OXIDATIVE STRESS AND IMMUNE REACTIVITY: THE ROLE OF LIPID PEROXIDATION AND ANTIOXIDANT SYSTEMS IN STRESS ADAPTATION

Hamidova Saodat Khikmatovna
Bukhara State Medical Institute

Abstract. This literature review analyzes the relationship between immunological reactivity, lipid peroxidation, and antioxidant defense mechanisms during stress conditions. Stress activates a complex cascade of neuroendocrine and biochemical reactions that disturb the balance between pro-oxidant and antioxidant systems. Excessive generation of reactive oxygen species (ROS) leads to lipid peroxidation, protein oxidation, and DNA damage, resulting in cellular dysfunction and immune imbalance. Numerous studies indicate that oxidative stress contributes to altered cytokine production, suppressed lymphocyte proliferation, and decreased phagocytic activity. The antioxidant system—comprising enzymes such as superoxide dismutase, catalase, and glutathione peroxidase—plays a compensatory role in neutralizing free radicals and maintaining redox homeostasis. The review highlights that prolonged or chronic stress depletes antioxidant reserves, weakens immune defense, and increases susceptibility to inflammatory and degenerative diseases. Understanding these interrelated processes provides insights for developing preventive and therapeutic approaches aimed at restoring oxidative and immune balance in stress-related disorders.

Keywords. immune response, thyroid, Selye stress.

According to Selye, stress is characterized by a number of stages successively replacing each other: anxiety, resistance and exhaustion. In recent years, ideas about stress have expanded. The concept of stress by G. Selye was transformed by W. Canon and developed by L. Levy into the concept of emotional stress [2]. From the position of the general theory of functional systems P.K. Anokhin, a conflict situation plays a decisive role in the genesis of emotional stress. A conflict situation develops when a subject, in the presence of a vital need, is unable to achieve a socially or biologically important result. A prolonged conflict situation, i.e. continuous negative emotional stress leads to a state of prolonged stagnant excitation of the brain and the development of systemic stress reactions [2]. Numerous works have shown that stress disrupts the functions of the thyroid gland, sexual, blood circulation, heart, and the state of the immune system [3–6].

Experimental studies have shown the participation of immune mechanisms in the formation of emotional reactions in animals. Moderate stress exposure leads to

potentiation of the immune response, and strong long-term stress exposure leads to immunosuppression [7]. Thus, in experiments on rats, it was shown that a short-term moderate effect of an emotional-pain stressor leads to an almost 2-fold increase in the activity of normal killers, then, under the influence of ongoing stress, a depression in the activity of immunocompetent cells occurs [8]. Also, with a moderate emotional stress reaction, animals were found an increase in the number of macrophages and an increase in phagocytic activity. Severe and prolonged stress leads to a stressor decrease in the response of T-lymphocyte blast transformation to a mitogen [9], a decrease in the lytic activity of T-lymphocytes and normal killers in relation to tumor target cells [10], and depression of the cytotactic function of macrophages [11].

It has been established that prolonged emotional stress reduces the activity of normal killers in the body of mice by almost 3 times. Adaptation to repeated short stressful situations largely or completely prevents depression caused by prolonged stress [12,13]. Inhibition of the immune system function under stress is associated with the suppression of the activity of the T-system, a change in the specific number of recirculating T-cells in relation to B-cells and macrophages. Also shown is the influence of the neuroendocrine system, an increase in the level of beta endorphins on the development of stress immunosuppression [14].

Under stress, lymphopenia, eosinopenia, and neutrophilic leukocytosis develop in the peripheral blood [15]. The cause of lymphopenia is the migration of lymphocytes to the bone marrow [16, 17]. The appearance of eosinopenia is associated with the migration of eosinophils into tissues, where they carry out immune reactions with tissue macrophages [18]. The development of leukocytosis in the first hours of stress occurs due to the release of mature granulocytes from the bone marrow. Activation of stress-realizing systems leads to an increase in exogenous catecholamines and glucocorticoids, which in turn increase neutrophilic leukocytosis [19,20]. Dhabhar F.S. (2009) in his works showed that stress and stress hormones play the role of regulators and modulators of the immune response. Stress and the release of glucocorticoid hormones can enhance or suppress immune function depending on the following factors: the duration of stress (acute or chronic), changes in the distribution of leukocytes in the body, the concentration and nature (endogenous, synthetic) of the effects of glucocorticoid hormones, the time of release of stress hormones depending from the stage of the immune response [19].

