PREVENTION AND CORRECTION OF BEHAVIORAL DISORDERS IN RATS WITH METABOLIC SYNDROME USING A COMPLEX PHYTOADAPTOGEN

Dzampaeva Zh.V.,
Datieva F.S.,
Takoeva E.A.,
Nartikoeva M.I.

Institute of Biomedical Researches – Branch of Vladikavkaz Scientific Centre, Russian Academy of Sciences (Pushkinskaya str. 47, Vladikavkaz 362045, Russian Federation)

Corresponding author:
Zhanna V. Dzampaeva,
e-mail: dzhanaeva_1991@mail.ru

ABSTRACT

The aim of the study. *To assess the possibility of correction and prevention of behavioral disorders in rats with metabolic syndrome using a complex phytoadaptogen (CPA).*
Material and methods. *The experiment was carried out on 30 male Wistar rats randomized into 3 groups: group 1 – control; group 2 – metabolic syndrome (MS); group 3 – treatment of metabolic syndrome using CPA. In groups 2 and 3, animals were on a high-carbohydrate and high-fat diet for 16 weeks. Group 3 received CPA for 14 days in drinking water after 16 weeks of a diet. CPA consists of official tinctures of Glycyrrhiza glabra, Rhodiola rosea, Acantopanax senticosus at a ratio of 1:2:1. Behavior was analyzed through the "open field" test using Realtimer software (Open Science, Russia). Data were analyzed using GraphPad Prism 8.03 software (GraphPad, USA).*
Results. *The experiment proved that metabolic syndrome is accompanied by increased anxiety (decreased horizontal ($p = 0.017$) and vertical ($p = 0.017$) motor activity) and fear (increased periods of immobility ($p = 0.011$)) in the open field. When corrected with a complex phytoadaptogen, the time spent in the open and closed arms of the maze did not differ statistically significantly from the values of similar control indicators.*
Conclusion. *Based on the data obtained in the group 3 (no statistically significant differences with control) – decreased manifestations of fear and anxiety (increased orientation and research activity) – we can talk about the effectiveness of complex phytoadaptogens as an anxiolytic. The mechanisms underlying this result remain to be explored, emphasizing the role of the autonomic nervous system, leptin and ghrelin in behavior and the influence of complex phytoadaptogens on them.*

Key words: *Acanthopanax senticosus, dyslipidemia, Glycyrrhiza glabra, metabolic syndrome, obesity, Rhodiola rosea*

Received: 01.02.2023
Accepted: 12.01.2024
Published: 26.03.2024

For citation: Dzampaeva Zh.V., Datieva F.S., Takoeva E.A., Nartikoeva M.I. Prevention and correction of behavioral disorders in rats with metabolic syndrome using a complex phytoadaptogen. *Acta biomedica scientifica*. 2024; 9(1): 233-240. doi: 10.29413/ABS.2024-9.1.23

ПРОФИЛАКТИКА И КОРРЕКЦИЯ НАРУШЕНИЙ ПОВЕДЕНЧЕСКОЙ АКТИВНОСТИ КРЫС С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ КОМПЛЕКСНЫМ ФИТОАДАПТОГЕНОМ

Дзампаева Ж.В.,
Датиева Ф.С.,
Такоева Е.А.,
Нартикоева М.И.

Институт биомедицинских исследований – филиал ФГБУН Федеральный научный центр «Владикавказский научный центр Российской академии наук» (362025, г. Владикавказ, ул. Пушкинская, 47, Россия)

Автор, ответственный за переписку:
Дзампаева Жанна Валерьевна,
e-mail: dzhanaeva_1991@mail.ru

РЕЗЮМЕ

Цель исследования. *Оценить возможность коррекции и профилактики нарушений поведенческой активности крыс с метаболическим синдромом комплексным фитоадаптогеном (КФА).*

Материал и методы. *Эксперимент проводили на 30 крысах-самцах линии Wistar, случайным образом разделённых на 3 группы: группа 1 – контроль; группа 2 – метаболический синдром (МС); группа 3 – лечение метаболического синдрома КФА. В группах 2, 3 животные находились на диете с высоким содержанием углеводов и жиров в течение 16 недель. Группа 3 получала КФА в течение 14 дней с питьевой водой после 16 недель диеты. КФА состоит из официальных настоек Glycyrrhiza glabra, Rhodiola rosea, Acantopanax senticosus в соотношении 1:2:1. Поведение анализировали с помощью теста «Открытое поле» (ОП) с использованием программного обеспечения Realtimer (Open Science, Россия). Данные анализировали с использованием программного обеспечения GraphPad Prism 8.03 (GraphPad, США).*

