INFLUENCE OF ADAPTOGENS ON THE MORPHOFUNCTIONAL STATE OF ADRENAL GLANDS IN STRESS

Solodkova O.A., Zenkina V.G.
Pacific State Medical University Russian Ministry of health, Vladivostok,
e-mail: solodkova.oksana@gmail.com

In conditions of long-term exposure, the stress response from the general adaptation syndrome is transformed into a factor of etiology and pathogenesis of ulcerative lesions of the mucous membranes of the stomach, duodenum, hypertension, atherosclerosis, cardiac dysfunction, secondary immunodeficiency states, and oncological diseases. Adrenal glands play a key role in the adaptation process, so their morphofunctional state directly affects the successful formation of adaptive mechanisms. According to modern ideas, to prevent the effects of stress, the focus is on limiting excessive stress and regulating the excess output of catecholamines and glucocorticoids. In this regard, correction of metabolic disorders that occur in pathological conditions due to stress, is one of the current biomedical problems. Over the past decades, a large clinical and experimental material has been accumulated, which has shown the effectiveness of prevention and correction of stress injuries with the help of adaptogens of plant and animal origin.

Keywords: stress, the adrenal glands, adaptogens

Stress is a non-specific reaction, by which the body adapts to the factors of daily life, industrial overload and environmental influence, i.e. adapts, which is one of the basic properties of life. The way to solve this problem is the mobilization of metabolic sources, allowing to produce additional energy. At the time of Selye identified three main stages in the development of the General adaptation syndrome: alarmrelay (alert phase), the stage of resistance and stage of exhaustion [14, 18, 22]. At the stage of alarm the regime of life support systems functioning is being reconstructed to work in extreme conditions, homeostatic regulation systems activation, organs and cells reserves mobilization due to the priority delivery of energy and plastic resources to them. This is necessary to increase the body's resistance to the effects, which is typical for the second stage – increased resistance. If extreme irritation continues, the reserves of the body are spent, and the maintenance of efficiency of cells, organs is carried out at the cost of destruction of their own vital structures [9, 10].

In the conditions of long-term exposure, the stress reaction from the General adaptation syndrome turns into a factor of pathogenesis. Currently, the role of stress as a factor of etiology and pathogenesis of neurotic, cardiovascular, endocrine, immune and other diseases has been proved [3, 19, 29]. A key role in the process of adaptation is played by the adrenal glands (NP), so their morphofunctional state directly affects the successful formation of adaptive mechanisms [8, 23]. The state of microstructure of NPP, synthesis and secretion of corticosteroids, adrenaline and noradrenaline are generally accepted indicators of stress reaction, reflect its duration, depth and stage [2, 25].

Numerous studies of a number of authors presented the results of morphofunctional state of NP of experimental animals under acute and chronic stress. When karyometry found that a single stress exposure increases the area of the nuclei of the beam zone cells, changes in the relative mass of NP does not occur. It is known that the increase in the size of nuclei in hormone-producing cells indicates their increased secretory activity [35, 36]. In the NP cortex, one can observe the pronounced fullness of sinusoidal capillaries, especially in the beam and mesh zones. Repeatedly repeated stress factors increase the area of the nuclei of the beam and mesh zones, thus indicating their significant activation. In the adrenal glands, there is a thinning of the capsule, an extension of the beam zone, a narrowing of the glomerular and mesh zones, a blurred border between the zones, a sharp expansion of the lumen of blood vessels. In addition, the expanding Stanovoy layer, which was probably due to the proliferation of cambial cells of the cortex of NP as a result of increased functional load on the body [34, 37].

Under severe stress, there is a sharp activation of NP. This is manifested by a significant expansion of the cortical substance due to the beam-mesh zone, an increase in the size of the nuclei in the cells of these zones. This is evidenced by the disappearance of lipid vacuoles in adrenocorticocytes, capillary dilation, swelling of their endothelium. In parallel, a pronounced alterative changes: granular, vacuolar and hyaline degeneration of epithelial cells, holocrine, disconnecktie epithelial cords, hemorrhage, various sizes necrosis [24, 28, 30].

Experimental data showed that if the functional load continues to increase, and the production of hormones does not replenish the

consumption – there is a complete delipoidization of the bark of the NP, the cytoplasm of all cells becomes somewhat basophilic with light grain. There are pockets of cell cytolysis. In compensation, when the production of hormones begins to exceed the demand-there are accumulation of lipids in part of the cells, i.e. part of the cells begins to work again "in reserve". Disappear foci of cytolysis. If stabilization does not occur – developing the picture of exhaustion, expressed in full delipidization bark NP. In this case, the cells are closely reduced in size, the nuclei become compact and smaller. The cytoplasm becomes basophilic, is densely granular. Speakers dramatically thinner, again showing foci of cytolysis [26, 30].

