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MEDICINE

Eating disorders: neuroendocrine changes and potential treatments (review)

Pavel I. Letyagin[1] , **Ludmila N. Stankevich[2]** , **Taisiia A. Ulianova[3]**

[1] Pavlov Institute of Physiology, Russian Academy of Sciences,
6 Makarov Emb., Saint-Petersburg, 199034, Russia
[2] Saint-Petersburg State University,
7-9 University Emb., Saint-Petersburg, 199034, Russia
[3] Potsdam University,
10 Am Neuen Palais, Potsdam, 14469, Germany
Corresponding author: Pavel I. Letyagin (letyagin.ps@gmail.com)

Abstract
Background: Eating disorders (EDs) are a group of conditions with an unknown etiology, which is why a comprehensive therapy program is not yet available. The high prevalence and mortality rates underline the interest and necessity of studying this disorder. Recently, accumulating data suggests potential options for hormonal therapy, both conducted on animals and humans. **The aim of the study:** The exploration of potential hormonal therapy for the treatment of EDs, analysis and synthesis of current approaches to treating hormonal and psychophysiological disturbances in EDs, as well as a review of research conducted on model objects. **Materials and methods:** In this study a comprehensive literature review to gather relevant articles and research papers was conducted. Various bibliographic databases, including Google Scholar, Web of Science, Scopus and etc. were utilized. The search was performed using a combination of key words related to the topic of EDs: eating disorders, hormonal disturbances in EDs, model organisms for studying EDs, and specific queries related to hormones, receptors, and animal models. **Results:** Current study presents the main hormonal disturbances involved in the development and maintenance of EDs. Various animal models of EDs are presented, along with the use of agonists of key hormones in animal subjects. Additionally, investigations of the medications *relamorelin* and *metreleptin* in humans were also included. **Conclusion:** The effectiveness of hormonal therapy in humans indicates significant improvement in overall condition within relatively short periods. However, such studies are conducted on insufficient sample sizes for representativeness and require comprehensive double-blind placebo-controlled trials to confirm the efficacy and safety of this therapy.
Keywords: eating disorders (EDs); activity-based anorexia (ABA); ghrelin; leptin; anorexia

Introduction. The problem of nervous anorexia has become increasingly relevant in recent years due to the rise in the number of cases among children and adolescents, as well as the insufficient effectiveness of treatment measures. Eating disorders (EDs) are spreading due to the higher socioeconomic status across all layers of the population in developed and developing countries. Available epidemiological data indicate a low likelihood of full recovery in EDs, as individuals with this disorder continue to hold distorted perceptions of their own body, experience disordered eating patterns, and exhibit associated psychological and psychiatric problems. For example, body dysmorphic disorder, dysthymia, dependence on drugs used in psychopharmacotherapy such as neuroleptics, tranquilizers, and antidepressants. It is also worth considering that EDs can be components of other mental disorders. In the EU countries, approximately 1 trillion euros are spent annually on the treatment of EDs [1]. The estimated prevalence of EDs among school children is 13%, with girls being 10 times more likely to be affected than boys. The average age of onset for these disorders is 12.5 years [2] In conjunction with the high percentage of fatalities, this trend underscores the need to establish the pathogenesis and nosology of this disorder. Interest among researchers from various fields in EDs is increasing each year. However, specific biological and psychological causes for the onset and development of this disorder have not yet been established, and as a result, comprehensive rehabilitation programs are lacking. Approximately 46% of patients with anorexia nervosa are capable of achieving full recovery, around one-third experience partial recovery, and approximately 20% progress to a chronic form with persistent cycles of remission and relapse [3]. The outlook for treating anorexia nervosa relies on the timely identification of the disorder and its related complications, the appropriate decisions made by healthcare professionals, and the patient's willingness to engage in therapy and actively pursue recovery. Moreover, data suggests that the duration of anorexia nervosa directly correlates with an increased risk of patient mortality [4]. Generally, death occurs as a result of comorbidities or suicide. It is also important to understand that EDs are not isolated conditions; for certain diseases, the likelihood of developing an ED increases, such as in type 1 diabetes where EDs are more prevalent [5].

The aim of the study. The exploration of potential hormonal therapy for the treatment of EDs, analysis and synthesis of current approaches to treating hormonal and psychophysiological disturbances in EDs, as well as a review of research conducted on model objects.

Materials and methods. The study used and analyzed a total of 54 articles, including 3 Russian-language and 51 English-language publications. The selection of literature sources was conducted using the bibliographic databases, such as Google Scholar, Web of Science, Scopus, DBLP, Medline, PubMed, Elibrary, ResearchGate and etc. by combination of key words. The keywords included: eating disorders, hormonal disturbances in EDs, model organisms for studying EDs, and specific queries related to hormones, receptors, and animal models. The study considered works conducted solely in the fields of physiology or psychiatry, as well as those carried out with an interdisciplinary approach, which held the greatest interest. This review encompasses physiological, biochemical, psychiatric, and psychological indicators of the effectiveness of ED therapy methods. It also includes a synthesis of anorexia nervosa models in experimental subjects and provides a brief characterization of their advantages and limitations.

