Minireviews

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MOLECULAR AND METABOLIC EFFECTS OF CHRONIC STRESS ON HEALTH, AGING AND CARCINOGENESIS

Chronic stress in modern society has many facets and sources of origin. The war in Ukraine, for instance, is a significant source of stress that could have adverse health consequences. Chronic stress has been shown to exert a multilevel, long-term, and delayed impact on health, aging, and the development of age-related diseases, including cancer. This mini-review briefly discusses a total landscape of the main aspects and directions of chronic stress, starting with the genetic and epigenetic factors that have been studied in this context. The general metabolic aspects and the effect of chronic stress on individual organs, body systems, and the role of lifestyle factors and their correction to eliminate the effects of stress and prevent the development of age-related and stress-related diseases are considered.

Keywords: *chronic stress, stress-related diseases, cancer, age-related diseases, genetic, epigenetic, metabolic disorders, lifestyle factors.*

Introduction

It seems that the ability of the human body to respond and adapt to the environment and social influences is a basic mechanism for maintaining metabolism and health [1, 2]. On the one hand, this ability is influenced by the innate genetic characteristics of a person [3]. On the other hand, it is influenced by indicators of stress factors, strength, duration, and nature of the stressor [4]. An individual's personal experience, perception, and response to these influences, as well as their perception of them as stressful, play a significant role [5]. The body's reaction to physical and chemical stimuli was described by Hans Selye in the mid-20th century. He named this phenomenon "stress" [6]. According to the duration of exposure, stress is conventionally divided into acute and chronic. It is important to note that exposure to chronic stressors can cause maladaptive reactions of the body

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and the development of many diseases [7]. Regarding the source of stress, it is generally categorized into traumatic, environmental, psychological, and physiological [7]. The development of modern molecular biotechnology has contributed to our understanding of the mechanisms of stress at the genetic, epigenetic, and metabolic levels and the development of diseases in various model systems [8—10].

It is important to acknowledge the challenges faced by Ukraine in the context of the ongoing three-year war, which has undoubtedly contributed to a state of chronic stress for all segments of the population. It has been observed to increase the risk of developing various chronic diseases, psychopathologies, such as post-traumatic stress disorder (PTSD), and stress-related disorders [11], which affect health and the development of age-related diseases, including cancer [12]. Therefore, it is important for scientists, doctors, and citizens to understand the mechanisms of action of chronic stress, identify specific biomarkers at the molecular level and in the body as a whole, and means of influencing and correcting both the process and its consequences. This is a task that must be addressed urgently in order to maintain health, longevity, and prevent stress-related diseases.

The effects of chronic stress on health

Much of research into chronic stress initially focused on the impact of the hypothalamic-pituitary-adrenal system in the context of elevated levels of cortisol, a stress hormone produced by the adrenal glands [13]. This system does play a very significant role, especially in the response to acute stress [14]. However, it is important to note that chronic stress can lead to a wide range of multilevel pathological changes in almost all organs and systems of the human body [15]. This can result in increased catabolic processes and functional exhaustion of the organs and systems, reduced regenerative processes, increased inflammation, disruption of circadian rhythms and microbiome, and many other molecular and metabolic disorders [16, 17, 18]. Constantly elevated levels of stress-associated hormones (glucocorticoids, mineralocorticoids, catecholamines, prolactin, thyroxine, vasopressin, and sex hormone disbalances) and chronic activation of the sympathetic nervous system create numerous pathological loads. This has been shown to affect the metabolism of target organs and cells [19] and to disrupt neuroendocrine regulation, which has been linked to a constant increase in blood glucose [20]. This, in turn, can have a negative impact on the blood vessels and cell metabolism in general.

In addition, it has been observed that chronic stress can disrupt the body's circadian processes, particularly the circadian functioning of the sympathetic and parasympathetic nervous systems. This, in turn, may contribute to the development of pathological changes in organs and tissues, disrupting normal blood supply, oxygen and metabolite metabolism, and regeneration of cells and tissues [21]. The multilevel disorders of cells, organs, and systems complicate therapeutic effects, which, when acting on only one specific pathology, may not be as effective when chronic stress affects the human body. An integrated multilevel approach may be necessary [22]. Researchers have found that chronic stress may play a role in the development of many age-related and chronic diseases, and it has been observed to contribute to cellular and body aging [23, 24]. Furthermore, stress-related diseases have been observed to develop into multimorbidities with age, meaning the presence of two or more pathologies simultaneously [25].