Stress effects lead to significant restructuring of the structural and functional apparatus of chromaffin cells, which are expressed in a noticeable devastation of Deposit catecholamines (KA) granules, swelling of mitochondria and enlightenment of their matrix, the expansion of elements of the Golgi complex and endoplasmic reticulum, reducing the number of ribosomes. With the continuing stress on the body, the content of SC in NP decreases gradually and changes as follows [20]. At the stage of anxiety, which is characterized by a tendency to reduce the weight of NP, reduce the mass of lymphoid organs (thymus, spleen) to 60-64 %, the KA content decreases slightly and by the end of this stage – the beginning of the adaptation stage is about 85 % of the control level. In the stage of adaptation, in which these indicators of somatic manifestations return to their values in intact animals, with the exception of hypertrophied NP, the KA content continues to decrease to 25 %. By the beginning of the stage of depletion of the KA content is reduced to the boundaries of the definition [1, 39].

Histologically method revealed that the allocation of chromaffin cell secretory material formed numerous clavate outgrowths of their cytoplasm, often with thinning of the foot to adjacent the lumen of the dilated sinusoidal capillaries. It can be assumed that the formation of these structures leads to extremely intense activity of chromaffin cells. KA content is reduced directly proportional to the time of stress exposure. The amount of adrenaline decreases more pronounced compared to the level of noradrenaline [11, 21].

Lipid peroxidation (LPO) with its excessive activation in many tissues causes destructive changes that affect the rate of cellular metabolism, and therefore, the specific function of the tissue. The bark of NP differs from other tissues by a significant amount of unsaturated lipids and a high content of transition valence metals, which is a prerequisite for the development of lipid peroxidation processes. In addition, it was found that cytochrome P450-reductase, which takes part in the hydroxylation of steroids, and located in the cells of the bark of NP on both the endoplasmic reticulum and mitochondria, can also be a link that initiates the formation of free radicals [4, 15, 16].

It is known that the adrenal glands are rich in natural antioxidant compounds that prevent the development of POL processes. This primarily applies to ascorbic acid and α – tocopherol. Their high content prevents uncontrolled development of the processes of SEX. However, with prolonged stress associated with depletion of functional resources of the crust of NP, there is activation in these glands of the processes of LPO. The reason for this may be a decrease in the content of NP in the cortex of ascorbic acid and α-tocopherol [5].

According to modern concepts, to prevent or limit the effects of stress, the main attention is paid to limiting excessive stress response and regulating the excessive output of KA and glucocorticoids [1, 23, 38]. In recent decades, a small clinical and experimental material has been accumulated, which showed the effectiveness of prevention and correction of stress injuries with the help of adaptogens of natural origin. Features of adaptogens of natural origin are due to the presence of biologically active compounds in them, which have immunomodulatory, antimicrobial, hypolipidemic, antitumor, antioxidant, wound healing, radioprotective and other effects [6, 7, 17, 32]. Dietary supplements differ from conventional medicines, above all, that carry out the regulation or stimulation of body functions strictly within the limits of physiological norm. A valuable property of biologically active additives is a characteristic adaptogenic normalizing action, which does not depend on the nature of the previous shifts [12, 27, 33].

In the work of E.I. Hasina, 2005, the effect of chitosan on the nonspecific resistance of the organism of laboratory animals in bacterial intoxication was investigated. The level of corticosterone in the blood during stress in animals on a background of reception of chitosan corresponded to the index of the intact animals. A day after the introduction of bacterial endotoxins, there was a significant increase in the relative weight of the adrenal glands, a decrease in the mass of the thymus, an increase in the level of corticosterone. Chitosan prevented hypertrophy of the adrenal glands and involution of the thymus. At the same time, there was a significant difference in the content

of corticosterone in blood plasma. The results of the study showed that chitosan increased the adaptive capacity of the body, influenced the endocrine system, in particular, the level of corticosteroids in the blood, which have a triggering effect, leading to complex changes in metabolic processes and the functional state of a number of endocrine organs and lymphoid tissues. Against the background of taking chitosan stress reaction was less pronounced [12].