According to Zhetpisbaev B.A. and Raisova T.K. [21,22], in the early stages of the adaptation syndrome in the peripheral blood, leukocytosis, lymphocytosis, a decrease in the functional activity of the cellular and humoral immunity and nonspecific resistance of the body are noted.

The next stage is characterized by leukopenia and lymphopenia, strengthening of the T-system of immunity, non-specific resistance of the body, lack of restoration of

the B-link of immunity. Musainova A.K. [23] studied the effect of emotional stress on cellular, humoral, and nonspecific phagocytic immunity on days 1, 2, and 3 after emotional stress was reproduced. In the peripheral blood on the 1st day after the stress exposure, the number of leukocytes significantly increased by 49% of the initial value, slightly decreased on the 2nd day, and reached the initial level on the 3rd day. The relative and absolute number of lymphocytes significantly increased after stress exposure by 1.6 and 3.5 times on days 1 and 2, respectively, and remained high on day 3. The absolute number of T-total lymphocytes after stress exposure significantly increased throughout the observation period. Lymphocytosis against the background of leukocytosis is associated with the migration of lymphoid cells and stress redistribution of blood against the background of microcirculation disorders in organs and tissues [24].

Consequently, there are conflicting data on the number of lymphocytes in emotional stress. When studying theophylline-resistant and theophylline-sensitive rosette-forming cells, a significant increase in the absolute number of theophylline-resistant rosette-forming cells was noted in the first two days, then decreased to the initial level. The relative number did not change within two days, decreased on the 3rd day after the stress exposure.

The absolute and relative number of theophylline-sensitive rosette-forming cells with suppressor activity significantly increased on days 1, 2, and 3. At the first stage of the general adaptation process, i.e. in the first two days, an increase in cells with helper and suppressor activity was observed, a decrease in the helper-suppressor index was noted, the number of leukocytes and all types of lymphocytes increased. The indicators of the humoral link of immunity changed in different directions. On the one hand, the suppression index and the number of B-cells increased, and on the other hand, the level of concentration of circulating immune complexes decreased.

According to Tanatova Z.A. et al. and Musainova A.K. [23,25] when studying the nonspecific phagocytic link of immunity during emotional stress, 1, 2, and 3 days after stress, an increase in the phagocytic number, HBT test indicators, and phagocytosis percentage was noted and confirmed the data obtained by other authors. The increase in the phagocytic activity of leukocytes is associated with the body's compensatory response to stress in the form of a "metabolic explosion" in the neutrophil.

Thus, at an early stage of the stress reaction, activation of the cellular and phagocytic link and depression of humoral immunity occur.

When students were observed during the examination session, a decrease in the level of immunoglobulin A in saliva was found, which returned to normal after the examination [26]. Suzdalnitsky R.S. and Levando V.S. noted a decrease in immunity during stressful loads in athletes [27].

The mechanism of changes in immunoreactivity under stress is associated with the activation of mediators of the stress system - corticorylizing hormone, adenocorticotropic hormone, glucocorticoids and catecholamines. With a moderate increase in the secretion of mediators, the blood system is mobilized and the immune response is activated. With increased secretion of these mediators, inhibition of immunoreactivity occurs [7].

Immunosuppression during stress is associated with an increase in the concentration of glucocorticoid hormones in the blood serum, redistribution of erythrocytes, and activation of T-suppressors. Stimulation of immunity in the form of mobilization of lymphocytes, interaction with hematopoietic stem cells of the bone marrow is an adaptive reaction, which results in a recovery period or, with prolonged exposure to a stressor, a state of secondary immunological deficiency develops.