Результаты. *В ходе эксперимента доказано, что метаболический синдром сопровождается повышенной тревожностью (снижение горизонтальной (p = 0,017) и вертикальной (p = 0,017) двигательной активности) и страхом (увеличение периодов неподвижности (p = 0,011)) в ОП. При коррекции комплексным фитоадаптогеном время пребывания в открытых и закрытых рукавах лабиринта статистически значимо не отличались от значений аналогичных показателей контроля.*

Заключение. *На основании данных, полученных в группе коррекции (отсутствие статистически значимых отличий относительно контроля): снижение проявлений страха и тревожности (повышении ориентировочно исследовательской деятельности), – можно говорить об эффективности комплексных фитоадаптогенов в качестве анксиолитика. Механизмы, лежащие в основе данного результата, ещё предстоит изучить, подчёркивая роль вегетативной нервной системы, лептина и грелина в поведении и влияние на них комплексных фитоадаптогенов.*

Ключевые слова: *Acanthopanax senticosus, дислипидемия, Glycyrrhiza glabra, метаболический синдром, ожирение, Rhodiola rosea*

Статья поступила: 01.02.2023
Статья принята: 12.01.2024
Статья опубликована: 26.03.2024

Для цитирования: Дзампаева Ж.В., Датиева Ф.С., Такоева Е.А., Нартикоева М.И. Профилактика и коррекция нарушений поведенческой активности крыс с метаболическим синдромом комплексным фитоадаптогеном. *Acta biomedica scientifica*. 2024; 9(1): 233-240. doi: 10.29413/ABS.2024-9.1.23

INTRODUCTION

Metabolic syndrome (MS) is becoming a serious medical and social problem worldwide. According to the World Health Organisation, more than 1.9 billion people are overweight [1, 2]. MS is characterised by insulin resistance, hyperglycaemia, dyslipidaemia, hypertension and obesity, and is a pro-inflammatory and pro-thrombotic condition. Visceral fat, a biologically active endocrine and paracrine organ, plays a key role in metabolic syndrome. It produces adipocytokines, the main pro-inflammatory mediators: plasminogen activator inhibitor-1 (PAI-1, plasminogen activator inhibitor-1), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α). The above cytokines contribute to *low-grade chronic inflammation*, the inflammatory response and reduce insulin receptor sensitivity. Obesity increases the risk of type 2 diabetes mellitus, cardiovascular disease associated with low intensity chronic inflammation and systemic endothelial dysfunction. In recent years, there has been growing interest in exploring the relationship between MS and psychosomatic disorders such as depression and anxiety. The results of studies are conflicting, but pro-inflammatory cytokines have been revealed to cause depressive disorders and depression itself induces eating disorders with subsequent MS formation and has pro-inflammatory properties [3, 4].

In this study, we have examined a new herbal formula that can be effectively used in the treatment and prevention of MS and obesity, a complex phytoadaptogen (CPA), which consists of commonly used phytoadaptogens: golden root (*Rhodiola rosea*), common licorice (*Glycyrrhiza glabra*), spiny eleuterococcus (*Acanthopanax senticosus*). *Glycyrrhiza glabra* and *Rhodiola rosea* have anti-inflammatory and antioxidant effects. *Acanthopanax senticosus* has a pronounced stress-limiting effect. They control stress-activated molecular chaperones (Hsp70), cortisol and nitric oxide (NO). Under stressful conditions, adaptogens modulate the function of the pineal gland [5]. Additionally, the literature suggests that CPAs are able to enhance performance and reduce fatigue, and modulate the inflammatory response in experiment and clinic.

THE AIM OF THE STUDY

To assess the possibility of correction and prevention of behavioral disorders in rats with metabolic syndrome using a complex phytoadaptogen.

MATERIALS AND METHODS

The experiment was performed on male Wistar rats (weight 330 ± 20 g; n = 30) obtained from the Rappolovo husbandry (St. Petersburg, Russia). The animals were housed in a room with artificial light (12/12), controlled temperature (21 ± 1 °C) and humidity (50–55 %). Rats were kept in cages (5 animals in each cage), food and water *ad libitum*.

