory test to determine the blood serum ghrelin using the enzyme-linked immunosorbent assay (ELISA) method at the Research Institute of Genetic, Immunological Foundations for the Development of Pathology and Pharmacogenetics of the Ukrainian Medical Stomatological Academy.

The study of the ghrelin level was carried out by the method using a standard set of reagents "Elisa kit (CEA991Hu)", (USA). The level of ghrelin (96 studies) was determined by the "competitive" ELISA method using the "Cloud-Clone Corp. (USA)" standard kit for the determination of ghrelin level in accordance with the manufacturers' instructions. Fasting blood serum ghrelin was estimated after 12-hour fast and 2 hours postprandially.

Statistical processing of the resulting data has been made using the IBM SPSS Statistics software package with the calculation of the mean value (M) and standard deviation (σ), descriptive methods, and calculating odds ratios. The Wilcoxon test was used to check for differences between associated patient groups. The Kruskal-Wallis test with a posteriori comparison on the Mann-Whitney U test was used to check the equality of medians between groups of patients. To analyze BMI and age in patient groups, we used a parametric ANOVA method with Bonferroni correction; the results are presented in mean values and standard deviations. The results were considered statistically significant in $p < 0.05$.

The study was carried out in compliance with the main provisions of the ICH GCP and the Helsinki Declaration on the Ethical Principles of Medical Research Relating to Human Subjects and its Revisions (Seoul, 2008), the Council of Europe Convention on Human Rights and Biomedicine (2007), recommendations of the Bioethics Committee at the Presidium of the National Academy of Medical Sciences of Ukraine (2002) and the relevant meeting of the Ethics Committee at the Bogomolets National Medical University.

Results of the study and their discussion. The examination has been revealed that patients of Group I and II, with mixed and akinetic-rigid forms of PD, are comparable in gender and age with the control group. All patients were examined according to the Hoehn and Yahr scale, as well as the UPDRS scale.

Table 1 shows that the average age of patients in Group I was 62.13±10.39 years, in Group II - 59.94±7.97 years and in the control group - 58.63±8.16 years; consequently, patients of Group I were slightly older than patients with akinetic-rigid form of the disease and patients of the control group.

Table 1

Age characteristics, body mass index and duration of the course of the disease in patient groups

Groups of patients	Age, years (M±SD)	BMI, kg/m^2, (M±SD)	Duration of the course of the disease, years ((M±SD)
Group I	59.94±7.97	27.13±3.59*	6.42±2.13
Group II	62.13±10.39**	25.4±3.93	9.13±1.87
Control group	58.63±6.16	22.41±3.37	-

Note: * - compared to control group ($p<0.05$); ** - between the patients of Group I and Group II ($p<0.05$).

The body mass index in the first two groups of patients with Parkinson's disease was excessive, which is consistent with a number of studies reported about increased risk for progression of the disease associated with overweight, including those with BMI over 23.

The body mass index in the patients of the studied groups was distributed as follows: 27.13±3.59 (Group I); 25.4±3.93 (Group II); 22.41±3.37 (control group). The above parameters show an increase in the BMI level, though they can be interpreted as "pre-obesity". These disorders in patients with Parkinson's disease are associated with several reasons. First of all, these are non-motor manifestations of Parkinson's disease, such as disorders of sleep and eating behavior associated with intake of antiparkinsonian drugs. It can be compulsive overeating with a subjective feeling of loss of control during overeating and a follow up distress, as well as night eating syndrome in PD patients.

The duration of the course of the disease in patients of Group I and Group II was 6.42±2.13 years and 9.13±1.87 years, respectively, which confirms the already studied fact that weight loss is associated with the progression of the disease, which means a decrease in BMI.

In our patients of Group II with akinetic-rigid-tremulous form of the disease, weight loss can also depend on mobility, less manifestations of rigidity compared to patients with akinetic-rigid form.

Table 2

The rates of diurnal fluctuations in ghrelin level in the patient groups

Forms of the PD	ghrelin level, Me (Q1-Q3), pg/mL		P-value (between morning and evening, Wilcoxon test)
	morning	evening	
mixed (n=14)	1275.33 (1132.68 – 1500.87)	1382.69 (1165.59 –1446.33)	0.652
akinetic-rigid (n=16)	1245.02 (864.94 – 1379.66)	987.01 (896.97 – 1393.08)*	0.993
controls (n=21)	1521.21 (1305.2 –1666.67)	1365.37 (1133.33 – 1507.36)**	0.049*
P-value – Kruskal-Wallis test (between the groups – Steel's test)	0.027 (1:3 = 0.029; 2:3 = 0.044)	0.048 (2:3 = 0.047)	-

Notes: * - in comparison between morning and evening ghrelin level in Group II / $p<0.05$); ** - in comparison between morning and evening ghrelin level in control group ($p<0.05$).

