



Review of Skin Problems Caused by Stress

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DOI: 10.32629/jcmr.v3i3.1047

Abstract: Long-term exposure to social and biological/physical stressful events produces stress responses. The hypothalamic-pituitary-adrenal (HPA) axis is one of the main neuroendocrine regulatory systems in the process of stress. Recent studies have shown that skin, as a large endocrine organ, also has peripheral neuroendocrine regulatory functions similar to the central HPA axis. The skin also responds positively to stress and produces a range of symptoms. This review will introduce a series of skin apparent problems caused by stress from the perspectives of molecular biology, skin neurology, endocrinology and immunology, hoping to provide another solution for cosmetic practitioners to deal with these skin apparent problems.

Keywords: stress, skin neurology, endocrine, molecular biology, skin problems

A little bit of stress is normal in everyday life, and sometimes these mild stressors can have many benefits, making people mentally stronger by overcoming stressful events. But when the body is exposed to severe social and biological/physical stressful events, such as severe or chronic stress caused by marriage or partnership breakdown, death of a family member, or bullying, the stress response occurs. Different degrees of stress will lead to different stress responses, which are manifested in physiological, psychological, cognitive and emotional aspects. For example, chronic stress can lead to a series of cardiovascular diseases[1], and physical and mental stress can lead to increased free fatty acids (FFA), norepinephrine, diastolic blood pressure and systemic vascular resistance[2].

The hypothalamic-pituitary-adrenal (HPA) axis is one of the main neuroendocrine regulatory systems in the process of stress[3]. HPA involves three endocrine glands, the hypothalamus, anterior pituitary gland, and adrenal gland, which are interlinked each other, regulating the body through a variety of endocrine hormones and other stress mediators when faced with stress response and adaptive response, and finally acting on various effector systems of the body (such as the immune system, nervous system, fat, cardiovascular system and various tissues)[4-6].

The skin is also the target of the stress mediators in the stress response of the body. The skin has a hypothalamic-pituitary-adrenal (HPA) system similar to the central HPA system where CRH, ACTH, and their receptors are produced in skin cells [7]. Different stress will produce different stress responses leading to different skin problems. In this article, we will review the latest research on how stress interacts with the brain and skin, how the skin reacts to stress through the endocrine system, the immune system, and the skin problems that arise under stress.

1. The connection between the brain and the skin under stress

1.1 Central HPA axis

Physical or psychological pressure is perceived by the central nervous system (CNS) and translated into biological responses by stimulation of the hypothalamus and pituitary activation (hypothalamic-pituitary-adrenal [HPA] axis). First, hypothalamic neurons respond to stress signals by secreting adrenocorticotropin-releasing hormone (CRH). CRH is transported to the pituitary gland, where it binds to CRH receptor type 1 (CRH-r1) and promotes the synthesis and secretion of pro-opiomelanocortin (POMC) peptide in the anterior pituitary. Under the action of prohormone convertase (PC1 or PC2), POMC is processed into different POMC-derived neuropeptide hormones such as adrenocorticotropin hormone (ACTH), α -melanocyte stimulating hormone (α -MSH), β -endorphin. ACTH is released into the blood and subsequently activates melanocortin receptor 2 (MC2R) on the adrenal gland, which stimulates adrenal gland synthesis and secretion of cortisol and corticosterone [8].

Cortisol combines with a variety of intracellular glucocorticoid receptors (GR) to exert depressive stress effect. At the same time, cortisol can stimulate glucocorticoid receptors (GR) in the hypothalamus and pituitary to inhibit the excessive secretion of CRH and POMC peptides, forming a negative feedback to regulate stress response and maintain the relative balance of various hormones in body fluids. Cortisol is the main stress hormone in the body, which can regulate human stress response through humoral and nerve transmission [9]. An in vitro study in teleost fishes showed that cortisol could

stimulate the proliferation and apoptosis of fish skin cells in a dose-dependent manner[10]. Other literatures have pointed out that patients with hypercortisolism may suffer from skin atrophy, weakened skin barrier function, decreased body immunity, opportunistic bacteria or fungal infection, etc., which hinder skin wound healing [11]. All these suggest that endocrine hormones can affect human skin and play a role in normal biological processes.

1.2 Skin HPA axis

As the largest organ of the human body, the skin can protect the body from various stimuli (physical, chemical, biological) damage of the external environment, sense cold, heat, swelling, pain and other stimuli, and make corresponding stress response. At the same time, the skin was also a peripheral neuroendocrine organ. Recent studies showed that the skin also had a neuroendocrine function similar to that of hypothalamo-pituitary-adrenal (HPA) axis, and could also carry out a similar feedback regulation mechanism [7]. Skin cells can also secrete CRH, ACTH and other hormones [12], for example, cortisol are secreted by dermal fibroblasts, epidermal keratinocytes, outer hair root sheath cells and sebaceous cells of hair follicles when under the stimulation of CRH and ACTH [13,14], playing the role of classic central HPA axis.

In addition to the stress hormones involved in the HPA axis, the skin sympathy-adrenal medulla (SAM) axis and peripheral nerves can also secrete stress hormones such as catecholamines (epinephrine and norepinephrine) and neuropeptide-neurotrophic factor (NNA) to cope with stress stimuli [15]. In the stress state, adrenaline is secreted by the adrenal glands, which cause blood vessels to constrict, blood pressure raised, the total amount of blood enlarged, this provide more energy for physical activities, make the reaction faster. However, skin has developed an independent catecholamine system in peripheral tissues[16], where keratinocytes can synthesize epinephrine and influence the biological functions of keratinocytes and melanocytes. For example, epinephrine synthesized by keratinocytes can affect the proliferation of melanocytes and melanin production through cyclic adenosine monophosphate signaling pathway[17].

