American Journal of Medicine and Medical Sciences 2025, 15(2): 351-355
DOI: 10.5923/j.ajmms.20251502.18

Modern Aspects of Stress-Induced Changes in Immobilization Stress

Azimova Sevara Bakhadirovna[1,*], Salikhova Yulduz Bakhtiyarovna[2], Khujakhmedov Jamoliddin Djalolovich[3]

[1]Professor, Department of Normal and Pathological Physiology, Tashkent Medical Academy, Tashkent, Uzbekistan
[2]Assistant, Department of Normal and Pathological Physiology, Tashkent Medical Academy, Tashkent, Uzbekistan
[3]Director of "Genotechnology" Limited Liability Company, Tashkent, Uzbekistan

Abstract This article discusses modern aspects of the pathogenesis of stress-induced changes in immobilization stress, which is one of the most common models for studying the physiological and biochemical reactions of the body to stress. Immobilization stress is characterized by activation of the hypothalamic-pituitary-adrenal axis (HPAS), release of corticosteroids, as well as changes in metabolism, immune function and structural and functional state of various tissues and organs. The mechanisms underlying such changes are considered, including oxidative stress, inflammatory reactions, neurotransmitter imbalances and disorders in neuroplasticity. Particular attention is paid to the effect of stress on the central nervous system, cardiovascular and endocrine systems, as well as on the adaptive capabilities of the body. Promising approaches to pharmacological correction and prevention of stress-induced disorders are presented. The conclusions of the article can be useful for further study of stress-associated diseases and development of effective strategies for their treatment.

Keywords Immobilization stress, Stress-induced changes, Hypothalamic-pituitary-adrenal system, Oxidative stress

1. Introduction

The intensive development of science and technology has brought a number of unfavorable factors into the life of mankind along with positive phenomena: physical inactivity, excessive nervous and physical stress, professional and domestic stress. Among them, physical inactivity is a way of life characterized by a decrease in physical activity, which negatively affects human health [3]. Physical inactivity leads to metabolic and energy disorders in the body, cardiovascular diseases, gastrointestinal diseases, excess weight, early aging, decreased ability of the body to resist various diseases, changes in the general condition of the body, etc. [3,6]. Such stress effects are observed at the cellular and molecular level [25,26]. As immobilization stress increases, metabolic disorders appear, activation of free radical oxidation leads to disruption of the main functions: barrier, receptor, catalytic functions of biological membranes. Stress is a constant component of human and animal life and its impact on the human body is especially great in the presence of ecologically unfavorable factors and social tension, the problem of "stress and health" acquires special significance. Stress-induced suppression of the immune system function "opens up the possibility" for the development of diseases of various origins (infectious, allergic, tumor). That is why the study of the mechanisms of development of stress-induced dysfunctions of the immune system is of current interest, especially relevant are studies of the molecular biological aspects of this problem.

Pathophysiological mechanisms of stress development are widely studied today. In response to stress, the body includes protective reactions that contribute to the development of an adaptive response [1].

As is known, the autonomic nervous and endocrine systems are also involved in the mechanisms of response to stress. N. Selye (1936) was the first to discover the participation of glucocorticoid hormones of the adrenal cortex in this process. The subsequent emergence of molecular biological research methods made it possible to study the central mechanisms of this process in more detail. In recent years, much attention has been paid to studying the effects and mechanisms of stress on the functions of the immune system [27]. As it turned out, stress exposure can have a stimulating or suppressive effect on the functions of the immune system, and therefore on the body's defense against genetically alien influences.

2. Purpose of the Research

The primary purpose of this research is to investigate the modern aspects of stress-induced changes in immobilization stress, focusing on its neuroendocrine, immune, and behavioral effects. By analyzing recent literature, this study aims to enhance

* Corresponding author:
sevara.azimova@yahoo.com (Azimova Sevara Bakhadirovna)
Received: Jan. 24, 2025; Accepted: Feb. 12, 2025; Published: Feb. 14, 2025
Published online at http://journal.sapub.org/ajmms

the understanding of stress mechanisms and their implications for health and disease. Furthermore, it seeks to identify potential therapeutic interventions to mitigate the adverse effects of immobilization stress, contributing to the development of effective stress management strategies.