Herbert and Cohen conducted a meta-analysis of studies on the relationship between stress and the immune system. And they identified three types of stressors - acute stressors (such as speaking in front of an audience), short-term stressors (such as exams), and long-term stressors (such as unemployment, bereavement). They reported that under stress there is an increase in circulating white blood cells and a decrease in circulating B cells, T cells, helper and suppressor/cytotoxic T cells, and large granular lymphocytes. They also reported that under stress there is a significant decrease in the percentage of T-cells, T-helpers, suppressors and cytotoxic T-cells. In addition, the immune response depended on the duration of exposure to the stressor. During acute stress, an increase in the number of circulating suppressor/cytotoxic T cells was noted, but long-term stress factors reduced their number. However, natural killer function decreased under both acute and chronic stress. In some studies, on the contrary, an increase in the number of natural killers was noted, which is apparently associated with a short-term increase in immune function due to acute secretion of stress hormones [26].

Segerstrom and Miller (2004) also conducted an extensive meta-analysis of 293 independent studies from 1960 to 2001 (N=18941). The analysis of the results confirmed that acute stress can increase the immune function of the adaptive response, but chronic stress suppresses the immune response, resulting in the depletion of the body's resources. In addition, older and sick people are more vulnerable to stress. The authors also assessed how different types of immune response correlated with different types of stress. And they identified 3 categories of stress:

Acute stress: Public speaking and mental work fall into this category. With this type of stress, natural immunity is enhanced, that is, an increase in the number of natural killer cells in the peripheral blood was noted.

Consequences of Stressful Situations: This category included a focal event such as a natural disaster or the loss of a spouse. This category of stress is not strongly

associated with immune changes. After the loss of a spouse, there is a decrease in natural immune responses. There was a non-significant increase in natural and specific immune responses after exposure to natural disaster and non-immune changes in breast biopsy. Chronic stressors: This category includes long-term stressors such as living with a disability, caring for someone with dementia, being unemployed. Chronic stressors have a negative impact on almost all functions of the immune system, regardless of gender and age [27].

The release of adaptive "stress" hormones - catecholamines [28], vasopressin, etc. leads to an increase in the entry of calcium into the cell, mobilization and decrease in the glycogen reserve, and to the implementation of the lipid triad. The lipid triad is the activation of lipase, phospholipases, and an increase in free radical lipid oxidation. As a result of the lipotropic effect of the stress reaction, a modification of the lipid bilayer of the membrane occurs, in particular, the phospholipid and fatty acid composition of the lipid bilayer of the membrane changes, the viscosity decreases and the fluidity of the membrane increases.

The lipotropic effect of the stress reaction provides an urgent adaptation of the body to the action of environmental factors. However, with an excessively long and intense stress reaction, excessive activation of phospholipases, lipases, and free radical oxidation can lead to membrane damage and acquire a key role in transforming the adaptive effect of the stress reaction into a damaging one.

An important factor in changing the lipid bilayer of the membrane is free radical lipid oxidation. Numerous studies have shown an increase in free radical lipid oxidation under stress [29-11]. Under stress or with the introduction of catecholamines, the activation of lipid peroxidation (LPO) in the heart, liver, skeletal muscles, and other organs has been proven [22]. Activation of lipid peroxidation under extreme conditions is a typical process in the development of the general adaptation syndrome.

On the model of emotional pain stress, it was shown that free radical oxidation of lipids (phospholipid hydroperoxides, Schiff bases) increases by 2–3 times depending on the duration of stress [23]. Prilipko L.L. [24] noted an increase in free radical

lipid oxidation during emotional stress in humans during operator work under time pressure.

There are works describing the suppression of lipid peroxidation in acute and in the initial phase of chronic stress [25-26]. According to Gulyaeva N.V. with co-authors under stress, LPO activation is preceded by inhibition of LPO. So in women with algomenorrhoea with menstrual pain, the level of Schiff bases in the blood plasma first decreased (0-12 hours), then (12-24 hours) increased. According to Devyatkina T.A. The dynamics of the course of acute stress is characterized by alternating periods of increased LPO intensity with periods of their decrease [17].