The experiment shows the stress-protective effect of the drug "Derinat" in cold stress. Derinat, which is a sodium salt of native DNA and obtained from the milk of salmon or sturgeon, is a unique polymer immunomodulator with radioprotective, antiviral, regenerative activity. In animals, which before application of both 10-minute cold and 30-minute combined stress were injected with Derinat, there were no changes in corticosterone concentration in blood compared to the same index in control stressed animals. Thus, the introduction of Derinat prevented the stress-induced increase of corticosterone concentration, providing a stress-protective action [28].

Mechanisms of antistress action of dry extract of Astragalus webbed studied in the model of immobilization stress in white rats. Prophylactic administration of the tested drug was accompanied by a decrease in the severity of adrenal hypertrophy and involution of immunocompetent organs. Adrenal mass in rats of the experimental group was 24% less than in the control group. The obtained data showed that the course administration of tarragal extract on the background of immobilization stress has a stress-protective effect, reducing the severity of catabolic changes in the internal organs of white rats, which is obviously associated with the optimization of the balance of stress-implementing and stress-limiting systems of the body, as well as the limitation of hyperactivation of free radical oxidation processes and increase in the power of the endogenous antioxidant system [3].

Stress-protective effect of the extract of alfredii drooping studied on models of hypercapnic hypoxia, tissue hypoxia, and acute immobilization stress in laboratory animals. In mice of the stress control group, ulceration of the gastric mucosa was observed. Spleen weight decreased by 42%, thymus-by 25%, NP increased by 1.5 times. The introduction of Alfredo extract more than 5 times reduced the amount of hemorrhages in the stomach and prevented atrophy of NP. The authors suggest that the activity of the extract can be caused by the presence of flavonoids and other phenolic compounds in the plant, antioxidant and antihypoxic activity of which is associated with mobile hydrogen atoms of hydroxygroups, in addition, they suggest the effect of flavonoids of the extract on the functioning of cytochromes and the restoration of oxidative metabolism [19].

Echinacea purple has become the most popular among herbal remedies. Fundamental and clinical studies have shown that Echinacea purpurea can be a preventive measure, optimizing the nonspecific resistance of the body to various adverse factors, thereby slowing the development of environmentally-related diseases. In the experiment, we simulated pathologies caused by three different environmental factors: physical, chemical and biological. The level of the stress marker-corticosterone exceeded the control values in laboratory animals by 32-43%. The introduction of Echinacea in parallel with the action of stressors significantly prevented hormonal hypersecretion. The level of corticosterone in the serum exceeded the level of untrained mice only by 6-14% [12].

Experimental studies of the action of the extract and hydrolyzate from the far Eastern holoturia Cucumaria japonica on the morphofunctional state of the adrenal glands in acute and chronic cold stress were carried out. According to the literature data, the triterpene glycosides included in their composition have a corticosteroid-like effect. It is assumed that the preliminary receipt of animal food additives data, accompanied by a decrease in the degree of activation of the pituitary-adrenal system, a decrease in the blood output of glucocorticoids. It was found that the development of stress reaction after the preliminary reception of the extract and hydrolyzate from Japanese cookumaria containing triterpene glycosides was accompanied by less pronounced fluctuations in the basic quantitative parameters of the functional elements of the adrenal cortex, which contributed to the stabilization of the level of cortisol in the blood, limiting the stress reaction in the stage of anxiety, the formation of a more pronounced stage of resistance and delay in the stage of depletion of the General adaptation syndrome [30, 31].

Conclusion

Short – term and long-term stress factors contribute to a significant activation of the adrenal cortex as a compensatory reaction of the body in the form of increased hormone production. As a result, there are functional and structural damage to tissues and organs, leading to a decrease in the quality of life, loss of efficiency, disability. In this regard, the correction of metabolic disorders that occur in pathological

conditions due to stress effects, the main attention is paid. Natural biological resources are an inexhaustible source for the development of valuable food products, biologically active additives and drugs of adaptogenic action. According to modern ideas, one of the approaches in the treatment of disorders caused by stress effects is the use of adaptogens. Drugs of this type activate metabolic adaptation to the action of damaging factors and the ability to maintain the basic parameters of homeostasis.

References

1. Ajdzanovic V., Jaric I., Miler M. et al. Diosgenin-caused changes of the adrenal gland histological parameters in a rat model of the menopause // Acta Histochem. – 2017. – V. 119, № 1. – P. 48-56.

2. Antonov Y.V., Alexandrovich Y.V., Redina O.E. et al. Stress and hypertensive disease: adrenals as a link. Experimental study on hypertensive ISIAH rat strain // Clin. Exp. Hypertens. – 2016. – V. 38(5). – P. 415-423.