The modern lifestyle may act potentially as an additional source of chronic stress. Some hazardous factors include an unbalanced diet, a sedentary lifestyle, circadian rhythm disorders, and environmental pollution in the area of habitation. It has been suggested that these factors may contribute to the development of stress-related and age-related diseases [20, 23, 25]. The impact of various pathological addictions on human health has been widely studied and is a separate topic for discussion.

Given the significant scale of multilevel pathological disorders in the body under stress, it is difficult to identify specific biomarkers of chronic stress to assess the state of the human body and predict the development of stress-related diseases. This is a matter of significant concern for modern biology and medicine, and it is an area that merits our collective attention and effort.

Genetic differences in the response to chronic stress

It has been determined that all processes in the human body and reactions to external influences have certain differences that are determined by the individual genetic characteristics. It has been described that hundreds of gene variants and dozens of loci may influence an individual's susceptibility to stress-related diseases. For instance, there have been reports of nominally considerable association between PTSD symptoms and certain genes related to neurotransmitters and neuropeptides (e.g., *HRT2A, SLC6A3, DRD3, NPY, CNR1, RGS2*), the opioid receptor gene *OPRL1*, and other genes associated with neuroendocrine functions [11]. Additionally, the studies have identified stress response genes, such as *INTS8* and *TP53INP1*, as potentially relevant [26]. In addition to stress-related genetic variants, other genetic markers have been described, including 22q1Del, which is one of the strongest known genetic risk factors for psychosis under stress, while 22q11Dup, on the contrary, offers protection against psychotic symptoms despite the high frequency of stressors [27].

There is also evidence of variants in genes that confer resistance to stress factors, particularly in the genes *OPRM1* (Opioid receptor mu 1), *NPY* (neuropeptide Y), *CACNA1C* (calcium voltage-gated channel subunit alpha1 C), *DCC* (deleted in colorectal carcinoma), and FKBP5 (FKBP prolyl isomerase 5) [28], *COMT* (catechol-O-methyltransferase) gene, *SLC6A4* (the serotonin transporter gene), and *NPY* (neuropeptide Y) [29].

The certain variants of a number of genes have been identified to have a protective effect against the development of stress-related pathologies [30]. Moreover, a number of databases have already been created that contain information on the gene variants that have a certain impact on the development of stress-related and age-related diseases. These resources include the GWAS Catalog (https://www.ebi.ac.uk/gwas/), dbSNP (https://www.ncbi.nlm.nih.gov/snp/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), GenAge (https://genomics.senescence.info/genes/), AlzGene (http://www.alzgene.org/), and SNPedia (https://www.snpedia.com/). It is also noteworthy that certain databases include information on the genetic variants that may either increase or decrease the risk of disease (GenAge, GWAS Catalog, PhenoScanner, *etc.*).

In this regard, it is obvious that the etiology of stress-related diseases is polygenic, with a genetic component that contributes to a risk. Therefore, it is important to consider the influence of various environmental factors throughout life in addition to an individual's biological age when assessing susceptibility to the specific disorders and the development of age-related diseases [23, 31].

In addition to congenital features, the manifestations of chronic stress are influenced by somatic disorders that can be acquired by the body's cells during life and the influence of various factors, including stress [32, 33]. It has been established that with age, there is an increase in the number of genetic mutations of various types in cells, resulting in somatic mosaicism, which can lead to functional loss of cells in various organs [34]. These processes are associated with increased genetic instability and oncogene activation under chronic stress, which can trigger tumor formation [35, 36], reduced cellular repair processes [23], and accelerate cellular aging [24].

Epigenetic alterations that cause chronic stress

Some researchers suggested that the effects of stress-related steroid and peptide hormones, metabolites, and altered organ innervation may result in changes in the expression of hundreds of genes in various

organs and tissues, which could potentially precede the development of stress-related diseases [37—39]. There was also assumption that chronic stress may affect a number of epigenetic mechanisms of gene expression regulation. For instance, it has been observed that chronic stress can influence the methylation of promoters of numerous genes and post-transcriptional modifications of proteins [40]. Additionally, studies have highlighted the potential impact of chronic stress on the expression and spectra of non-coding RNAs [41, 42].

It has been proposed that chronic stress may potentially alter the methylation of an evolutionarily conserved intergenic region in chromosome X, which could possibly affect the development of mental illness [43]. Furthermore, there have been shown that epigenomic disorders in germlines caused by stressors may potentially be transmitted through generations, which could increase the susceptibility to stress-related diseases [44].