The study was approved by the Ethics Committee of the Institute of Biomedical Research – branch of the Vladikavkaz Scientific Centre of the Russian Academy of Sciences (Minutes No. 7 dated February 20, 2019). The study was conducted in accordance with the ethical standards established by the World Medical Association Declaration of Helsinki (2000).

After the adaptation period (2 weeks), the animals were randomly divided into 3 experimental groups: group 1 – control; group 2 – metabolic syndrome; group 3 – treatment of metabolic syndrome with complex phytoadaptogen. Animals of groups 2 and 3 were on a high-carbohydrate high-fat diet (HCHF). The diet included: 175 g of fructose, 395 g of sweetened condensed milk, 200 g of beef fat, 155 g of powdered rat food, 25 g of Hubble, Mendel and Wakeman salt mixture and 50 g of water per kilogram of diet. Additionally, the drinking water for the MS group was supplemented with 25 % fructose [6]. The total feeding time was 16 weeks. The presence of metabolic syndrome in animals was confirmed by biochemical, pathomorphological and functional methods of study according to the applied experimental model [6]. Group 2 rats were removed from the experiment after 16 weeks of feeding to evaluate the progression of pathophysiological changes in the metabolic syndrome. Animals were removed from the experiment by decapitation under thiopental anaesthesia (40 mg/kg).

After 16 weeks of diet, Group 3 rats received a complex phytoadaptogen for 14 days. CPA consists of 40 % alcoholic extracts of *Glycyrrhiza glabra*, *Rhodiola rosea, Acanthopanax senticosus* in the ratio of 1:2:1 respectively. The dose was calculated based on the average daily fluid intake and a factor (×10) for small laboratory animals (0.1 ml/100 g per day).

Behavior was recorded and calculated using computer software for monitoring animal activity (Real Timer, Open Science, Russia) in «open-field» and «elevated plus maze» tests.

The «open-field» test is a square arena with sides equal to 100 cm and a height of 40 cm, divided into equal 25 squares ($40 \times 40 \times 30$ cm^3). It has been proved that the open field of grey colour fails to reveal intergroup differences in animal behavior, as a specific type of stress behavior emerges, manifested in a mixed anxious-phobic state in animals regardless of their predicted resistance to stress [3]. Considering this, the animals in this experiment were not divided into groups based on their tolerance to stress. Parameters assessed in the open field: vertical activity (number of rears), horizontal activity (distance expressed in squares), number of grooming and defecation acts.

The elevated plus maze is a plus-shaped apparatus with four arms connecting at right angles to each other, as described by Handley and Mitani. The elevated plus maze consists of two closed ($30 \times 5 \times 30$ cm^3) and two open arms ($30 \times 5 \times 1$ cm^3) perpendicular to each other and connected by a central arena (5 × 5 cm^2). Closed arms have a high wall (16 cm), whereas open arms have no side wall. Rats were placed in the center platform facing the closed arm. The parameter evaluated is the total time spent in open and closed arms. Entry was recorded when the rat entered the arm with all four limbs.

On the day of testing, the rats were transported to the test room for 2 hours. Each rat was then placed in the same corner of the open-field arena and the elevated plus maze; behavior was recorded for 5 min each in both tests. To avoid the presence of olfactory cues, all equipment (open field, elevated plus maze) was thoroughly cleaned with 20 % ethanol and then wiped with dry paper after each trial. The studies were conducted in the time interval from 9 to 14 hours.

Data analysis was performed using GraphPad Prism 8.03 software (GraphPad, USA). The distribution of continuous variables was tested for normality using the Shapiro – Wilk test. Since in some cases there was no conformity of numerical populations to the principle of normality of distribution and a small number of variants in the compared groups ($n < 30$), nonparametric block statistics was used in the work. The Kraskell – Wallis criterion was used to compare independent data sets. The Wilcoxon criterion was used to compare dependent data sets. Median (25–75‰) values were given as descriptive statistics because of the small number of variants in the sample. A p value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Animal behavior is one way of actively adapting to environmental factors. The animal is stressed when placed in an «open-field» experimental facility, which is reflected in its behavior during the first 4 minutes of the test [3].