Ghrelin is associated with increased appetite: its fasting concentration is the highest that promptly falls postprandially. The maximum concentration of ghrelin is observed at night.

Table 2 shows that in patients of control group with normal body mass index, there is a pulsating concentration of blood ghrelin: the maximum in the morning, after wake up, with an increase in hunger (1521.21 pg/mL), and decreased after 2 -3 hours after evening meal (1365.37 pg / mL).

In the groups of patients with Parkinson's disease, there is a morning fall of ghrelin level, compared to patients in the control group: 1275.33 pg / mL in patients of Group I and 1245.02 pg / ml in Group II patients. Group I patients (mixed form of the disease) showed insignificant increase, compared to the morning rates of ghrelin level, and Group II patients (akinetic-rigid form of the disease) showed decrease in the morning and evening levels of ghrelin. These changes can be possibly related to patients' circadian rhythms and the duration and quality of their sleep.

The human circadian system regulates hunger independently of behavioral factors. There is a large endogenous circadian rhythm of hunger, with a peak in biological evening and a minimum in biological morning. This circadian rhythm of hunger may explain why, despite prolonged overnight fasting, people are often least hungry in the morning and skip breakfast. However, the neuroendocrine mechanisms by which the circadian system regulates hunger and appetite remain unclear. Ghrelin, a peptide secreted primarily by the stomach, is the only known circulating orexigenic hormone and a key element in a complex energy balance signaling network.

The central circadian pacemaker located in the suprachiasmatic nucleus affects the hypothalamic nuclei and related endocrine factors such as leptin, ghrelin, glucagon-like peptide, cholecystokinin, and insulin. It is currently unknown if a true endogenous circadian rhythm exists in ghrelin regardless of behavior, including sleeping and feeding, but there are circadian oscillators in the stomach, and ghrelin continues to

fluctuate under fasting conditions in mice and humans, with a drop in humans at around 8 a.m. potentially associated with the endogenous circadian hunger failure found in our study. Ghrelin, a peptide secreted primarily by the stomach, is the only known circulating orexigenic hormone and is a key element in a complex energy balance signaling network [10].

Obesity is a well-known risk factor for a number of metabolic and vascular disorders such as type 2 diabetes, coronary artery disease and stroke, some of which can be associated with Parkinson's disease. The link between obesity and the occurrence of Parkinson's disease is not fully understood. Some evidence suggests that being overweight, but not obese, is associated with an increased risk of PD. Consideration of potential confounding factors, such as smoking, alcohol and coffee consumption, and physical activity is of particular importance, as these can be associated with both BMI and Parkinson's disease [4, 13].

Body mass changes in Parkinson's disease are common. The dependence of BMI on the risk for the disease, between the thickness of the skin fold and the progression of the process is described [13]. Publications highlight the leading role of central obesity, not obesity in general. The decrease in body weight with the progression of the disease can be also explained by the gradual development of motor disorders, disorders of swallowing, chewing, hypersalivation, gastrointestinal disorders, disturbances in food consumption associated with frequent intake of levodopa, which is recommended to take 1 hour after meal and 1 hour before meal, especially protein one [15].

The literature indicates the leading role of central obesity, rather than obesity in general. It has also been found that hyperglycemia, in particular with aging, is also associated with Parkinson's disease due to damage to the central nervous system that is a consequence of prolonged exposure to glucose. Epidemiological studies have shown that prior type 2 diabetes is also a risk factor for Parkinson's disease.

Neuroinflammation which was induced by exposure to either toxicants or infectious agents with proinflammatory characteristics as a major factor in the pathogenesis of PD is wildly accepted at present [9].

Oxidative stress also is a crucial feather of metabolic syndrome. Undoubtedly, Parkinson's disease should be treated as a metabolic disease. Numbers of antioxidants are effective and efficient in the prevention and treatment of Parkinson's disease by modulating the oxidative stress [9].

he decrease in body weight with the progression of Parkinson's disease can also be explained by the fact that movement disorders, disorders of swallowing, chewing, hypersalivation, disorders of the digestive tract function, disorders in food intake associated with frequent intake of levodopa, which is best taken 1 hour after and 1 hour before meals, especially protein.