It is important to acknowledge the significant role that epigenetic mechanisms play in the impact of stress on aging processes and the development of stress-related diseases [45].

Metabolic dysfunction in chronic stress

In different types of cells, chronic stress has been observed to cause specific changes inherent in a particular specialized tissue, as well as some typical changes affecting energy metabolism and mitochondrial dysfunction [46, 47]. Increased lipid peroxidation, which is also associated with mitochondrial function, has been noted. There is also an increase in signs of cellular aging, including oxidative stress, telomere shortening, chromatin disruption, and oncogene signaling [23]. The senescence-associated secretory phenotype (SASP) has been found to be acquired by aging cells [48].

Under chronic stress, it appears that almost all types of metabolism are disrupted in various target cells that have the membrane and nuclear receptors of stress-related steroid and peptide hormones [22, 49].

The study of the long-term effects of chronic stress demonstrated a decrease in mitochondrial respiratory function, as well as a decrease in the glycolytic activity of immune cells in the veterans with chronic diseases with multiple symptoms (GWI). This finding aligns with a decrease in energy availability, particularly in peripheral blood mononuclear cells, in these individuals, as supported by studies in animal models [50, 51]. These studies suggest that even after decades of stress, it may have a lasting impact on the health of individuals who have not fully processed their stress through psychological coping mechanisms.

The impact of chronic stress on some organs and body systems

It is suggested that different organs and systems of the body may have varying sensitivities to environmental factors, chronic stress, and aging processes [17]. It is noteworthy that differences in response may be observed among people of different genders [52]. Furthermore, chronic stress was observed to exert different influences on different organs and systems, potentially affecting their functioning, structure, and metabolism.

It has been observed that under chronic stress, various cells of the immune system (e.g., macrophages, neutrophils, T cells), adipocytes, vascular endothelium, and others, as well as body tissues, including brain cells, produce catabolic cytokines (TNF-α, IL-6, IL-1β, IFN-γ, IL-10, HIF-1α, and others). This response is managed by signals from the central nervous system and the neuroendocrine system, particularly the sympathetic-adrenal system. Chronic exposure to the catabolic cytokines was shown to disrupt immune and inflammatory reactions that precede chronic inflammation [53]. In addition, it has been suggested that cytokines, in turn, affect the functioning of the brain's glymphatic system and lead to the accumulation of ROS in the neuronal microenvironment, inducing cellular damage signaling that causes inflammation and, in this way, provokes the development of many brain diseases, including mental

disorders and neurodegenerative diseases [54, 55]. Moreover, these processes have the potential to adversely affect the gut-brain-microbiome axis [55].

Chronic stress has the effect of reducing the immune defenses of humans, particularly through immunosensing. Stress has been shown to affect both the reactivation of latent viruses in the body and the incidence of respiratory viral infections [56, 57].

In case of abnormal activation of the neuroendocrine system during chronic stress, thestress-related hormones have been observed to contribute to increased oncogene expression, exacerbation of chronic inflammation, and impaired immunological function, as well as accelerate tumor formation and progression [58]. In a mouse model, it was demonstrated that chronic stress activates the expression of endogenous retroviruses and immunoinflammation in the brain, potentially contributing to depressive and anxious behavior in animals [59].

The influence of chronic stress through stress-related hormones has been shown to change the state of the intestinal mucosa and immune system responses, which are closely related to the gut microbiome and the microbiota-gut-immune system-brain axis. This has been linked to intestinal inflammation, dysbiosis, and dysregulation of the immune system, including oncological and autoimmune diseases [60].

There are some data that the body's natural rhythm, or circadian dysregulation, may be influenced by chronic stress, which can lead to changes in various physiological processes, including gene expression, immune responses, and behavior. These changes have been linked to the development of various diseases, such as PTSD, type 2 diabetes, metabolic syndrome, certain female and male diseases, and cancer [21, 61]. Moreover, chronic stress, together with lifestyle factors, has a cumulative effect in the pathogenesis of various endocrine diseases [62].

Chronic stress has been linked to adverse cardiovascular changes, including age-related ones [63]. Some epidemiologic studies indicated that chronic stress may contribute to an increased risk of vascular disease due to endothelial damage, which can lead to the formation of foam cells and atherosclerotic plaques [64].

