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FOUR STAGES AFTER STRESS REACTIONS

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Abstract

Stress is the main cause of non-communicable diseases. Currently, the prevailing concept is that there are two stages of post-stress reactions: the sympathetic and the neuroendocrine stages, as defined by Selye.

Taking into account the ideas of nervism and in accordance with the available biochemical and pathophysiological data, we propose to consider post-stress reactions in the form of 4 stages: 1. Sympathetic. 2. Parasympathetic. 3. Neuroendocrine. 4. Dysmetabolic.

At the first stage, the mediators are norepinephrine and adrenaline, at the second stage – acetylcholine, kinins, lipopolysaccharide, at the third – corticosteroids, thyroxine, at the fourth – various metabolites and microbe forums.

Keywords: stress; post-stress reactions; biochemistry and pathophysiology of stress.

Stress arises due to various reasons (trauma, pain, intoxication, inadequate living conditions, excessive emotions) and largely determines the development of many diseases (atherosclerosis, myocardial dystrophy, neurotrophic disorders, metabolic diseases) (Table 1) [1, 2].

Table 1. Etiological classification of human and animal diseases

№№	Group of diseases	Etiological factor	Condition of the body
1	Infectious	Pathogenic bacteria and viruses	Immunodeficiency
2	Alimentary	Inadequate nutrition macroorganisms and endogenous microbiota	Deficiency of essential compounds in food. Hyperphagia. Dysbacteriosis .
3	Hereditary	Genetic disorders	Deficiency of beneficial genes. Excess of pathogenic genes.
4	Stress-induced diseases	Stress	Injuries, pain, intoxication, inadequate living conditions, excessive emotions

Based on the principles of nervism, substantiated by I.P. Pavlov, we propose to consider stress as a chain of interconnected stages (Table 2).

Post-stress reactions consist of four stages. The first stage is stimulation of the sympathetic nervous system, including the adrenal medulla. The active neurotransmitters at this stage are norepinephrine and adrenaline.

The effects of catecholamines (epinephrine and norepinephrine) depend on their dose: at low concentrations, they perform a protective function, stimulating cardiovascular activity and activating hydrolytic systems (adipose tissue lipase, glycogen phosphorylase, and intravascular proteolysis). A very important property of catecholamines is the activation of free-radical oxidation processes ("oxidative stress") [3]. At high concentrations, catecholamines can cause heart attacks and strokes.

Table 2. Stages of post-stress reaction development

		Location Syndrome	Mediators	Syndrome
	Stress	Cerebral cortex, hypothalamus	Acetylcholine, adrenaline, dopamine	Overexcitation of the cerebral cortex
	Post stress reaction			
1	Sympathetic	Sympathetic nervous system, the adrenal medulla	Norepinephrine, adrenaline	Oxidative syndrome (oxidative stress)
2	Parasympathetic	Parasympathetic nervous system, secretory organs	Acetylcholine, kinins. Lipopolysaccharide (LPS)	Hemodynamic impairment. Increased permeability of the intestinal barrier and histohematic barriers. Dysbiotic syndrome.
3	Neuroendocrine	Pituitary gland, adrenal cortex, thyroid gland	ACTH, TSH, corticosteroids, thyroxine	Anti-inflammatory effect. Adaptation syndrome.
4	Dysmetabolic	Liver, kidneys, gastrointestinal tract, bone tissue, nervous system	Elevated levels of free fatty acids, glucose, uric acid, toxins	Main diseases: atherosclerosis, diabetes, obesity, NASH

During the second stage of post-stress reactions, the parasympathetic nervous system (n. vagus) is activated, using acetylcholine as its active mediator. It stimulates the activity of secretory organs (primarily the salivary and gastric glands), resulting in an increase in kallikrein activity in the blood due to activation of the salivary glands. Kallikreins form kinins (bradykinin) from kininogen circulating in the blood, which significantly increase the permeability of the histohematic and intestinal barriers [4].

The activity of the enzyme hyaluronidase, which is produced by the salivary glands and which causes the breakdown of hyaluronic acid ("intercellular cement"), is also activated [4].

The effect of kinins is a decrease in blood pressure and a strong increase in the permeability of the intestinal barrier, leading to the translocation of bacteria and their toxins into the bloodstream. Among microbial toxins, lipopolysaccharide (LPS) plays a special role. Our studies have shown that it possesses the highest pro-inflammatory activity, exceeding other toxic substances by hundreds and even thousands of times. The resulting dysbiotic syndrome [4] is the pathogenetic basis for many non-communicable diseases (obesity, non-alcoholic steatohepatitis, type 2 diabetes, and other metabolic diseases) [5].

The third stage of stress is the activation of the neuroendocrine system, particularly the pituitary gland, which produces hormones that act on the endocrine glands: ACTH (adrenocorticotropic hormone), TSH (thyroid-stimulating hormone), and others [1]. This stage of the post-stress response was first substantiated by G. Selye [1] and was the primary focus of research for many years. Corticosteroids, formed under the influence of ACTH on the adrenal cortex, have become firmly established in the arsenal of therapeutic anti-inflammatory agents.

We propose a fourth stage in the development of post-stress reactions, manifested as dysmetabolic and immune processes in which impaired liver function plays a crucial role. In addition to its metabolic functions, the liver has antimicrobial and antitoxic functions [5].

Each stage of post-stress functions requires a selective approach to prevent its development. Thus, the first stage requires the use of antioxidants. The second stage requires the use of anti-acetylcholine drugs, antidysbiotics, and protease inhibitors (primarily kallikrein inhibitors). The third stage requires the use of agents that prevent the antimetabolite effects of corticosteroids. Finally, the fourth stage requires the use of hepatoprotectors and antitoxic agents used to treat emerging diseases.

Author Contributions

The authors agree to equal distribution of partial participation.

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Informed Consent Statement

Informed consent was obtained from all subjects who participated in the study.

Data Availability Statement

All information is in the public domain and specific graphic data can be obtained upon request from the corresponding senior author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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