3. Results and Discussion

It is known that stress can stimulate or suppress the activity of the immune system, and the nature of the effect depends on the intensity and duration of the stressful impact, as well as on the initial functional state of the body. The stimulating effect of stress is observed mainly in short-term, adaptive forms of stress. As is known, stress causes a complex of neurohumoral changes that affect the activity of cells of the immune and nervous systems. The main manifestations of stress include an increase in the blood level of glucocorticoid hormones, catecholamines, the number of granular neutrophils, as well as a decrease in the mass of the thymus [2]. When an antigen enters the body, it is itself a stress agent that not only changes the functional state of the cells of the immune system, but also causes a complex of neuroendocrine changes, including an increase in the level of glucocorticoids in the blood [29]. By now, there is a concept of two possible ways of transmitting efferent information from the nervous system to the immune system: humoral and through nerve fibers innervating immunocompetent organs. The nerve pathways of the autonomic nervous system also contain neuropeptide fibers [4,5]. The main link implementing the influence of the central nervous system on the immune system is the hypothalamus [6]. Other parts of the central nervous system also participate in regulating the functions of the immune system, but this participation is mainly mediated through the influence on the functions of the hypothalamus. Hypothalamic hormones - oxytocin and vasopressin - have an immunomodulatory effect. Modulation of the functions of the immune system is mediated by the hypothalamic-pituitary system, which participates in the hormonal regulation of the work of immunocompetent organs and cells [7,8]. The intensity and nature of changes in immunological processes during stress largely depend on the characteristics of the psychoemotional status, the functional activity of the natural anti-stress system, which protects the body from excessive reaction and the development of stress-induced damage. In outwardly identical emotional-stressful situations, different individuals experience psychoemotional tension of varying strength and duration, which determines the development of different phases of stress: physiological stress, stress of transient states, pathological stress. Thus, according to J. Palmood (1981), in students with a stable psychoemotional status, the indicators of the functions of the immune system and non-specific anti-infective resistance during the examination session remain within the normal range or increase slightly. During this period, the number of B-lymphocytes in students may increase and the level of immunoglobulins in the blood increases with an insignificant decrease in the number of T-lymphocytes.

It is known that stress-induced changes in immune system functions, including the intensity of the cellular and humoral immune response, are mediated through the central nervous system, which exerts its influence through the hypothalamic-pituitary-adrenal and sympathoadrenal systems [27]. One of the important mechanisms for implementing the influence of stress on immunological processes is an increase in the suppressor activity of immunocompetent cells. A special population of T-lymphocytes, T-regulatory cells, which are most sensitive to the action of GC, participates in the immunosuppressive effect [28]. An increase in the concentration of GC in the blood, characteristic of a stress reaction, can lead to a decrease in the activity of T-regulatory cells and, consequently, to the suppression of the intensity of immune reactions. A number of studies have shown that the introduction of GC leads to inhibition of IL-2 production and IL-2 mRNA synthesis in T-lymphocytes of the spleen and peripheral blood, preventing the binding of transactivating factors of the IL-2 gene: AP-1 and NF-AT to the corresponding sites of the promoter part of the gene. It is known that stress can have a pronounced negative effect on the formation of a cellular immune response in general and on the production of IL-2.

Currently, more and more attention is paid to an integrated approach to the treatment and prevention of diseases. There are studies that examine the effect of acute and chronic immobilization stress on erythrocyte membranes. As a result of studies, it was found that the effect of immobilization stress leads to a decrease in the osmotic and peroxide resistance of erythrocytes and an increase in the yield of hemoglobin [25]. The use of vitamin E reduces the damaging effects of both acute and chronic immobilization stress. Stress-specific hormonal responses and other biomarkers affected by the stress response are commonly used to quantify or monitor stress [9]. Acute stress in humans is accompanied by a decrease in the intensity of aerobic glycolysis, the pentose phosphate cycle, gluconeogenesis, activation of lipolysis, and impairment of the esterifying function of the liver, with lipids being the predominant energy substrates [10].