Regulatory peptides in the pathogenesis of anorexia nervosa. While investigating the secretion patterns of ghrelin, leptin, and neuropeptide Y, substantial evidence was discovered, supporting the existence of feedback mechanisms that play a crucial role in regulating eating behavior. There is a hypothesis suggesting that the concentration of leptin in the bloodstream is not only responsible for regulating daily energy intake but also plays a role in the circadian rhythms of ghrelin and neuropeptide Y secretion [6]. Other hormones, such as amylin, brain-derived neurotrophic factor, and others, are also involved in the regulation

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of eating behavior. These hormones have an impact on maintaining EDs and contribute to the development of various psychological disturbances, which will be discussed further.

Ghrelin. Ghrelin, a 28-amino acid peptide, functions as the natural ligand for the growth hormone secretagogue receptor-1a, which, in turn, stimulates the secretion of growth hormone [7]. Ghrelin plays an important role in several physiological processes, including increasing appetite by stimulating the production of orexigenic neurons such as neuropeptide Y and agouti-related protein (AgRP). Furthermore, studies have revealed that individuals suffering from anorexia nervosa exhibit notably elevated levels of ghrelin in their plasma compared to those without the disorder [8, 9]. However, the effects of ghrelin go beyond appetite control and food intake; they also include modulation of reward-related behavior through the mesocorticolimbic dopaminergic system [10]. Patients with anorexia nervosa exhibit altered reward processing, including abnormal brain responses to food. Moreover, it has been shown that changes in leptin and ghrelin occurring during the acute phase of anorexia nervosa may sustain aberrant behavior [11]. Additionally, it has been found that patients with anorexia have significantly higher levels of ghrelin in their plasma compared to patients without anorexia. However, despite the elevated ghrelin levels, patients are unable to increase their food intake. Clinical trials involving ghrelin and ghrelin agonists have demonstrated encouraging outcomes in enhancing appetite, increasing food intake, promoting lean body mass, and improving the overall quality of life in patients affected by cancer cachexia [12]. However, in two recent substantial randomized double-blind phase III trials, significant effects on physical functioning and survival were not demonstrated [13]. The impact of ghrelin on appetite regulation has been associated with active ghrelin, although the primary form of ghrelin found in the bloodstream is des-acyl ghrelin. In a study conducted by Garcia et al. [14], it was observed that subjects experiencing cancer-induced cachexia displayed notably higher levels of active ghrelin and a higher ratio of active ghrelin

to total ghrelin compared to both cancer patients without cachexia and a control group unrelated to cancer. However, there is increasing evidence that des-acyl ghrelin (DAG) in is also closely associated with food intake and gastrointestinal motility. Specifically, patients with anorexia nervosa have higher levels of ghrelin in their plasma [15]. It is essential to acknowledge that the absolute concentrations of ghrelin detected in plasma can vary depending on the analytical method employed. Therefore, caution must be exercised when comparing absolute values obtained in a study with previously reported literature data on ghrelin levels, using different methods. In the case of anorexia nervosa, data may vary due to small sample sizes. In an analytical review, it was shown that exogenous ghrelin or ghrelin receptor agonists may improve the course of anorexia nervosa by stimulating appetite and reducing gastric discomfort, leading to increased energy intake and body weight. However, since these findings were obtained from small pilot studies, these effects need to be confirmed or refuted in larger clinical studies [16]. The inability of anorexia nervosa patients to respond to increased ghrelin levels may be related to decreased expression, sensitivity, or function of the ghrelin receptor GHS-R1. However, the exact cause of disrupted ghrelin signaling in anorexia nervosa has not been elucidated to date. Thus, several studies have provided data suggesting that elevated ghrelin levels in the acute phase of anorexia nervosa may be an ineffective compensatory mechanism during chronic starvation. However, recent research on underweight anorexia nervosa patients has shown that certain ghrelin agonists (e.g., relamorelin) can help restore ghrelin sensitivity, increase hunger sensation, and lead to weight gain after a short treatment period [17]. Currently, relamorelin is actively being developed in phase I and II clinical trials for the treatment of diabetic gastroparesis [18]. Over the past years, accumulating data indicating the development of gastroparesis in patients who have been taking opioid medications for an extended period [19]. Therefore, research on relamorelin as a potential therapy for anorexia

nervosa not only contributes to the development of new treatment methods for anorexia nervosa but also opens up possibilities for potential combination therapy in opioid therapy programs for agitation.