Rats with MS (group 2) showed a tendency to decrease horizontal motor activity (HMA) compared to controls (group 1) within 5 min. The number of rears with support (vertical motor activity (VMA)) on the arena wall in group 2 showed statistically significant differences relative to the control ($p = 0.017$) (Table 1). Consequently, in metabolic syndrome, there is a decrease in orienting and exploratory activity (↓HMA and VMA). No statistically significant differences in relation to the control both GDA and VMA were observed during correction with complex phytoadaptogen; the indices were restored within the confidence interval of control, i.e. there was a tendency to normalisation of orientation-research activity.

The main significant manifestation of severe fear in animals with metabolic syndrome in OF was the period of immobility, which was statistically significantly different from control values ($p = 0.011$). This fact confirms the presence of statistically significant differences of this indicator with the control in group 3 ($p = 0.025$). However, the use of CPA resulted in a statistically significant difference from the MS group with respect to periods of immobility ($p = 0.014$).

In the second group, the duration of grooming was statistically significantly different from the control group ($p = 0.011$). When CPA was corrected, statistically significant differences in the number of grooming acts to MS were observed ($p = 0.017$).

Analysis of the parameters of the Elevated Plus Maze test revealed increased anxiety and fear symptoms in the animals. In rats of the second group (MS) relative to controls, there was a decrease in the time spent in the open arm ($p = 0.012$), an increase in the time spent in the dark arm ($p = 0.043$), and the number of head dippings ($p = 0.043$) (Table 1), indicating increased anxiety. When corrected with a complex phytoadaptogen, the time spent in the open and closed arms of the maze did not differ statistically significantly from the values of similar control indicators (Table 1).

DISCUSSION

Almost all overweight patients have an eating disorder [4]. An understanding of the pathophysiological relationships between stress, neurobiological adaptation and obesity is important for the development of effective prevention and correction methods.

Proceeding from the data obtained during parallel testing of animals during OF and EPM, it is possible to speak about the effectiveness of complex phytoadaptogen as an anxiolytic: normalisation of indices within the confidence interval of control of the test ‘open field’ (horizontal and vertical motor activity and periods of immobility), test ‘elevated plus maze’ (time of staying in open and closed arms, number of head dippings, defecation acts) is revealed. This indicates a decrease in the manifestations of fear and anxiety, which was expressed in the activation of orienting and exploratory activity.

The effectiveness of complex phytoadaptogen can be explained by several mechanisms, and first of all it is the effect of increasing adaptation to stress. The autonomic nervous system provides various forms of response to emotional stress – changes in temperature, sweating, cardiovascular and gastrointestinal indices, respiratory rhythmicity. In chronic stress, psychovegetative disorders occur. In normal stress, corticotropin-releasing factor is produced and eventually glucocorticoids are produced [7], which inhibit corticotropin-releasing factor secretion by a feedback mechanism, then the system returns to its initial state. Corticotropin-releasing factor reduces the synthesis of key neuropeptides such as brain-derived neurotrophic factor (BDNF). Chronic stress disrupts the feedback mechanism, glucocorticoids persist for a long time, which leads to neuronal insufficiency in brain structures containing glucocorticoid receptors, for example, the hippocampus, damage to which can lead to a failure of adaptation of the individual under

TABLE 1

CHANGE IN THE ASSESSED INDICATORS IN THE "OPEN FIELD" TEST AMONG ALL EXPERIMENTAL GROUPS

Indicators	Control (Group 1)	MS (Group 2)	MS + CPA (Group 3)
Open field			
Number of crossed squares	58.5 (36; 65.5)	29.5 (25; 45) $p = 0.017$*	45 (33.5; 53)
Number of rears without support on the open field wall	9 (5.5; 13)	2.5 (2; 6) $p = 0.017$*	7 (3.5; 8.5)
Number of rears supported on the open field wall	7 (3; 8.5)	6.5 (4; 9)	5 (3; 7)
Immobility period (s)	20 (15; 32.5)	60 (45; 75) $p = 0.011$*	39 (32.5; 45) $p = 0.025$* $p = 0.014$**
Grooming acts number	7 (3.5; 13.5)	27.5 (20; 40) $p = 0.011$*	15.5 (14.5; 16) $p = 0.017$**
Elevated plus maze			
Time spent in open arms (s)	50.32 (37.1; 77.7)	21.83 (10.11; 32.51) $p = 0.012$	37 (27.28; 49.35) $p = 0.05$
Time spent in closed arms (s)	250.8 (228.3; 258.3)	272.5 (253.4; 287.9) $p = 0.043$	228.8 (214.8; 245.1) $p = 0.009$
Head dipping number	3 (0; 5)	0 (0; 2) $p = 0.043$*	0 (0; 0.5)
Number of defecations	3 (2; 3)	4.5 (2; 6) $p = 0.017$*	0 (0; 2)
Grooming acts number	2 (2; 3)	2 (1; 3)	2 (1; 3)