With immobilization stress, changes in the levels of catecholamines, norepinephrine, and dopamine were found depending on the areas of the rat brain and the duration of stress. At the same time, a relationship was found between disturbances in electrodermal activity and changes in norepinephrine metabolism in the central nervous system (CNS). Immobilization stress leads to a 1.6-fold increase in the concentration of corticosterone in the blood serum, a sharp decrease in the levels of thyroid-stimulating hormone (TSH) and thyroxine, inhibition of proliferative processes in the epithelium of the cornea and pyloric part of the stomach of rats, production of active oxygen metabolites by granulocytes and an increase in the activity of their enzyme, myeloperoxidase. Thyroliberin against the background of stress causes a decrease in lysosomal cationic proteins and a decrease in cell viability [11]. Long-term immobilization stress is accompanied by a change in metabolism in the blood plasma of rats: activation of catabolic reactions (a decrease in the level of glycosaminoglycans, hexosamines, inhibition

of hexosamine synthetase activity), subsequently replaced by the predominance of anabolic processes. The nature of changes in the indices of biopolymer metabolism in connective tissue correlates with the level of glucocorticoid hormones in the blood: an increase in their amount leads to a decrease in anabolism processes. Under the influence of prolonged immobilization, a reliable depletion of the prefrontal cortex of the rat brain in phospholipids was noted [12].

A number of studies have shown that immobilization stress in rats leads to disruption of microcirculation and liver metabolism processes, cholestasis, which is reflected primarily in the suppression of liver enzyme activity, disruption of glycolysis, increased consumption of glucose and fats by the body, and damage to cell membranes. These processes vary depending on the emotional lability of animals, with the greatest fluctuations observed in the levels of LDH, alkaline phosphatase, and cholesterol. The degree of influence of combined immobilization stress on the indices of orienting behavior depends on the stage of the estrous cycle and the age of the animals. The effect of immobilization stress is more pronounced in old animals in the estrus stage. The effect of stress-inducing factors and α-tocopherol on behavior and free-radical processes in female white rats in different phases of the estrous cycle. According to other authors, immobilization stress, regardless of the age of the animals, causes intensification of free radical processes in the hypothalamus and liver with a sharp increase in erythrocyte hemolysis. The results obtained by us and other authors indicate that for the pharmacocorrection of stress effects, and in particular, under immobilization stress (hypodynamia, old age, etc.), it is necessary to use agents that simultaneously have a positive effect on liver metabolism and an antioxidant effect.

One of the components of a healthy lifestyle is constant physical activity. Limitation of physical activity is a powerful stress factor that causes an emotional reaction in animals. Under conditions of insufficient movement, the activity of a number of body systems is disrupted - immune, nervous, endocrine, cardiovascular and others.

One of the target organs of stress is the liver. The formation of stress is accompanied by the inhibition of microsomal reductases and a violation of hydroxylation, a violation of the synthesis of coenzymes. Other authors have found that modeling of immobilization stress in rats led to suppression of anaerobic glycolysis, inhibition of the pentose phosphate cycle, gluconeogenesis and activation of lipolysis in adipose tissue [30]. The results obtained in the work indicate a pronounced activation of lipid peroxidation processes in the blood serum of rats under stress in the form of 12-hour immobilization.

It was proven that under conditions of immobilization stress, suppression of the functional state of the testes is noted. Relative to the testes, the pituitary gland mass under immobilization tends to increase. This circumstance speaks in favor of suppression, first of all, of the secretory function of the pituitary gland, which is associated with the regulatory influence of the higher center of regulation of vegetative functions - the hypothalamus [13]. It was found that 28-day immobilization stress caused dysfunctions of the nervous system in the form of increased anxiety, horizontal, vertical, locomotive activity, emotionality and severity of depressive behavior, as well as an increase in the concentration of corticosterone in the blood serum of experimental animals [14]. Scientists have identified age-related features of changes in the "peroxidation and antioxidant activity" system in the body of rats under immobilization stress and under conditions of correction with neurotransmitters. Immobilization stress causes negative hyperlipidemic changes in the peripheral blood of old rats, but under the influence of a combination of L-tryptophan and nicotinic acid, the lipid and lipoprotein composition of the blood is normalized, which demonstrates geroprophylactic, hypolipidemic qualities of non-antioxidant genesis [15].