Leptin. Leptin is a peptide hormone primarily synthesized by white and brown adipose tissue cells. It is important to note that leptin concentration positively correlates with the amount of adipose tissue, thereby transmitting information to the brain about the level of fat stores in the body [20]. Leptin acts as an afferent signal in a negative feedback loop that maintains homeostatic control of adipose tissue mass and links changes in energy stores to a set of adaptive physiological responses. Leptin receptors (LepR) have several isoforms in humans, but it is through the LepRb isoform that intracellular signaling occurs. Leptin regulates the activity of key neural populations in the arcuate nucleus of the hypothalamus, where it inhibits orexigenic neuropeptide Y (NPY)/agouti-related peptide (AGRP) neurons while simultaneously stimulating anorexigenic pro-opiomelanocortin (POMC) neurons [21]. The loss of adipose tissue in individuals with anorexia nervosa leads to a decrease in circulating leptin levels derived from adipocytes. Subsequent hypoleptinemia represents a key endocrine feature of this ED and serves as a major signal for adaptation to starvation [22]. Amenorrhea, hematological changes, depressed mood, cognitive rigidity, and repetitive thoughts about food are clinically significant examples of starvation-related symptoms that may be caused or exacerbated by hypoleptinemia [23]. There is evidence linking weight loss in individuals with EDs, including anorexia nervosa, to the duration of the illness mediated by decreased leptin levels [24]. For example, in a study by Keel [25], significant associations were found between more pronounced weight suppression and lower leptin concentrations in a sample of 53 women with bulimia nervosa and purging disorder, indicating that leptin mediated the relationship between weight suppression and illness duration. Leptin tends to decrease the motivation for food seeking by modulating the activity of the mesolimbic dopamine system in response to food cues or odors. A large population of dopaminergic neurons in the nucleus accumbens (NAc) is innervated by GABAergic neurons in the adjacent nucleus, which express LepRb receptors in the ventral tegmental area. Leptin enhances the activity of these GABAergic neurons, thereby inhibiting dopaminergic neurons in the adjacent nucleus. Additionally, in a study on transgenic mice [26], it was found that leptin inhibits neurons in the hypothalamus that express LepR and project to the ventral tegmental area (VTA). However, activation of LepR-expressing neurons in the lateral hypothalamus increases motivation for food reward only when mice are in a positive energy balance state. In anorexia nervosa, hyperactivity is observed, which is also evident in animal models [27]. In relation to this, research studies are emerging with the aim of potential treatment for EDs using metreleptin. Metreleptin is a recombinant analog of human leptin that is used for the treatment of metabolic disorders in congenital or acquired generalized lipodystrophy, as well as in patients with congenital leptin deficiency. It has been shown to rapidly reduce hunger and induce significant weight loss over time, as well as normalize metabolic and hormonal functions. In a study by Milos et al. [28], involving three individuals with anorexia nervosa, the authors reported results indicating a decrease in repetitive thoughts about food, internal restlessness, and fear of weight in two patients. The manifestation of depression decreased in all patients, and no serious adverse events occurred. Furthermore, there is information about a clinical case of a male adolescent treated with metreleptin [29]. The authors noted that during the observation period, the target weight was achieved, mood did not worsen, and hyperactivity ceased. The findings of these studies are of interest for further research on larger sample sizes. Hebebrand's work [23] provides a list of the most common side effects during treatment with metreleptin: development of antibodies to metreleptin, headache, nausea, hypoglycemia, weight loss and increased risk of infections. At the same time, attention is paid to the fact that the initiation of treatment with metreleptin will be ac-

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companied by an increase in food consumption, which complicates therapy in individuals with EDs.

Amylin. Amylin is synthesized in the beta cells of the pancreas and in the lateral part of the hypothalamus, which is involved in metabolic control. The function of amylin is to serve as a satiety signal – chronic administration of amylin has been shown to reduce food intake and consequently decrease body weight [30]. The following brain structures are involved in the effect of amylin on food intake: the area postrema and the nucleus of the solitary tract [31]. Control of food intake is regulated by two pathways – the hedonic pathway, which acts through the reward system, and the homeostatic pathway, which involves the hypothalamus. Reward in the control of food behavior can be interpreted as the "desire" for specific foods, and this behavioral response is mediated by the modulation of the mesolimbic dopamine system – by altering dopamine synthesis levels in the ventral tegmental area, whose neurons project to the nucleus accumbens. The study on a sample of women with bulimia nervosa and women with purging disorder, which involves behaviors such as self-induced vomiting, suggests that individuals with bulimia nervosa experience reduced satiety after eating, potentially contributing to a propensity for consuming large amounts of food during binge eating episodes [32]. In contrast, purging disorder is characterized by excessive fullness and urges to vomit after consuming a normal amount of food [33]. Amanda et al.'s study [34] aimed to investigate the relationship between food intake and the release of insulin or amylin with changes in eating behavior in individuals with bulimia nervosa or purging disorder. Participants were offered a meal (900 kcal), after which they completed questionnaires to provide subjective reports of hunger, satiety, nausea, stomach pain, binge urges, and vomiting urges. Blood samples were also collected twice: before the meal and after it, for further analysis. After the test breakfast, vomiting urges increased and then gradually decreased. Insulin was significantly and positively associated with vomiting urges. However, no significant statistical differences were found between the group of 19 women with bulimia nervosa and the control group of 14 women without EDs regarding the role of amylin in the manifestation of purging behaviors. The authors of this study suggest that increased sensitivity to the effects of insulin on subjective experiences may be associated with destructive behaviors, while differences in the release of insulin and amylin may contribute to differences in the amount of food preceding purging in purging disorder compared to bulimia nervosa. Recently, abnormalities in central and peripheral regulatory peptides have been a topic of discussion regarding the development of anorexia nervosa [35]. These regulatory proteins play a vital role in monitoring food intake, primarily in the hypothalamus, where they influence the homeostatic control of feeding. Additionally, their receptors in the cortico-limbic system can also impact the consumption of non-homeostatic food. Higher-order brain structures associated with emotions, motivation, physical activity, and reward evaluation are also essential in regulating food intake and contribute to the etiology of anorexia nervosa.