Chronic stress can increase bone resorption by activating osteoclasts and releasing calcium into the bloodstream under the influence of stress hormones [65]. In addition, there is a slowdown in bone remodeling due to inhibition of osteoblast functioning by glucocorticoids, decreased levels of sex hormones, inflammation, and chronic activation of the sympathetic nervous system. These phenomena may contribute to a decrease in bone density, which can be a risk factor for developing osteopenia and osteoporosis. Some studies indicate a potential link between chronic stress and an increased risk of bone fractures and a slower recovery process [66].

The stress-related hormones and chronically elevated sympathetic nervous system functioning may have a negative impact on the muscle metabolism. Actively functioning muscles secrete a variety of metabolically active substances and myokines, which have been found to be involved in the regulation of almost all processes in the body. Myokines have been shown to have anti-inflammatory and regenerative effects [67]. Conversely, it has been observed that chronic stress can lead to an increase in catabolic processes within muscles [68] and an escalation in the secretion of proinflammatory myokines and cytokines, such as TNF-α, IL-6, and IL-1β [69]. These inflammatory agents, in turn, have the potential to affect target cells, including vascular endothelial cells, fibroblasts of organs and tissues, and immune cells, thereby amplifying the manifestations of chronic stress. These effects have the potential to reduce the synthetic and tumor-suppressive function of fibroblasts, impair vascular regeneration, dysregulate immune responses, and even reduce cognitive abilities, among other potential consequences [68, 69].

Many studies indicate the potential impact of chronic stress as an inducer of thepsychiatric disorders (depression, posttraumatic stress disorder, bipolar disorder) [60, 70] and neurodegenerative diseases such as Alzheimer's and Parkinson's [71].

These are just general ideas that cover only a small part of the research on the impact of chronic stress on various human organs and systems.

Conclusions

It has been observed that specific human diseases emerge under the influence of chronic stress, and future studies will explore the impact of genetic characteristics. Furthermore, the impact of a modern person's lifestyle on prolonged exposure has been observed to have very specific effects. These include a sedentary lifestyle, constant psychological stress, a diet high in carbohydrates and junk food, non-compliance with circadian rhythms, and exposure to carcinogens, among others. These factors can have a negative impact on human health, contributing to the development of age-related, stress-related, and cancerous diseases [72, 73]. However, it is important to acknowledge that the human body is often subject to various lifestyle factors that may contribute to the development of pathologies. Conversely, a well-organized lifestyle, taking into account a person's genetic, metabolic, mental, emotional, and age-related characteristics, along with programs designed to reduce psychological stress and lifestyle factors, has the potential to enhance well-being. It has the capability of positively impacting the physical, mental, and emotional states of individuals, potentially acting as a preventative measure against age-related, stress-related, and cancerous diseases [73—75].

It is important to determine the body's susceptibility to certain factors, its adaptation capabilities, and its physiological and metabolic state. This would provide a basis for assessing the body's resources and endurance in the presence of chronic stress, with the aim of preventing the development of stress-related diseases.

It is suggested that the development of an integrated approach to the evaluation of lifestyle factors and their beneficial effects on the body could help neutralize the pathogenic factors of chronic stress and enhance the body's regeneration and recovery. This approach may contribute to the preservation of health for current and future generations. This could be considered a key area of focus for preventive personalized medicine, molecular biology and genetics, and a new area of lifestyle medicine.

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МОЛЕКУЛЯРНІ ТА МЕТАБОЛІЧНІ ВПЛИВИ ХРОНІЧНОГО СТРЕСУ
НА ЗДОРОВ'Я, СТАРІННЯ ТА КАНЦЕРОГЕНЕЗ

Хронічний стрес у сучасному суспільстві має багато граней та джерел походження. Війна в Україні є таким критичним стресовим фактором, який може мати жахливі наслідки для здоров'я населення. Хронічний стрес має багаторівневий, тривалий та відстрочений вплив на здоров'я, старіння, розвиток вікових захворювань, у тому числі онкологічних. У міні огляді висвітлено сукупність основних аспектів та напрямків впливу хронічного стресу, починаючи з генетичних, епігенетичних факторів, які досліджено в цьому контексті. Розглянуто загальні метаболічні аспекти та вплив хронічного стресу на окремі органи на системи організму та роль факторів стилю життя та їх корекції для усунення наслідків впливу стресу та попередження розвитку вікових та стрес-пов'язаних захворювань.

***Ключові слова*:** хронічний стрес, стрес-пов'язані захворювання, рак, вікові захворювання, генетичні, епігенетичні, метаболічні порушення, фактори стилю життя.