In the group of animals subjected to immobilization, the myocardial relaxation index remained at the control level, which may reflect compensation of the positive inotropic effect by an adequate relaxation process, which did not occur in the case of EMR exposure - the relaxation index was significantly reduced both before the ischemic test and in the post-ischemic period. Therefore, it can be concluded that EMR and immobilization stress have opposite negative effects on the myocardium: EMR exposure affects the relaxation function, and immobilization affects the contractile function. The combined effect of these factors did not lead to reliable differences in the functioning of the isolated heart. Immobilization stress also increases the intensity of the contractile function of the myocardium and the pressure developed by the heart muscle [16]. One of the key brain structures involved in the formation of the response of a multicellular organism to external stimuli, and in particular, stressors, is the hippocampus [17,18]. The hippocampus plays an important role in regulating animal behavior, memorization and learning processes, and collecting and retrieving information from memory. Its activity is modulated by both acute and chronic stress [19,20]. The latter causes dendritic atrophy in stressed rats [21], structural and functional changes [22]. The hippocampus is one of the unique brain structures where neurogenesis continues throughout life. Its activity is modulated by stressors, which may determine sensitivity/resistance to external influences [23]. It has been shown that 30-minute immobilization increases the level of TOB protein (a regulator of cell proliferation, c-Myc activity) in the hippocampus three and five hours after the end of stress [19]. Stressors of various natures, affecting the cells of target organs, can lead to genomic instability and even disintegration, which may play a role in the formation of post-stress pathologies. It was shown that both the classical mouse stressor – immobilization – and 2,5-dimethylpyrazine damage the genome of cells of both studied organs. Destabilization of the genome of cells of various organs is considered as a necessary stage in the development of a stress reaction in the body's attempt to adapt to extreme environmental influences [24]. It was found that 28-day immobilization stress caused dysfunctions of the nervous system in the form of increased anxiety, horizontal, vertical,

locomotive activity, emotionality and severity of depressive behavior, as well as an increase in the concentration of corticosterone in the blood serum of experimental animals. The introduction of tuftsin-PGP against the background of preliminary stress (from the 15th to the 28th day of the experiment) contributed to a decrease in the severity of stress-induced changes in the behavior of rats: at a dose of 750 μg/kg, the peptide had an anxiolytic effect, 250 μg/kg – an antidepressant effect. Moreover, these changes occurred against the background of a significant decrease in the level of corticosterone in the blood serum. Conclusion. Thus, Selank corrects stress-induced changes in the state of nervous system functions under conditions of 28-day immobilization stress. The use of immobilization of varying duration allows us to assess changes in the body that occur under the influence of stress factors of varying strength. In the process of life, a person is constantly exposed to physical, emotional, psychological factors that cause stress reactions that can lead to a decrease in the activity of the body's protective functions, as a result of which the risk of developing infectious, allergic and tumor diseases increase. It is known that under the influence of stress (trauma, surgery, excessive psychoemotional stress, etc.), the course of acute and chronic diseases differs from their classical manifestation. It should also be noted that the available data from clinical and experimental studies aimed at studying immobilization stress are somewhat contradictory. Therefore, the search for pathogenetic mechanisms of the development of the disease against the background of stress is an urgent and necessary task of modern science.

