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Review

Pathophysiological and Genetic Aspects of the Brain–Skin Axis: The Role of Stress and Inflammation in Skin Aging

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Abstract: Aging is a genetically programmed process that is influenced by a large number of external and internal factors. The most frequently discussed factor accelerating aging is UV radiation. But among other factors that accelerate aging, we should not forget about chronic stress and chronic inflammation. These factors are interrelated with each other and can mutually enhance the effect of each other. In particular, chronic stress and inflammation can also affect skin aging. So, the skin is an organ of stress factors, as well as sources of some stress factors. Since the topic of the effects of chronic stress and inflammation, and especially its genetic aspects, are quite rare in the literature, the purpose of this review was to combine the available data on the pathogenesis and genetic aspects of stress and inflammation when exposed to skin aging.

Keywords: *skin aging, chronic stress, chronic inflammation, genetic polymorphisms*

Introduction

Skin aging is a multifactorial process involving 2 groups of factors: internal (telomere shortening, hyperproduction of reactive oxygen species (ROS)): external (such as ultraviolet irradiation (UV), inflammation, stress) [1]. Psychological stress and post-traumatic stress disorder are often mentioned as significant factors of skin aging, as well as factors of various skin diseases. For example, depressive disorders are one of the seven factors affecting perceived age, along with genetic predisposition, smoking, exposure to ultraviolet radiation (UV), body weight, socio-economic factor [2]. Nevertheless, the mechanisms of psychological stress are not widely covered, so the task of this review is to summarize the results of fundamental and clinical studies of the pathophysiological and genetic aspects of the brain–skin axis underlying stress and inflammation, and to assess their impact on skin aging.

Psychological Stress and Skin

Psychological stress occurs when an individual feels that mental, physical or emotional pressure on him exceeds his adaptive capabilities. In response, the release of stress hormones increases, whose task is to adapt the body to stress due to a wide range of physiological and behavioral changes [3]. Violation of adaptation to psychological stress can be of different etiologies, including the reaction to stress is genetically determined. Thus, one of the reasons for the maladaptation and development of obsessive-compulsive disorder is the carriage of single-nucleotide polymorphisms (SNP) in the genes encoding serotonergic drugs, for example: in the HTR2A gene [4]. Obsessive-compulsive disorders can manifest themselves in the form of dysmorphic phobias. At the same time, this condition

further increases the patient's stress level, which has an even greater impact on the body as a whole.

The main stress hormones include: corticotropin-releasing hormone, glucocorticoids and adrenaline. Inadequate or excessive stress reactions can be the cause of adverse physiological events: they can cause and/or worsen many somatic diseases, such as cardiovascular diseases, migraines, multiple sclerosis, neurodegeneration, and others [3]. The main theories of aging recognize that aging is the result of an imbalance between stress factors and stress buffering mechanisms, resulting in loss of compensatory reserve and accumulation of non-renewable damage [5].

The skin is both a source of stress and a target for stress reactions. The protective function of the skin is manifested in maintaining homeostasis between the external environment and internal tissues due to the mechanical and immune barrier [6, 7]. The main way stress conditions affect the skin is through the hypothalamic-pituitary-adrenal axis. Cortisol binds to the glucocorticoid receptor, which in turn separates from the complex binding the heat shock protein, moves to the nucleus and affects the expression of various genes: activating protein (AP-1), nuclear factor-kB (NF-kB). The latter is a well-known regulator of tissue homeostasis and its role in skin aging has recently been emphasized [7].

There are also local neuropeptides in the skin (substance P or SP, neutrophins) secreted by peripheral nerves, mediating neurogenic inflammation. With neurogenic inflammation, keratinocyte proliferation and protection from UV-induced apoptosis occur, induction of proliferation, migration and differentiation of fibroblasts into myofibroblasts. Substance P (SP) is a pro-inflammatory neuropeptide that stimulates the degranulation of mast cells and increases infiltration by macrophages, with repeated exposure to it, nerve fibers may increase. SP can also induce the release of various cytokines from monocytes and T cells, including Interleukin 1 (IL) (IL1), IL6, IL12, leading to T cell proliferation and inflammation.

Stress can lead to increased transepidermal water loss and impaired barrier function, which can lead to peeling and the formation of wrinkles. Thus, in one of the studies of insomnia, it was noted that stress can worsen the proliferation and differentiation of the epidermis, reduce the size and density of the corneodesmosomes, as well as lipid synthesis and production of the lamellar body [8]. According to other studies, stress caused a delay in the restoration of barrier function, increased plasma cortisol levels and activated several inflammatory and immune factors (such as IL1, IL10, tumor necrosis factor-α (TNFα) and circulating killer cells [9].

Stress is associated with impaired healing and dysregulation of healing biomarkers. Perceived stress and elevated cortisol levels are the main factors delaying the healing of chronic wounds in anxiety and depression [10]. Endogenous glucocorticoids also alter the expression of TGF-β, affecting the proliferation, migration and differentiation of fibroblasts [11].

Repeated action of epinephrine (systemic or local) can also negatively affect the mobility of keratinocytes and the re-capitalization of the wound. The action of adrenaline leads to stabilization of the active cytoskeleton and an increase in the formation of focal adhesion, which prevents migration and proper wound healing. Epinephrine also reduces fibroblast migration and MMP2 secretion *in vitro*, which also reduces collagen deposition by fibroblasts [12]. An increase in adrenaline disrupts inflammatory reactions in the healing wound: the level of IL6 increases, the migration of neutrophils is disrupted, and peripheral vessels narrow, which limits the oxygen supply to the wound site [13].