Note. Results are presented as Me (25‰; 75‰); * – to control; ** – to metabolic syndrome ($p < 0.05$).

subsequent stressors. Accordingly, depressive, anxiety, and somatoform disorders occur [7, 8].

A complex phytoadaptogen can influence animal behavior by several mechanisms. Specifically, CPA increases the production of neurohormones (endorphins, dopamine) in stress by modulating the synthesis of adrenocorticotropic hormone and cortisol in the adrenal glands. In addition, it has a neuroprotective effect [9, 10]. CPA secondary metabolites contribute to the adaptation of cells to stress, which is called the hormesis phenomenon or preconditioning [10].

One other possible mechanism is related to the CPA reduction in the production of inflammatory mediators in the metabolic syndrome. TNF-α is considered as a mediator of insulin resistance and a regulator of energy metabolism in the body. TNF-α has been evidenced to affect insulin receptors and glucose transport, increasing insulin resistance and, consequently, stimulating leptin secretion [5]. TNF-α increases the production of IL-6, which also inhibits the metabolic effects of insulin by blocking insulin-dependent activation of signalling transducers, insulin-induced glycogen synthesis. Consistent with the cytokine hypothesis, psychosomatic changes with increased cytokines may lead to the induction of indolamine-2,3-dioxygenase to form tryptophan (TRP) catabolites with subsequent decreased availability of TRP and serotonin (5-HT), which also increases anxiety and the development of depressive states [11].

TNF-α has a direct impact on the formation of insulin resistance at the level of hepatocytes. Progression of insulin resistance increases leptin resistance. Leptin («the voice of adipose tissue») regulates eating behavior by acting on the hypothalamic satiety center. Leptin also increases sympathetic nervous system tone; increases thermogenesis in adipocytes; inhibits insulin synthesis; and acts on the cell's insulin receptor to reduce glucose transport. However, in MS, leptin does not fulfil its basic biological functions. The increased anxiety behavior in animals with MS can be explained by the development of leptin resistance in response to a diet rich in carbohydrates and fat, in particular leptin resistance in its main targets, the hypothalamus [12] and ventral tegmental area [13]. This condition possibly develops as a result of decreased leptin receptor gene expression accompanied by reduced signal transduction and/or presumably reduced leptin transport into the cerebrospinal fluid in insulin resistance [14, 15]. It is widely recognised that the amygdala plays a major role in the modulation of anxiety, and dopaminergic receptor mechanisms play an important role in this modulation. To the extent that neurons in the ventral tegmental area are the source of dopamine innervation of the amygdala, it is possible that leptin resistance in it may underlie the anxious behavior observed in our experiment.

Another peripheral hormone that plays an important role in the regulation of homeostatic nutrition is ghrelin. As discussed above in relation to leptin, ghrelin has recently been implicated in stress-induced changes in eating and behavior. Activation of ghrelin signalling pathways in response to chronic stress has been evidenced to be a homeostatic adaptation that helps individuals cope with stress, but at the expense of increased caloric intake. Catecholamines secreted in response to stress appear to directly stimulate ghrelin cells. Like leptin, ghrelin is an efficient modulator of mesolimbic dopaminergic chains [8].

From the third side, chronic low-intensity inflammation leads to increased oxidative and nitrosative damage to neurons, pancreatic and endothelial cells. Inflammatory and nitrosative (O&NS, oxidative and nitrosative stress) pathways are linked in a vicious circle in which immune-inflammatory reactions deplete endogenous antioxidant stores and reactive oxygen intermediates (ROI) activate proinflammatory promoter genes through intracellular signalling cascades such as mitogen-activated protein kinases (MAPKs) and NF-kB; in addition, there is an alteration of insulin-producing cells in the pancreas and an increase in insulin resistance [16].

We can therefore observe a number of overlapping pathophysiological mechanisms contributing to the development of behavioural disorders in chronic low-intensity inflammation against the background of MS, which accounts for the obtained positive effects of complex phytoadaptogen acting at the central (central nervous system), systemic (hormonal regulation) and cellular levels.