Brain-Derived Neurotrophic Factor (BDNF) and oxytocin. BDNF and oxytocin are neuropeptides with important roles in regulating various physiological processes, including food intake and metabolism. These neuropeptides have also been linked to affective and cognitive symptoms in different psychiatric disorders. In a study [36], researchers aimed to measure the serum levels of BDNF, its receptor (TrkB), and oxytocin in underweight patients with anorexia nervosa (AN) and after partial weight restoration. The findings showed significant negative correlations between BDNF levels and the severity of EDs symptoms. However, there were no significant correlations observed between the levels of these neuropeptides and depressive or obsessive-compulsive symptoms in either underweight or partially weight-restored patients with anorexia nervosa. It was found that OXY levels in the serum of underweight anorexia nervosa patients increased the levels of BDNF did not return to normal even after partial

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weight restoration, supporting previous hypotheses regarding its involvement in the development of anorexia nervosa. This suggests that BDNF might be linked to abnormal eating behavior in individuals with anorexia nervosa. It is worth noting that the study in question investigated the roles of OXY, BDNF, and TrkB in adult patients with anorexia nervosa. However, it remains uncertain whether the mechanisms involved in the regulation of food intake in developing adolescents are the same as those observed in adults. Nevertheless, studying groups of adolescents may provide insights into different regulatory mechanisms, including neuroplastic changes resulting from prolonged illness duration.

Animal models mimicking anorexia nervosa. The main mechanism and pathogenesis of anorexia nervosa are still not fully understood. Treatment options remain limited, primarily consisting of nutritional support, psychotherapy, and pharmacotherapy, with a high frequency of relapse. To better understand the underlying pathophysiology of anorexia nervosa and investigate potential treatment approaches, various animal models resembling the characteristics of anorexia nervosa have been created. These models offer valuable insights into the condition and serve as valuable tools for further research. Researchers frequently endeavor to create animal models of diseases as a means to comprehend the fundamental neurobiological mechanisms that underlie these conditions, providing a conceptual understanding of the subject under investigation. Various animal models resembling anorexia nervosa have been employed to better understand the underlying pathophysiology of EDs and to investigate potential treatment approaches [37]. The activity-based anorexia model is the most widely utilized animal model, with 75 studies employing it. In this model, young rodents are typically exposed to time-restricted access to food (limited hours per day) while having unrestricted access to a running wheel. Additionally, the "anxious" mouse model, among the genetically modified animal models, holds particular significance and is a subject of special interest in research

[38]. Study using animal models has contributed significantly to understanding hunger and satiety mechanisms, physical activity and cognition in a state of reduced body weight, and other mechanisms related to anorexia nervosa in humans. A systematic review of animal models for anorexia nervosa [38] examined various animal species. In these studies, eighteen different animal models of anorexia nervosa were utilized. For example, in the calorie restriction model, calorie restriction was used as a means to investigate the cognitive and behavioral effects of body weight loss in animals. In one study [39], caloric intake in mice was reduced to 60% and 40% of their original calorie consumption. In another study, the mice's caloric intake was reduced to 40% of the food intake of control animals [40]. In other studies, a time-restricted access to food model was employed. Weight loss in mice was achieved by reducing the time of access to food to 2.5 hours per day [41] or gradually reducing it to 2 hours per day [42]. Many studies evaluating animal models of anorexia nervosa have assessed various parameters, including changes in body weight, food intake, physical activity, cessation of estrous cycle in female animals, behavioral alterations, and metabolic and hormonal changes.