3. Batotsyrenova E.T., Antanova L.N., Toropov A.A. et al. Anti-stress effect of dry extract of Astragalus membranaceus // Bulletin of the Buryat state University. – 2012. – Special Issue S. – P. 55-59.

4. Bestervelt L.L., Piper D.W., Pitt J.A. Lipid peroxidation in the adrenal glands of male rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) // Toxicol. Lett. – 1994. – Vol. 70, № 2. – P. 139-145.

5. Bähr V., Pfeiffer A.F., Oelkers W. Is there a need for vitamin C supplementation of the normal diet? Effects of in vivo ascorbate depletion on adrenal function // Am. J. Clin. Nutr. – 2008. – Vol. 87, № 1. – P. 191-192.

6. Feng L., Liu X.M., Cao F.R. et al. Anti-stress effects of ginseng total saponins on hindlimb-unloaded rats assessed by a metabolomics study // J. Ethnopharmacol. – 2016. – № 188. – P. 39-47.

7. Filaretov A.A., Bogdanova T.S., Mitiushov M.I. et al. Effect of adaptogens on the activity of the pituitary-adrenocortical system in rats // Biull Eksp. Biol. Med. – 1986. – V. 101(5). – P. 573-574.

8. Gillis-Germitsch N., Vybiral P.R., Codron D. et al. Intrinsic factors, adrenal gland morphology, and disease burden in captive cheetahs (Acinonyx jubatus) in South Africa // Zoo. Biol. – 2017. – Vol. 36, № 1. – P. 40-49.

9. Gallo-Payet N. 60 YEARS OF POMC: Adrenal and extra-adrenal functions of ACTH // J. Mol. Endocrinol. – 2016. – V. 56(4). – P. 135-156.

10. Ibrahim I.Y., Abdel-Hakim S.M., Nazmy W.H. et al. Biological variations in adrenal gland response to immobilization and glucoprivation stressors in rats // Endocr. Regul. – 2015. – V. 49(4). – P. 217-226.

11. Jaroenporn S., Yamamoto T., Itabashi A. et al. Effects of pantothenic acid supplementation on adrenal steroid secretion from male rats // Biol. Pharm. Bull. – 2008. – V. 31(6). – P. 1205-1208.

12. Khasina E.I. Echinacea purpurnaya as a means of correction of ecologically caused pathologies // Proceedings of the Samara scientific center of the Russian Academy of Sciences. – 2014. – Vol. 16, № 5 (2). – P. 1030-1032.

13. Khasina E.I. Chitosan and nonspecific resistance of the organism // Vestnik DVO RAN. – 2005. – № 1. – P. 62-71.

14. Khnychenko L.K. Stress and its role in the development of pathological processes // Reviews in clinical pharmacology and drug therapy. – 2003. – Vol. 2, № 3. – P. 2-15.

15. Lyle N., Bhattacharyya D., Sur T.K. et al. Stress modulating antioxidant effect of Nardostachys jatamansi // Indian. J. Biochem. Biophys. – 2009. – V. 46, № 1. – P. 93-98.

16. Liu Y., Tipoe G.L., Fung M.L. Melatonin attenuates intermittent hypoxia-induced lipid peroxidation and local inflammation in rat adrenal medulla // Int. J. Mol. Sci. – 2014. – V. 15, № 10. – P. 18437-18452.

17. Liu F., Chen J., Shi F. et al. Phytosterol additive boosts adrenal response to ACTH in male Japanese quail (Coturnix coturnix japonica) // Endocrine. – 2012. – V. 41(2). – P. 338-341.

18. Lupien S. The history of the Science of Stress: From Hans Selye to the discovery of anti-inflammatory medication // Sante Ment Que. – 2015. – V. 40(2). – P. 225-286.

19. Mustafin R.N., Zelenskaya K.L., Shilova I.V. Antihypoxic and stress protective effect of Alfred extract of drooping // Chemistry of plant raw materials. – 2012. – № 1. – P. 211-214.

20. Malendowicz L.K., Markowska A. Neuromedins and their involvement in the regulation of growth, structure and function of the adrenal cortex // Histol Histopathol. – 1994. – V. 9(3). – P. 591-601.

21. Men'shikov V.V., Cherkasov V.L., Meshcheriakova S.A. Disorders of the glucocorticoid function of the adrenal cortex and metabolism of biologically activesubstances in the tissues in erysipelas // Sov. Med. – 1980. – № 12. – P. 50-53.