The complex phytoadaptogen inhibits transcription factors – NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), receptor activator of nuclear factor kappa-B (RANK, receptor activator of nuclear factor κ B)), and FOXO3, a key transcription factor regulating the cellular response induced by oxidative stress - which results in neurons adapting to stress. Glycyrrhizin, a constituent of *Glycyrrhiza glabra*, reduces oxidative stress by inhibiting the 5'-adenosine monophosphate-activated protein kinase (AMPK) and transcriptional NF-κB pathways and activating AMPK/NRF2 (nuclear factor erythroid 2-related factor 2) signalling [17-19].

Acanthopanax senticosus increases the activity of antioxidant enzymes - superoxide dismutase, glutathione peroxidase, catalase - in the liver, thereby reducing the accumulation of ROIs [18]. The most widely known plant-derived antioxidant is *Rhodiola rosea*, which enhances the endogenous antioxidant enzymatic response. Administration of *Rhodiola rosea* extract inhibits the activity of proline dehydrogenase (PDH) and glucose-6-phosphate dehydrogenase (G6PDH, glucose-6-phosphate dehydrogenase). *Rhodiola rosea* extract and its main biologically active substance, tyrosol, increase the activity of superoxide dismutase, which leads to a decrease in the content of free radical oxidation products during adipogenesis [20]. In combination, phytoadaptogens modulate and potentiate the effects of each other, which provides their protective effect.

CONCLUSION

The results substantiate the idea that a diet high in carbohydrate and fat induces a metabolic syndrome in rats, which contributes to behavioral impairment in the form of impaired orienting and exploratory activity and increased anxiety. Further studies are needed, however, to identify the mechanisms underlying the behavioral changes in leptin resistance that may underlie the anxious behavior observed in our experiment. Biologically active substances of complex phytoadaptogen can be a promising addition to the correction of anxiety, depressive disorders in metabolic syndrome, affecting both through the autonomic nervous system and central structures - targets of leptin and ghrelin, and as protectors of neurons and peripheral tissues from oxidative and nitosative stress, eliminating resistance to insulin, reducing the release of cytokines.

Conflict of interest

The authors of this article declare no conflicts of interest.

REFERENCES

1. Collaborators GBDO, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017; 377: 13-27. doi: 10.1056/NEJMoa1614362

2. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018; 20(2): 12. doi: 10.1007/s11906-018-0812-z

3. Lyapina LA, Grigorjeva ME, Obergan TY, Myasoedov NF, Andreeva LA. Correction of manifestations of the experimental metabolic syndrome in rats with some arginine-containing peptides. *Vestnik Moskovskogo universiteta. Seriya 16. Biologiya*. 2017; 72(2): 92-98.

4. Lavallee KL, Zhang XC, Schneider S, Margraf J. Obesity and mental health: A longitudinal, cross-cultural examination in Germany and China. *Front Psychol*. 2021; 12: 712567.

5. Monserrat-Mesquida M, Quetglas-Llabres M, Capo X, Bouzas C, Mateos D, Pons A, et al. Metabolic syndrome is associated with oxidative stress and proinflammatory state. *Antioxidants (Basel)*. 2020; 9(3): 236. doi: 10.3390/antiox9030236

6. Panchal SK, Poudyal H, Iyer A, Nazer R, Alam A, Diwan V, et al. High-carbohydrate high-fat diet-induced metabolic syndrome and cardiovascular remodeling in rats. *J Cardiovasc Pharmacol*. 2011; 57(1): 51-64. doi: 10.1097/FJC.0b013e3181feb90a

7. Mulkey SB, du Plessis AJ. Autonomic nervous system development and its impact on neuropsychiatric outcome. *Pediatr Res*. 2019; 85(2): 120-126. doi: 10.1038/s41390-018-0155-0

8. Sadock BJ, Sadock VA. *Kaplan & Sadock's comprehensive textbook of psychiatry*. Philadelphia: Lippincott Williams & Wilkins Publishers; 2000.