Multiple animal models of anorexia nervosa have been developed, representing different approaches to defining the nosology of EDs. In the mentioned review, 18 different animal models were identified and described. Among genetic animal models, the anxiety/distress model is particularly intriguing. In this model, researchers have made fascinating discoveries regarding the impact of hunger/satiety regulatory peptides like neuropeptide Y and agouti-related peptide. One advantage of this model is that the animals have unrestricted access to food but still experience weight loss, effectively mimicking one of the symptoms of anorexia nervosa. However, a limitation of the model is that the animals display numerous other neurological changes along with reduced food intake, and they generally have a short survival time [38]. Consequently, numerous researchers have reached the conclusion that

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the genetic expression profile and phenotype exhibited in these animal models bear a closer resemblance to cachexia syndromes observed in conditions like cancer or chronic diseases rather than anorexia nervosa [43]. The activity-based anorexia (ABA) model is the most frequently employed animal model for investigating anorexia nervosa. This model replicates several aspects of the disorder, such as body weight loss, heightened physical activity, cessation of the estrous cycle in females, and changes in the hypothalamic-pituitary-adrenal axis [38]. However, two factors that have not been adequately represented in this model are genetic predisposition, which increases the risk of developing anorexia nervosa, and the psychosocial factor, which plays a crucial role in patients with the disorder both at onset and throughout its development. In the ABA model, specific neurocognitive and behavioral changes have been observed, including anxiety-like behavior, where estrogen reduction can further exacerbate anxiety [44]. Additionally, individual rats' level of anxiety-like behavior can correlate with their physical activity during running. Neuroendocrine alterations observed in the ABA model encompass an up-regulation of α4 GABA receptors in the hippocampus and amygdala [45, 46], as well as modifications leading to reduced cell proliferation in the hippocampus, as well as decreased astrocyte density and reduced volume of the cerebral cortex and amygdala [47]; all of which can be fully reversible upon refeeding [48]. Several studies have investigated the effects of various compounds on ABA, including chlorpromazine [49], fluoxetine [50], olanzapine [51], amisulpride, and cis-flupenthixol [52], which have been shown to reduce ABA symptoms, suggesting potential directions for future research on pharmacological interventions in the treatment of anorexia nervosa.

Results. The medication relamorelin has shown promise in restoring sensitivity to ghrelin and enhancing feelings of hunger, resulting in weight gain after a short period of treatment. Metreleptin has also shown improvements in the somatic and psychological state of patients. The effects observed with

these therapeutic approaches indicate significant improvement in patients' condition within a short timeframe.

Discussion. Patients with anorexia nervosa experience a multitude of hormonal disturbances that contribute to the maintenance of the disorder and future relapses. These hormonal imbalances need to be considered when selecting treatment approaches. Several studies have already explored the use of different medications in animal models, most of which are neuroleptics such as fluoxetine, olanzapine, amisulpride, and cis-flupenthixol. These drugs have shown efficacy in treating and alleviating symptoms in animal models of EDs. However, it should be noted that findings from animal models may not directly translate to humans, as these models have certain assumptions and limitations that only approximate the symptomatology of anorexia nervosa. Nonetheless, this field holds great potential for development as the demand for anorexia nervosa therapy continues to rise each year and is expected to increase further. Currently, it is impossible to fully meet this demand due to the lack of a comprehensive therapeutic approach that includes both psychopharmacotherapy and psychotherapy in sufficient quantity and quality. Additionally, there are studies investigating the use of hormone agonists in the treatment of anorexia nervosa. These studies have been conducted on a limited sample size, ranging from 1 to 3 individuals, and represent an exploration of potential treatment methods. Potentially, fundamentally new opportunities for the treatment of EDs can be achieved through the development of ghrelin antagonists. It is possible that the hopes placed on these antagonists will be justified. The existing knowledge about the effects of ghrelin provides insights into various aspects of metabolic and appetite regulation. Considering the orexigenic effect of ghrelin, appetite agonists or antagonists could be utilized as novel therapeutic agents for EDs. As stated earlier, AN is characterized by various hormonal imbalances, however, this aspect is well researched in women, but virtually unreported among men and other gender minorities [53], since these groups are the least represented in the clinical picture of EDs.

Resolving the complex genesis of EDs requires the collaboration of medicine and other specialists, particularly psychologists and psychotherapists, who work on addressing the causes that initiate and sustain disordered eating behaviors.

Conclusion. In conclusion, this study aimed to investigate the potential of hormonal therapy in the treatment of EDs. The current strategies for managing hormonal and psycho-physiological disruptions in EDs, as well as a review of research involving model organisms were combined and analyzed. The positive outcomes of hormonal therapy in humans suggest substantial enhancements in overall well-being over a relatively short timeframe.

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Conflict of interests
The authors have no conflict of interest to declare.