4. Study Limitations

Despite the advancements in research on immobilization stress, several limitations exist. Many studies rely on animal models, which, while valuable, may not fully translate to human responses due to physiological and psychological differences. Additionally, variations in experimental conditions, including the duration and intensity of immobilization stress, make it challenging to standardize findings across studies. Another limitation is the focus on specific biomarkers and pathways, which may overlook the broader systemic interactions involved in stress responses. Future research should aim to incorporate longitudinal studies, diverse population samples, and integrative approaches to better understand the complexities of stress-induced changes in immobilization stress.

5. Conclusions

Modern literature continues to shed light on the complex mechanisms underlying stress-induced changes due to immobilization stress. The interplay between neuroendocrine regulation, immune function, and behavioral outcomes remains a focal point of ongoing research. As advancements in neurobiology and psychoneuroimmunology progress, novel therapeutic interventions are anticipated to enhance stress resilience and improve overall well-being. Understanding these modern aspects is crucial for developing effective strategies to mitigate the adverse effects of immobilization stress in both clinical and everyday settings.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to all researchers and scholars whose work has contributed to the understanding of stress-induced changes in immobilization stress. Special thanks to academic institutions and funding agencies that have supported this area of research. Their contributions have been instrumental in advancing knowledge and potential therapeutic approaches.

Conflicts of Interest

The authors declare no conflicts of interest regarding this research. All sources cited are based on peer-reviewed literature, and no financial or personal affiliations have influenced the findings presented in this study.

REFERENCES

[1] Litennikova M. Phenomenon of stress. Emotional stress and its role in pathology // Actual problems of pathophysiology (selected lectures) / B.B. Moroz (ed.). Moscow: Medicine, 2001, pp. 220-353.

[2] Charmandari E., Tsigos C., and Chrousos G. Endocrinology ofthe stress response // An. Rev. Physiol. 2005. Vol. 67. P. 259- 284.

[3] Bikbulatova A. A., Andreeva E. G. Restoration Of The Profile Of Bioregulators Of Blood Plasma In People Of Second Adulthood With Osteochondrosis Of The Spine Against The Background Of Daily Wearing Of Medical And Preventive Clothing / Bikbulatova A.A, Andreeva E.G. // Research Journal of Pharmaceutical, Biological and Chemical Sciences. A. – 2018, № 9. – P. 413–419.

[4] Bedoui S., Kavamu1a N., Straub R.H. et al. Releance of neuopeptide Y for the neuroimmune crosstalk // J. Neuroimmunol. 2003. Vol. 134, № 1-2. P. 1-11.

[5] Liu Y., Li Z., Svaren-Quiding C et al. Splenic denervation suppresses mRNA gene expression and protein production of IL-l beta and IL-6 by peritoneal macrophages in both Trypanosoma brucei- infected and non-infected rats // Neuroimmunomodulation. 2004. Vol. 11, № 2, P. 113-118.

[6] Makarov E.S., Kravchenko A.D., Zayats O.V. Prevalence of physical inactivity among modern schoolchildren // International Student Scientific Bulletin. - 2022. - No. 6.

[7] Hefco V., Olshin A., Hevco A. et al. The modulator role of tl1e hypothalamic paraventricular nucleus on immune responsiveness // Brain Behav. Immunol. 2004., Vol. 18, № 2, P. 158-165.

[8] Webster J I., Tonelli L., Sternberg E.M Neuroendocrine regulation ofimmunity // An. Rev. Immunol. 2002., Vol. 20., P. 125-163.

[9] Alyautdin R.N., Guseinov M.D., Zilfikarov I.N., Romanov B.K. Stress-protective phytotherapy. Biomedicine, No. 3, 2011, pp. 115-119).

[10] Guilbert J.J. The world health report 2002—reducing risks, promoting healthy life. Educ. Health (Abingdon) 2003; 16: 230.

[11] Klatenberg J., Plum L.M., Ober-Blobaum J.L., Honscheid A., Rink L., Haase H. Zinc signals promote2-dependent proliferation of T cells. Eur. J. Immunol. 2010; 40: 1496–1503.

[12] Kirichek L.T., Perepelitsa A.V., Kalchuk R.O. Medicinal anti-stress in the experiment (immobilization, trauma, inflammation). Monograph. - Kharkov: IPT "Contrast", 2015, pp. 94.