Many researchers have found a decrease in the body's antioxidant system under

stress [27,28]. When studying lipid peroxidation and the antioxidant system in rats of different strains, intensification of lipid peroxidation (an increase in the level of malondialdehyde - MDA) and a decrease in antioxidant protection - an increase in glutathione peroxidase, a decrease in glutathione reductase and superoxide dismutase, i.e. a state of decompensation of the reserve capacity of antioxidant functions and a violation of the detoxification of the superoxide anion radical develops [17]. Studies have shown high levels of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, glutathione reductase) in the hypothalamus in control animals. Higher catalase activity was also found in the hypothalamus [19]. However, short-term emotional stress causes the most pronounced decrease in the activity of antioxidant enzymes in the hypothalamus [18]. In the study of changes in glutathione-dependent enzymes of the antioxidant system in young and old rats in response to stress, a higher level of the glutathione reductase enzyme was noted in young rats compared to old rats at different time intervals after the onset of stress exposure. The activity of glutathione peroxidase and glutathione reductase did not change significantly. According to the authors, lower antioxidant activity in stressed old rats can lead to a decrease in the reliability of antioxidant activity and activation of LPO [10].

Surina-Marysheva E.F. (2008) noted a decrease in the intensity of lipid peroxidation processes in blood plasma due to an increase in the activity of antioxidant enzymes - superoxide dismutase and catalase, glutathione reductase during short-term immobilization stress. An increase in the activity of the antioxidant system in response to the intensification of free radical oxidation processes due to the depletion of the resources of antioxidant enzyme systems leads to the inhibition of the antioxidant system. Apparently, the insufficiency of antioxidant protection is characteristic not of stress itself, but of a late and more severe phenomenon of tissue damage.

With the progression of free radical lipid oxidation, a large number of unsaturated phospholipids are oxidized and the number of unsaturated phospholipids in the microenvironment of functional proteins increases in membranes. This leads to a decrease in the fluidity of the membrane and the mobility of the peptide chains of these proteins and a decrease in the activity of the proteins. Further accumulation of oxidized unsaturated phospholipids leads to an increase in permeability and destruction of the membrane [11].

LPO in tissues changes depending on the phase of development of emotional stress and correlates with changes in animal behavior [42,43]. The high reactivity of the nervous-endocrine system and, accordingly, the high supply of oxygen and fatty acids to the tissues and the relatively low functional activity in rats leads to an increase in free radical processes.

oxidation. Emotional stress activates free radical

oxidation of triglycerides and acids that have not been used for a long time in the

course of enzymatic oxidation [14, 15].

Thus, free radical lipid oxidation and LPO activation is one of the early factors of physiological dysfunction during emotional stress.

An analysis of the literature data showed that immunological changes develop depending on the stage of stress, the strength and duration of the stress factor. And there are also different opinions about changes in lipid peroxidation and antioxidant protection during emotional stress.

REFERENCES

1. Khikmatovna, Hamidova Saodat. "Drinking water quality source of life." Web of Scientist: International Scientific Research Journal 2.10 (2021): 35-40.
2. Sobirjonovna, Kurbonova Nozima. "Factors determining the clinical significance of depiptidyl peptidase 4 inhibitors in the treatment of patients with type 2 diabetes mellitus." *World Bulletin of Public Health* 8 (2022): 67-72.
3. Каримова Н. А., Курбанова Н. С. Нарушение физического развития у подростков и его осложнения //Журнал кардиореспираторных исследований. – 2021. – Т. 2. – №. 2.
4. Каримова Н. А., Курбанова Н. С. Нарушение физического развития у подростков и его осложнения //Журнал кардиореспираторных исследований. – 2021. – Т. 2. – №. 2.
5. Yakubova M. M. et al. Clinical and neurological aspects of multiple sclerosis during infection with covid-19 in uzbekistan //Central asian journal of medical and natural sciences. – 2021. – Т. 2. – №. 3. – С. 186-190.
6. Якубова М. М. Клинико-молекулярно-генетические показатели ишемического инсульта у лиц узбекской национальности в зависимости от полиморфизмов генов FII, FV, MTHFR //Клиническая неврология. – 2008. – №. 2. – С. 16-19.
7. Якубова М. М. и др. Клинические особенности нарушения обоняния и вкуса при covid–19 //журнал неврологии и нейрохирургических исследований. – 2021. – №. Special 1.
8. Yakubova M. M., Mukhiddinova M. A. The Value of Neurospecific Protein S-100 and Lipoproteins in the Development of Multiple Sclerosis //Indian Journal of Forensic Medicine & Toxicology. – 2020. – Т. 14. – №. 4.
9. Yakubova, M. M. "New aspects of mri research in the differential diagnosis of binswanger disease." (2019).
10. Khuseynovna, Khuseynova Gulshan. "Morphometric parameters of the thyroid gland and physical development." Биология и интегративная медицина 2 (55) (2022): 5-13.