References

1. Schmidt U, Adan R, Bohm I, et al. Eating disorders: the big issue. The Lancet Psychiatry. 2016;3:313-315. DOI: https://doi.org/10.1016/S2215-0366(16)00081-X

2. Musatova LA, Krasnova LI, Borisova AM, et al. Features of eating disorders prevalence among adolescents in Penza. University proceedings. Volga region. Medical sciences. 2023;1:49-58. Russian. DOI: https://doi.org/10.21685/2072-3032-2023-1-5

3. Arcelus J, Mitchell AJ, Wales J, et al. Mortality rates in patients with anorexia nervosa and other eating disorders a meta-analysis of 36 studies. Archives of General Psychiatry. 2011;68(7):724-731. DOI: https://doi.org/10.1001/archgenpsychiatry.2011.74

4. Zakharova LI. Anorexia nervosa: prevalence, diagnostic criteria and psychosomatic relations (review). Research Results in Biomedicine. 2019;5(1):108-121. Russian. DOI: https://doi.org/10.18413/2313-8955-2019-5-1-0-8

5. Pursey KM, Hart M, Jenkins L, et al. Screening and identification of disordered eating in people with type 1 diabetes: a systematic review. Journal of Diabetes and its Complications. 2020;34(4):107522. DOI: https://doi.org/10.1016/j.jdiacomp.2020.107522

6. Dube MG, Beretta E, Dhillon H, et al. Central leptin gene therapy blocks high fat diet-induced weight gain, hyperleptinemia and hyperinsulinemia: effects on serum ghrelin levels. Diabetes. 2002;51(6):1729-1736. DOI: https://doi.org/10.2337/diabetes.51.6.1729

7. Kojima M, Hosoda H, Matsuo H, et al. Ghrelin: a growth hormone-releasing acylated peptide from the stomach. Nature. 1999;402(6762):656-660. DOI: https://doi.org/10.1038/45230

8. Rossi E, Cassioli E, Gironi V, et al. Ghrelin as a possible biomarker and maintaining factor in patients with eating disorders reporting childhood traumatic experiences. European Eating Disorders Review. 2021;29(4):588-599. DOI: https://doi.org/10.1002/erv.2831

9. Seidel M, Markmann SJ, Healy D, et.al. A Systematic Review and Meta-Analysis Finds Increased Blood Levels of All Forms of Ghrelin in Both Restricting and Binge-Eating/Purging Subtypes of Anorexia Nervosa. Nutrients. 2021;13(2):709. DOI: https://doi.org/10.3390/nu13020709

10. Müller TD, Nogueiras R, Andermann ML, et al. Ghrelin. Molecular Metabolism. 2015;4(6):437-460. DOI: https://doi.org/10.1016/j.molmet.2015.03.005

11. Monteleone AM, Castellini G, Volpe U, et al. Neuroendocrinology and brain imaging of reward in eating disorders: A possible key to the treatment of anorexia nervosa and bulimia nervosa. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;80(Part B):132-142. DOI: https://doi.org/10.1016/j.pnpbp.2017.02.020

12. Blauwhoff-Buskermolen S, Langius JAE, Heijboer AC, et al. Plasma ghrelin levels are associated with anorexia but not cachexia in patients with NSCLC. Frontiers in Physiology. 2017;8:119. DOI: https://doi.org/10.3389/fphys.2017.00119

13. Temel JS, Abernethy P, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. The Lancet Oncology. 2016;17(4):519-531. DOI: https://doi.org/10.1016/S1470-2045(15)00558-6

14. Garcia JM, Garcia-Touza M, Hijazi RA, et al. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. Journal of Clinical Endocrinology and Metabolism.

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Letyagin PI, et al. Eating disorders: neuroendocrine changes and ...

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2005;90(5):2920-2926. DOI: https://doi.org/10.1210/jc.2004-1788

15. Chen CY, Asakawa A, Fujimiya M, et al. Ghrelin gene products and the regulation of food intake and gut motility. Pharmacological Reviews. 2009;61(4):430-481. DOI: https://doi.org/10.1124/pr.109.001958

16. Schalla MA, Stengel A. The Role of Ghrelin in Anorexia Nervosa. International Journal of Molecular Sciences. 2018;19(7):2117. DOI: https://doi.org/10.3390/ijms19072117

17. Fazeli PK, Lawson EA, Faje AT, et al. Treatment with a ghrelin agonist in outpatient women with anorexia nervosa: A randomized clinical trial. Journal of Clinical Psychiatry. 2018;79(1):1-16.

18. Ahmedov VA. Motor disorders of the digestive tract: therapy with prokinetics. Russian Medical Inquiry. 2022;6(5):252-257. Russian. DOI: https://doi.org/10.32364/2587-6821-2022-6-5-252-258

19. Hasler WL, Wilson LA, Nguyen LA, et al. Opioid Use and Potency Are Associated With Clinical Features, Quality of Life, and Use of Resources in Patients With Gastroparesis. Clinical Gastroenterology and Hepatology. 2019;17(7):1285-1294. DOI: https://doi.org/10.1016/j.cgh.2018.10.013

20. Smith PM, Brzezinska P, Hubert F, et al. Leptin influences the excitability of area postrema neurons. American Journal of Physiology - Regulatory Integrative and Comparative Physiology. 2016;310(5):440-448. DOI: https://doi.org/10.1152/ajpregu.00326.2015