9. Panossian A, Seo EJ, Efferth T. Effects of anti-inflammatory and adaptogenic herbal extracts on gene expression of eicosanoids signaling pathways in isolated brain cells. *Phytomedicine*. 2019; (1): 1528-1581. doi: 10.1016/j.phymed.2019.152881

10. Panossian AG, Efferth T, Shikov AN, Pozharitskaya ON, Kuchta K, Mukherjee PK, et al. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. *Med Res Rev*. 2020; 20(4): 1-74. doi: 10.1002/med.21743

11. Tian C, Hao L, Yi W, Ding S, Xu F. Polyphenols. Oxidative stress and metabolic syndrome. *Gxid Med Cell Longev*. 2020; 2020: 7398453. doi: 10.1155/2020/7398453

12. Zhang Y, Scarpace PJ. The role of leptin in leptin resistance and obesity. *Physiol Behav*. 2006; 88: 249-256. doi: 10.1016/j.physbeh.2006.05.038

13. Scarpace PJ, Matheny M, Kirichenko N, Gao YX, Tumer N, Zhang Y. Leptin overexpression in VTA trans-activates the hypothalamus whereas prolonged leptin action in either region cross-desensitizes. *Neuropharmacology*. 2013; 65: 90-100. doi: 10.1016/j.neuropharm.2012.09.005

14. Pertsov SS, Alekseeva IV, Abramova AYu, Nikenina EV, Kozlov AYu, Koplik EV, et al. Metabolic parameters in rats at various stages of the post-stress period under conditions of antigenic exposure by administration of lipopolysaccharide. *Russian Journal of Physiology*. 2021; 107(3): 321-331. (In Russ.). doi: 10.31857/S086981392103008

15. Pezze MA, Feldon J. Mesolimbic dopaminergic pathways in fear conditioning. *Progr Neurobiol*. 2004; 74: 301-320. doi: 10.1016/j.pneurobio.2004.09.004

16. Marazziti D, Rutigliano G, Baroni S, Landi P, Dell'Osso L. Metabolic syndrome and major depression. *CNS Spectr*. 2014; 19(4): 293-304. doi: 10.1017/S1092852913000667

17. Hasan MK, Mondal MSA, Kabir Y. Phytochemistry, pharmacological activity and potential health benefits of *Glycyrrhiza glabra*. *Heliyon*. 2021; 7(6): 07240. doi: 10.1016/j.heliyon.2021.e07240

18. Zheng Y, Lee J, Lee EH, In G, Kim J, Lee MH, et al. A combination of Korean red ginseng extract and *Glycyrrhiza glabra* L. extract enhances their individual anti-obesity properties in 3T3-L1 adipocytes and C57BL/6J obese mice. *J Med Food*. 2020; 23(3): 215-223. doi: 10.1002/med.21743

19. Li Z, Chen C, Zhu X, Li Y, Yu R, Xu W. Glycyrrhizin suppresses RANKL-Induced osteoclastogenesis and oxidative stress through inhibiting NF-κB and MAPK and activating AMPK/Nrf2. *Calcif Tissue Int*. 2018; 103(3): 324-327. doi: 10.1007/s00223-018-0425-1

20. Lee OH, Kwon YI, Apostolidis E, Shetty K, Kim YC. Rhodiola-induced inhibition of adipogenesis involves antioxidant enzyme response associated with pentose phosphate pathway. *Phytother Res*. 2011; 25(1): 106-115. doi: 10.1002/ptr.3236

Information about the authors

Zhanna V. Dzampaeva – Junior Research Officer, Institute of Biomedical Researches – Branch of Vladikavkaz Scientific Centre, Russian Academy of Sciences, e-mail: dzhanaeva_1991@mail.ru, https://orcid.org/0000-0002-0778-5117

Fatima S. Datieva – Dr. Sc. (Med.), Leading Research Officer, Director, Institute of Biomedical Researches – Branch of Vladikavkaz Scientific Centre, Russian Academy of Sciences, e-mail: faaroo@mail.ru, https://orcid.org/0000-0002-1636-9174

Elena A. Takoeva – Cand. Sc. (Med.), Research Officer, Institute of Biomedical Researches – Branch of Vladikavkaz Scientific Centre, Russian Academy of Sciences, e-mail: elena_takoeva@mail.ru, https://orcid.org/0000-0001-7248-5244

Marina I. Nartikoeva – Junior Research Officer, Institute of Biomedical Researches – Branch of Vladikavkaz Scientific Centre, Russian Academy of Sciences, e-mail: nartikoeva_m@mail.ru, https://orcid.org/0000-0001-9235-7303