22. Miller WL. The Hypothalamic-Pituitary-Adrenal Axis: A Brief History // Horm. Res. Paediatr. -2018. – doi: 10.1159/000487755.

23. Panossian A., Gabrielian E., Wagner H. On the mechanism of action of plant adaptogens with particular reference to cucurbitacin R diglucoside // Phytomedicine. – 1999. – Vol. 6, № 3. – P. 147-155.

24. Pokusa M., Prokopova B., Hlavacova N. et al. Effect of blockade of mGluR5 on stress hormone release and its gene expression in the adrenalgland // Can J. Physiol. Pharmacol. – 2014. – V. 92(8). – P. 686-692.

25. Pertsov S.S., Grigorchuk O.S., Koplik E.V. et al. State of Stress-Marker Organs in Rats with Various Behavioral Characteristics during Repeated Stress Exposures // Bull. Exp. Biol. Med. – 2015. – V. 160 (1). – P. 20-23.

26. Pakkarato S., Thoungseabyoun W., Tachow A. et al. Ultrastructural histometric evidence for expansion of the sustentacular cell envelope in response to hypersecretion of adrenal chromaffin cells in mice // Anat. Sci. Int. – 2018. – V. 93(1). – P. 75-81.

27. Panosian A.G., Dadaian M.A., Gevorkian G.A. // Action of adaptogens: cucurbitacin R diglucoside as a stimulator of arachidonic acid metabolism in the rat adrenal gland // Probl. Endokrinol. (Mosk). – 1989. – V. 35(2). – P. 70-74.

28. Rybakina, E.G., Shanin S.N., Fomicheva E.E., et al. The Activity of protective functions of the organism under stress and their correction with the drug Derinat // Medical immunology. – 2008. – Vol. 10, № 4-5. – P. 431-438.

29. Rubin de Celis M.F., Bornstein S.R., Androutsellis-Theotokis A. et al. The effects of stress on brain and adrenal stem cells // Mol. Psychiatry. – 2016. – V. 21, № 5. – P. 590-593.

30. Solodkova O.A., Zenkina V.G. Cold stress and its correction by a hydrolyzate of cucumaria Japanese // International journal of applied and fundamental research. – 2016. – № 3 (part 4). – P. 591-594.

31. Solodkova O.A., Zenkina V.G. The Biological effects of cucumaria Japanese // Pacific medical journal. – 2015. – № 3 (Annex). – P. 83.

32. Studentsov E.P., Ramsh S.M., Kazurova N.D. Adaptogens and related groups of drugs – 50 years of research // Reviews of clinical pharmacology and drug therapy. – 2013. – Vol. 11, № 4. – P. 3-43.

33. Stonic V.A. Some results and trends of marine biologically active metabolites research // Pacific medical journal. – 2016. – № 4. – P. 16-18.

34. Stepanyan Yu.S. Structural changes of the adrenal cortex in case of death from General hypothermia // Medical examination and the right. – 2012. – № 4. – P. 37-39.

35. Schloms L., Smith C., Storbeck K.H. et al. Rooibos influences glucocorticoid levels and steroid ratios in vivo and in vitro: a natural approach in the management of stress and metabolic disorders? // Mol. Nutr. Food Res. – 2014. – Vol. 58, № 3. – P. 537-549.

36. Umriukhin A.E, Sudakov K.V. Open field behavior and the state of the thymus and adrenal glands in rats after exposure tostress and elevation of blood level of autoantibodies to dopamine and glutamate // Bull Exp. Biol. Med. – 2013. – V. 155(5). – P. 587-590.

37. Umryukhin A.E., Sotnikov S.V., Chekmareva N.Y. et al. Stress-sensitive organs and blood corticosterone after immobilization of active and passive rats immunized with glutamate-bovine serum albumin conjugate // Bull Exp. Biol. Med. – 2014. – V. 158(2). – P. 177-180.

38. Unno K., Hara A., Nakagawa A. et al. Anti-stress effects of drinking green tea with lowered caffeine and enriched theanine, epigallocatechin and arginine on psychosocial stress induced adrenal hypertrophy in mice // Phytomedicine. – 2016. – V. 23(12). – P. 1365-1374.

39. Yanagita T., Kobayashi H., Yamamoto R. et al. Protein kinase C and the opposite regulation of sodium channel alpha- and beta1-subunit mRNA levels in adrenal chromaffin cells // J. Neurochem. – 1999. – V. 73(4). – P. 1749-1757.