Insufficient sleep is associated with a high concentration of blood plasma ghrelin and obesity: the longer sleep lasts, the lower the concentration of blood plasma ghrelin and the less the likelihood of obesity. Ghrelin levels are higher in people with shorter sleep, are positively associated with hunger ratings, but decline with increasing BMI. A decrease in BMI is associated with an increase in ghrelin and a decrease in leptin. However, with sleep deprivation, relatively high ghrelin levels and low leptin levels are associated with an elevated BMI. It can be assumed that these changes play an auxiliary rather than compensatory role in the development of overweight and obesity with limited sleep [12].

Calorie restriction in the diet has neuroprotective effect in Parkinson's disease, although the mechanisms are unknown. Elevated ghrelin level, a gut hormone with neuroprotective properties, during caloric restriction, prevents neurodegeneration, loss of dopamine neurons in the substantia nigra and dopamine turnover in the striatum.

Conclusion

An increased risk of Parkinson's disease is associated with an increased body mass index. However, the progression of the disease causes weight loss and, hence, a decrease of BMI. Patients with akinetic-rigid-tremulous form of the disease show a decrease in body weight, which may depend on mobility, less manifestations of rigidity compared to patients with akinetic-rigid form of the disease.

Group I patients (mixed form of the disease) showed insignificant increase, compared to the morning rates of ghrelin level, and Group II patients (akinetic-rigid form of the disease) showed decrease in the morning and evening levels of ghrelin. Diurnal fluctuations in ghrelin level in patient groups are associated with circadian rhythms and sleep quality and duration.

The study of diurnal fluctuations in the level of ghrelin is an extremely promising method for finding a solution to the problem of progression and treatment of Parkinson's disease, namely, the selection of the adequate regimen for taking antiparkinsonian drugs that are associated with food consumption.

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ASSESSMENT OF COGNITIVE DYSFUNCTION IN THE MILITARY WITH ALCOHOL-INDUCED MENTAL AND BEHAVIORAL DISORDERS WITH DEPRESSION COMORBIDITY

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The article presents the results of a psychodiagnostic study aimed to identify cognitive impairment and comorbid depressive states in the military with alcohol-induced mental and behavioral disorders. Up to 50 % of borderline cognitive disorders were found in patients of both groups (N = 85). Depressive symptoms were found in 100 % of p□t□□ts □ the ex□er□me□t□l grou□; 95.21 % demonstrated anxiety symptoms. Depression has been shown to correlate with cognitive impairment in patients with alcohol-induced mental and behavioral disorders. To reduce cognitive impairment, the patients of both groups were administered Cytoflavin metabolic drug in combination with traditional treatment. Following the course of treatment with addition of Cytoflavin, in 68 (80 %) patients of both groups there was a decrease in the cognitive dysfunction symptoms, normalization of sleep, and improvement of mood, which affected the quality of life in patients of both groups.

Key words: cognitive impairment, alcoholism, depression, Cytoflavin.

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ОЦІНКА КОГНІТИВНОЇ ДИСФУНКЦІЇ У ВІЙСЬКОВИХ З РОЗЛАДАМИ ПСИХІКИ ТА ПОВЕДІНКИ ВНАСЛІДОК ВЖИВАННЯ АЛКОГОЛЮ КОМОРБІДНОГО З ДЕПРЕСІЄЮ

У статті викладено результати психодіагностичного дослідження з метою виявлення когнітивних порушень та коморбідних депресивних станів у військових з розладами психіки та поведінки внаслідок вживання алкоголю. У пацієнтів обох груп (N=85) виявлено до 50% пограничних когнітивних відхилень. У 100% пацієнтів дослідної групи виявлено депресивні симптоми; у 95,21% - симптоми тривоги. Доведено, що депресія корелює з проявами когнітивних порушень у пацієнтів з розладами психіки та поведінки внаслідок вживання алкоголю. Для усунення когнітивних порушень пацієнтам обох груп було призначено в комплексі до традиційного лікування метаболічний препарат цитофлавін. У 68 (80%) пацієнтів обох груп після курсу лікування з додатковим призначенням цитофлавіну відзначалися зменшення проявів когнітивної дисфункції, нормалізація сну, покращення настрою, що впливало на якість життя пацієнтів обох груп.

Ключові слова: когнітивні порушення, алкоголізм, депресія, цитофлавін.

The work is a fragment of the research project "Features of comorbid states' clinical polymorphism in psychiatry and narcology", state registration No. 0119U100172.

Alcohol abuse and alcohol-induced disorders remain a pressing problem of modern healthcare and of society as a whole. As indicated by recent literature data, the growth of alcohol consumption has led to a