Stress Neurotransmitters and Skin

With short-term stress, the action of all neurotransmitters is tightly regulated by feedback mechanisms. Also, during acute stress, lymphocytes may be redistributed from the blood into the skin, which leads to increased skin immunity and successful adaptation to stress, and suppression of reactive oxygen species (ROS) also occurs [14].

Unlike acute stress, chronic stress usually suppresses immune protection, increases susceptibility to infections and aggravates some allergic and inflammatory diseases [15]. This is due to the so–called "habituation" to stress, which damages the brain-skin axis and leads to increased sensitivity to new stimuli. Skin aging also has a negative effect on the skin–brain feedback system [16].

One of the theories of skin aging indicates the importance of external factors through damage to deoxyribonucleic acid (DNA), inflammation and the formation of free radicals. Thus, UV is one of the main stress factors responsible for premature aging of the skin [2]. UV induces the expression of CRH and stress mediators. Glucocorticoids can have a negative effect on the extracellular matrix of the skin (including collagens I and III types, proteoglycans and elastin). This is confirmed by the fact that with prolonged use of glucocorticoids for the treatment of inflammatory skin diseases – the development of skin atrophy, with a decrease in the thickness of the epidermis, flattening of the derma-epidermal junction, a decrease in the number of fibroblasts, destruction of the collagen network [17].

An example of the effects of chronic stress is a violation of the quality and quantity of sleep, which can have a negative impact on skin aging. Thus, in people with chronic insomnia, signs of accelerated aging were found: wrinkles, hyperpigmentation, decreased elasticity, reduced recovery after the destruction of the skin barrier. Sleep disturbance contributes to mental stress due to an increase in the level of circulating inflammatory cytokines [18].

Stress Epigenetics and Skin

The increase in corticoids that occurs during chronic stress can increase DNA damage, preventing DNA repair, altering the transcriptional regulation of the cell cycle. Chronic stimulation with catecholamines leads to degradation of p53 and accumulation of DNA damage [19].

Repetitive stress is also able to enhance the manifestation of aging through ROS: repetitive short-term stress causes increased regulation of NF-kB, which induces the production of ROS. Stress causes depletion of the cellular antioxidant mechanism and mitochondrial dysfunction, which further enhances the effect of ROS on tissues, accelerating aging, including skin [20].

According to other theories of aging, various chronic stressful situations have been associated with shortening the length of chromosome telomeres, which ultimately leads to replicative aging and premature cellular aging. The exact mechanisms of this are still being discussed, but cortisol and epigenetic modulation have been proposed as possible ways [21]. Also, shortening of telomeres can lead to a decrease in the regulation of mitochondrial biogenesis and ROS production. All this represents a vicious circle in which stress caused by lifestyle or habits further exacerbates skin damage and signs of aging.

Stress, Inflammation and Skin

Inflammation is a common sign of tissue aging. Chronic inflammation is a risk factor leading to a decrease in tissue repair and regenerative capacity, which is associated with aging [22]. Psychological stress is one of the factors of increased proinflammatory cytokines in the blood [23]. There are many factors contributing to chronic inflammation. Aging cells themselves are sources of chronic inflammation; immunosensitization, intestinal dysbiosis, chronic inflammatory diseases, obesity, hormonal disorders, smoking, sedentary lifestyle – all this contributes to an increased level of chronic inflammation affecting skin aging [24]. Chronological aging of the skin at the cellular level is associated with redox processes: with chronic inflammation associated with aging and mitochondrial dysfunction, the accumulation of ROS occurs. As a result of these processes, the composition of skin lipids also changes: aging fibroblasts are characterized by increased production of leukotrienes [25].

The exact mechanism of the effect of inflammation on aging is not known, but many factors are assumed to be involved, including oxidative stress, pro-inflammatory cytokines, DNA damage, dysfunction of cellular organelles, autophagy defects and dysfunctional differentiation of stem cells [24].

With age, the level of TNF-α, IL6 and their receptors increases in tissues, and it has been shown that an increase in their level is important in the pathogenesis of aging [26, 27]. The proinflammatory cytokine TNF-α inhibits collagen synthesis and enhances collagen degradation by increasing the production of MMR9. Various studies suggest the influence of genetic polymorphisms of the *TNFA* gene (responsible for TNF-α expression) in various chronic diseases [28, 29, 30]. In another study, it was suggested that *IL6* (the gene responsible for IL6 expression) is a biomarker of health status in the elderly [31]. A number of studies have confirmed the association of the *IL6* gene with longevity and diseases associated with premature aging [32, 33].

Conclusions

Thus, the violation of the brain–skin axis as a result of psychological stress and other stressful factors, along with a genetic predisposition to increased reactivity in response to stress and epigenetic processes, is one of the important pathophysiological mechanisms of early skin aging. In addition, an increase in the level of stress factors leads to an increase in inflammatory processes, including in the skin, skin aging accelerates, and the skin, in turn, also increases the release of stress factors, disrupting the inverse axis of the skin - brain. It is necessary to understand how this pathological closed cycle can be interrupted.

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