21. Friedman JM. Leptin and the endocrine control of energy balance. Nature Metabolism. 2019;1(8):754-764. DOI: https://doi.org/10.1038/s42255-019-0095-y

22. Friedman J. The long road to leptin. Journal of Clinical Investigation. 2016;126(12):4727-4734. DOI: https://doi.org/10.1172/JCI91578

23. Hebebrand J, Milos G, Wabitsch M, et al. Clinical trials required to assess potential benefits and side effects of treatment of patients with anorexia nervosa with recombinant human leptin. Frontiers in Psychology. 2019;10:769. DOI: https://doi.org/10.3389/fpsyg.2019.00769

24. Lee DJ, Elias GJB, Lozano AM. Neuromodulation for the treatment of eating disorders and obesity. Therapeutic Advances in Psychopharmacology. 2018;8(2):73-92. DOI: https://doi.org/10.1177/2045125317743435

25. Keel PK, Bodell LP, Haedt-Matt AA, et al. Weight suppression and bulimic syndrome maintenance: Preliminary findings for the mediating role of leptin. International Journal of Eating Disorders. 2017;50(12):1432-1436. DOI: https://doi.org/10.1002/eat.22788

26. de Vrind VAJ, Rozeboom A, Wolterink-Donselaar IG, et al. Effects of GABA and Leptin Receptor-Expressing Neurons in the Lateral Hypothalamus on Feeding, Locomotion, and Thermogenesis. Obesity. 2019;27(7):1123-1132. DOI: https://doi.org/10.1002/oby.22495

27. Barrios-Correa AA, Estrada JA, Contreras I. Leptin signaling in the control of metabolism and appetite: lessons from animal models. Journal of Molecular Neuroscience. 2018;66:390-402. DOI: https://doi.org/10.1007/s12031-018-1185-0

28. Milos G, Antel J, Kaufmann LK, et al. Short-term metreleptin treatment of patients with anorexia nervosa: rapid on-set of beneficial cognitive, emotional, and behavioral effects. Translational Psychiatry. 2020;10(1):303. DOI: https://doi.org/10.1038/s41398-020-00977-1

29. Antel J, Tan S, Grabler M, et al. Rapid amelioration of anorexia nervosa in a male adolescent during metreleptin treatment including recovery from hypogonadotropic hypogonadism. European Child and Adolescent Psychiatry. 2022;31:1573-1579. DOI: https://doi.org/10.1007/s00787-021-01778-7

30. Lutz TA. Control of energy homeostasis by amylin. Cellular and Molecular Life Sciences. 2012;69(12):1947-1965. DOI: https://doi.org/10.1007/s00018-011-0905-1

31. Potes CS, Lutz TA. Brainstem mechanisms of amylin-induced anorexia. Physiology and Behavior. 2010;100(5):511-518. DOI: https://doi.org/10.1016/j.physbeh.2010.03.001

32. Keel PK, Haedt-Matt AA, Hildebrandt B, et al. Satiation deficits and binge eating: Probing differences between bulimia nervosa and purging disorder using an ad lib test meal. Appetite. 2018;127:119-125. DOI: https://doi.org/10.1016/j.appet.2018.04.009

33. Keel PK, Eckel LA, Hildebrandt BA, et al. Disturbance of gut satiety peptide in purging disorder. International Journal of Eating Disorders. 2018;51(1):53-61. DOI: https://doi.org/10.1002/eat.22806

34. Dossat AM, Bodell LP, Williams DL, et al. Preliminary examination of glucagon-like peptide-1 levels in women with purging disorder and bulimia nervosa. International Journal of Eating Disorders. 2015;48(2):199-205. DOI: https://doi.org/10.1002/eat.22264

35. Duriez P, Ramoz N, Gorwood P, et al. A metabolic perspective on reward abnormalities in anorexia nervosa. Trends in Endocrinology and Metabolism. 2019;30(12):915-928. DOI: https://doi.org/10.1016/j.tem.2019.08.004

36. Tyszkiewicz-Nwafor M, Rybakowski F, Dmitzak-Weglarz, et al. Brain-Derived Neurotrophic Factor and Oxytocin Signaling in Association With Clinical Symptoms in Adolescent Inpatients With Anorexia Nervosa - A Longitudinal Study. Frontiers in Psychiatry. 2020;10:1032. DOI: https://doi.org/10.3389/fpsyt.2019.01032

37. Mequinion M, Chauveau C, Viltart O. The use of animal models to decipher physiological and neurobiological alterations of anorexia nervosa patients. Frontiers in Endocrinology. 2015:6:68. DOI: https://doi.org/10.3389/fendo.2015.00068

38. Scharner S, Stengel A. Animal Models for Anorexia Nervosa - A Systematic Review. Frontiers in Human Neuroscience. 2021;14:596381. DOI: https://doi.org/10.3389/fnhum.2020.596381

39. Avraham Y, Bonne O, Berry EM. Behavioral and neurochemical alterations caused by diet restriction - the effect of tyrosine administration in mice. Brain Research. 1996;732(1-2):133-144. DOI: https://doi.org/10.1016/0006-8993(96)00514-8