[13] Loginov P.V. Effect of immobilization stress on the functional state of the testes of white rats // International Journal of Applied and Fundamental Research. - 2014. - No. 10-1. - pp. 149-150.

[14] Bobyntsev I.I., Krivoshlykova M.S., Medvedeva O.A., Vorvul A.O., Andreeva L.A., Myasoedov N.F. The state of the nervous system functions of Wistar rats when using the peptide tuftsin-PGP (selank) under immobilization stress. Man and his health. 2023; 26(3): 58-68.

[15] Shcherbakov DL, Meshchaninov VN. Effect of neurotransmitters on lipid peroxidation under immobilization stress in rats of different ages. Kazan med. j. 2021, no. 5, pp. 87-95.

[16] Bakshaeva M., Kadukova E. Effect of immobilization stress and electromagnetic radiation of industrial frequency on the behavior and functional activity of the isolated rat heart. Žmogaus ir gamtos sauga 2018, pp. 78-85.

[17] Anand K.S., Dhikav V. Hippocampus in health and disease: An overview. Ann Indian Acad Neurol 2012, 15: 239–246.

[18] Goldfarb EV, Rosenberg MD, Seo D, Constable RT, Sinha R. Hippocampal seed connectome-based modeling predicts the feeling of stress. Nat Commun 2020, 11: 2650.

[19] Youssef M.M., Hamada H.T., Lai E.SK., Kiyama Y, El-Tabbal M, Kiyonari H, Nakano K., Kuhn B., Yamamoto T. TOB is an effector of the hippocampus-mediated acute stress response. Transl Psychiatry 2022, 12: 302.

[20] Love J, Zelikowsky M. Stress Varies Along the Social Density Continuum. Front Syst Neurosci 2020, 14: 582985.

[21] Conrad C.D., Magariños A.M., LeDoux J.E., McEwen B.S. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci, 1999, 113: 902–913.

[22] Ortiz J.B., Conrad C.D. The impact from the aftermath of chronic stress on hippocampal structure and function: Is there a recovery? Front Neuroendocrinol 2018, 49: 114–123.

[23] Levone B.R., Cryan J.F., O'Leary O.F. Role of adult hippocampal neurogenesis in stress resilience. Neurobiol Stress, 2015, 1: 147–155.

[24] Shcherbinina V. D., Bakulevsky B. V., Glinin T. S., Daev E. V. Destabilization of the genome of hippocampal and bone marrow cells of male mice after immobilization and pheromonal stressor. Sechenov Russian Physiological Journal, 2023, Vol. 109, No. 7, pp. 844-861

[25] Zhamanbaeva G., Zhaparkulova N., Usipbek V., Murzakhmetova M. Study of the effect of immobilization stress on erythrocyte membranes. Bulletin of KazNU. Biological Series, 2023, 95(2), 156–166.

[26] Novozhilov A. V., Tavrovskaya T. V., Ivanov V. A., Morozov V. I. Hematological indices and redox balance of rats in the dynamics of immobilization // Bulletin of experimental biology and medicine. - 2013. - Vol.155. - No. 4. - P. 439-442.

[27] Lauten T. H., Natour T., Case A. J. Innate and adaptive immune system consequences of post-traumatic stress disorder // Autonomic Neuroscience. – 2024.

[28] Aiello, A.E., et al. PTSD is associated with an increase in aged T cell phenotypes in adults living in Detroit. Psychoneuroendocrinology 2016, 67, 133–141.

[29] Gotovac, K., et al., 2010. Natural killer cell cytotoxicity and lymphocyte perforin expression in veterans with posttraumatic stress disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 597–604.

[30] Goncharova N.D., Shmaliy A.V., Marenin V.Yu., Smelkova S.A. Hypothalamic-pituitary-adrenal system and enzymes of the glutathione-dependent antioxidant system during stress and aging // Bulletin of Experimental Biology and Medicine. - 2007. - V.144. - No.11. - pp. 574-577.