11. Khuseynova, Gulshan Khuseynovna. "Biology and iintegrative medicine." Biology and iintegrative medicine Учредители: Малое частное предприятие «Магия здоровья» 2: 5-13.
12. Khuseynovna, Khuseynova Gulshan. "Morphological Features of the Kidneys after Drug Correction of Moderate-Severe Cranio-Brain Injury." Miasto Przyszłości (2022): 19-22.
13. Хусейнова Г. Х. Морфометрическиепокозатели В Почкахпосле Нанесённый Травмы //Central asian journal of medical and natural sciences. – 2021. – С. 187-190.
14. Хусейнова, Г. "Macroscopic and microscopic characteristics of kidneys of white unbored rats after severe cranial injury." Журнал вестник врача 1.1 (98) (2021): 109-112.
15. Khuseynovna K. G. Morphological Changes in the Kidneys in Easy Degree of Cranio-Brain Injury //Vital Annex: International Journal of Novel Research in Advanced Sciences. – 2022. – Т. 1. – №. 1. – С. 5-7.
16. Kabilova, Gulshan. "General incidence with temporary loss of employment in silk milling plants." *InterConf* (2021).
17. Kobilova, Gulshan. "Modernization of production is a decisive factor of reducing the incidence of diseases in silk industries." *InterConf* (2021).
18. Кобилова Г. А., Жумаева А. А. Факторы риска развития внутрибольничных инфекций в акушерских стационарах Бухарской области //Материалы межвузовской научно-практической конференции «Актуальные вопросы медицины», инициированной Южно-казахстанской медицинской академией и шымкентским медицинским институтом международного казахско-турецкого университета имени ха ясауи. – 2018. – С. 61.
19. Кобилова Г. А., Саломова Х. Ж. Показатели здоровья рабочих в шелкомотальном производстве «бухара бриллиант силк» //Новый день в медицине. – 2020. – №. 2. – С. 407-408.
20. Ishanova B. Design and development of system to control, synchronize and coordinate multiple high-performance microvalves //Вестник. Серия Физическая (ВКФ). – 2014. – Т. 49. – №. 2. – С. 8-13.
21. Ishanova M. et al. Prevalence, prophylaxis and treatment principles of primary teeth erosion in children. – 2020.
22. Kh, Y. F., Ishanova, M. K., Akhmedov, A. B., Kodirova, M. T., Kh, D. E., & Utesheva, I. Z. (2021). Estimation of the diagnostic value of amino acid composition of oral fluid and blood serum in children wiyth dental arosion and their effectiveness of pathogenetic treatment. *International Journal of Pharmaceutical Research*, 3155-3161.

23. Ишанова, Мунира Каримуллаевна, and Гулчехра Кайратовна Есбосинова. "Проблема кариеса зубов у детей младшего возраста." *Вестник науки и образования* 13-2 (116) (2021): 4-8.
24. Ишанова М. К. Гидротерапия и её роль в лечении заболеваний пародонта/Ишанова МК, Кучкарова МК //Биология ва тиббиёт муаммолари. – 2018. – №. 4. – С. 1.105.
25. Ишанова М. К., Ташкенбаева И. У. Сравнительная оценка эффективности традиционной реминерализующей терапии и минерализующих зубных паст в лечении начального кариеса //Биология ва тиббиёт муаммолари. – 2018. – №. 4. – С. 1.
26. Akhmedov A. B. et al. Incidence, prophylaxis and treatment principles of primary teeth erosion in children //Toshkent tibbiyot akademiyasi axborotnomasi. – 2019. – №. 5. – С. 73-76.
27. Khikmatovna, Hamidova Saodat. "Establishing the systematic position of fungi of the genus trichoderma, isolated from soils of the bukhara region." International Engineering Journal For Research & Development 5.7 (2020): 6-6.
28. Хамидова, Саодат Хикматовна. "Создание таксономического положения грибов, относящихся к типу триходермий, выделенных из почвы." Интернаука 2-1 (2021): 19-20.