40. Campos GV, de Noronha SR, de Souza AA, et al. Estrogen receptor beta activation within dorsal raphe nucleus reverses anxiety-like behavior induced by food restriction in female rats. Behavioural Brain Research. 2019;357-358:57-64. DOI: https://doi.org/10.1016/j.bbr.2018.03.029

41. Avraham Y, Paturski I, Magen I, et al. 2-Arachidonoylglycerol as a possible treatment for anorexia nervosa in animal model in mice. Brain Research. 2017;1670:185-190. DOI: https://doi.org/10.1016/j.brainres.2017.06.003

42. Mequinion M, Le Thuc O, Zgheib S, et al. Long-term energy deficit in mice causes long-lasting hypothalamic alterations after recovery. Neuroendocrinology. 2017;105(4):372-383. DOI: https://doi.org/10.1159/000455048

43. Mercader JM, Saus E, Aguera Z, et al. Association of NTRK3 and its interaction with NGF suggest an altered cross-regulation of the neurotrophin signaling pathway in eating disorders. Human Molecular Genetics. 2008;17(9):1234-1244. DOI: https://doi.org/10.1093/hmg/ddn013

44. Kinzig KP, Hargrave SL. Adolescent activity-based anorexia increases anxiety-like behavior in adulthood. Physiology and Behavior. 2010;101(2):269-276. DOI: https://doi.org/10.1016/j.physbeh.2010.05.010

45. Aoki C, Sabaliauskas N, Chowdhury T, et al. Adolescent female rats exhibiting activity-based anorexia express elevated levels of GABA A receptor α4 and δ subunits at the plasma membrane of hippocampal CA1 spines. Synapse. 2012;66(5):391-407. DOI: https://doi.org/10.1002/syn.21528

46. Wable GS, Barbarich-Marsteller NC, Chowdhury TG, et al. Excitatory synapses on dendritic shafts of the caudal basal amygdala exhibit elevated levels of GABAA receptor α4 subunits following the induction of activity-based anorexia. Synapse. 2014;68(1):1-15. DOI: https://doi.org/10.1002/syn.21690

47. Frintrop L, Liesbrock J, Paulukat L, et al. Reduced astrocyte density underlying brain volume reduction in activity-based anorexia rats. World Journal of Biological Psychiatry. 2018;19(3):225-235. DOI: https://doi.org/10.1080/15622975.2016.1273552

48. Frintrop L, Trinh S, Liesbrok J, et al. The reduction of astrocytes and brain volume loss in anorexia nervosa - the impact of starvation and refeeding in a rodent model. Translational Psychiatry. 2019;9(1):159. DOI: https://www.nature.com/articles/s41398-019-0493-7

49. Adams KL, Parfeniuk GG, Eikelboom R. Chlorpromazine specifically prevents the wheel-induced feeding suppression in rats. Pharmacology Biochemistry and Behavior. 2009;93(4):470-473. DOI: https://doi.org/10.1016/j.pbb.2009.06.010

50. Karth MD, Baugher BJ, Pallechia SA, et al. Brain serotonin deficiency and fluoxetine lead to sex-specific effects on binge-like food consumption in mice. Psychopharmacology. 2022;239(9):2975-2984. DOI: https://doi.org/10.1007/s00213-022-06181-x

51. Kooij KL, Luijendijk MCM, Drost L, et al. Intranasal administration of olanzapine has a beneficial outcome in a rat activity-based anorexia model. European Neuropsychopharmacology. 2023;71:65-74. DOI: https://doi.org/10.1016/j.euroneuro.2023.03.008

52. Schalla MA, Stengel A. Activity-based anorexia as an animal model for anorexia nervosa – a systematic review. Frontiers in Nutrition. 2019;6:69. DOI: https://doi.org/10.3389/fnut.2019.00069

53. Haines MS. Endocrine complications of anorexia nervosa. Journal of Eating Disorders.

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Information about the authors

Pavel. I. Letyagin, Junior Researcher at the Laboratory of Physiology of Hearing, Pavlov Institute of Physiology, Russian Academy of Sciences, Saint-Petersburg, Russia, E-mail: letyagin.ps@gmail.com, ORCID: https://orcid.org/0000-0003-0138-4459.

Ludmila N. Stankevich, Cand. Sci. (Biology), Associate Professor at the Department of Physiology of Higher Nervous Activity and Psychophysiology, Saint-Petersburg State University, Saint-Petersburg, Russia, E-mail: l.stankevich@spbu.ru, ORCID: https://orcid.org/0000-0002-6197-3266.

Taisiia A. Ulianova, Research Assistant at the Potsdam Embodied Cognition Group, Potsdam University, Potsdam, Germany, E-mail: taisiia.ulianova@uni-potsdam.de, ORCID: https://orcid.org/0000-0002-9561-5811.