In short, a variety of cells in skin epidermis and dermis secrete and express HPA axis and SAM axis components and other endocrine signals, and exercise the functions of HPA axis and SAM axis to convert hormone signals into biological responses, so as to regulate epidermal hyperplasia, skin barrier repair, melanogenesis and dermal fiber synthesis[8, 16]. At the same time, hormones (such as neuropeptide substance P, etc.) secreted by nerves around the skin are involved in the regulation of neuroinflammation and other symptoms as local stress responses[18].

2. Skin problems caused by stress

2.1 Pressure and skin barrier and wound healing

As the skin's first line of defense, the cuticle (SC) plays an important role in regulating the skin's water-oil balance, osmotic pressure balance and preventing the invasion of harmful factors. In the stratum corneum of healthy skin, keratinocytes and intercellular lipids are arranged in a structure resembling a stable brick wall, with keratinocytes as bricks and intercellular lipids as mortar. The integrity of the "bricks" and "mortar" ensures the integrity of the skin barrier.

When the skin barrier is damaged, the cuticle structure is destroyed, which easily leads to the loss of skin moisture and lipid structure, and eventually leads to the rise of skin percutaneous water loss rate (TEWL), peeling and dryness, etc. In severe cases, a series of skin diseases such as specific dermatitis and urticaria will occur [19]. Anxiety, depression and insomnia can inhibit the recovery of human skin barrier function [20]. A study of acute or chronic sleep deprivation show that lack of sleep affects a variety of skin characteristics, including the percutaneous moisture loss increase (TEWL: barrier damaged mark), heavy color of skin, desquamation and other[21], there are some other forms of stress (such as the students under the pressure of test) will affect the skin permeability barrier function recovery[22].

Skin wound healing is a complex and orderly biological process. It can be divided into three stages, namely, inflammatory stage, proliferative stage and repair stage. These three stages are not independent but interleaved and overlapping with each other, and involve the common participation of various inflammatory cells, repair cells, inflammatory mediators, growth factors and extracellular matrix.

In a systematic review and meta-analysis of 22 papers and 11 subsamples, the authors examined the effects of stress on wound healing in a variety of settings, including acute and chronic clinical wounds, experimental perforated biopsies and blister wounds, and minor skin lesions caused by duct tape dissection. The results of this paper show that stress is associated with impaired wound healing or dysregulation of biomarkers related to wound healing [23], and a number of experimental data have proved that acute stress in the laboratory can delay the recovery of skin barrier after disruption [24, 25].

Among them, the HPA axis plays an important role in wound healing[26]. Local blockade of glucocorticoid (GC) activation can reverse the stress and glucocorticoid-induced delay in skin wound healing [27], and glucocorticoid (GC) can also inhibit the proliferation of fibroblasts and the expression of collagen synthesis in intracellular genes[28]. Glucocorticoid

(GC) attenuates the expression of epidermal growth factor at both mRNA and protein levels in fibroblasts in vitro, possibly due to the regulation of cells and cytokines involved in the healing process by stress hormones in the HPA axis of skin synthesis and secretion. For example, it can regulate cell proliferation and differentiation by inhibiting IL-1 β , TNF- α and other inflammatory factors [29, 30].

2.2 Stress and acne

Acne is a chronic inflammatory disease of hair follicle and sebaceous gland units common in dermatology, which tends to occur in adolescence. Almost everyone will have acne problems at some time in their life, with the incidence of acne reaching 85% in adolescents and accounting for 10%-20% in dermatological outpatient clinics, second only to allergic skin diseases[31]. The pathogenesis of acne is mainly affected by the following four factors: 1. Excessive secretion of oil by sebaceous glands affected by hormones; 2. Excessive thickening of the cuticle of the skin; 3. Colonization of propionibacterium acnes and other bacteria; 4. The inflammatory reaction was aggravated[32].

The relationship between acne and emotional stress has been studied for a long time[33]. A survey pointed out that students with acne would have more acne when facing exam pressure, which may be related to the severity of stress. However, acne may be related to the secretion of HPA axis components. Relevant experiments have shown that CRH, CRHR and MC1R are abnormally high expressed in acne patients [34]. A large number of CRH and its receptors are detected in the sebaceous cells of acne patients, and these CRH can up-regulate the activity of a key enzyme to promote the growth of adipocytes [35, 36]. ACTH and α -MSH, two pressure mediators with the same effect, are also believed to promote oil secretion [37]. Peripheral neuropeptides such as SP have also been shown to promote the generation of sebaceous glands [38], which can promote the expression of PPAR- γ gene and thus play a special role in promoting adipocyte generation [38].

Stress hormones can not only increase the incidence of acne by promoting oil secretion, but also affect the clinical process of acne by promoting the release of inflammatory factors. Substance P (SP) can stimulate the release of various proinflammatory cytokines from sebaceous cells, including interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)[39], and CRH can induce the production of cytokines IL-6 and IL-11 in keratinocytes. [40]

2.3 Pressure and pigmentation

The color of normal skin is mainly determined by three factors: 1. The content and distribution of various shades in the skin; 2. The content of oxygenated hemoglobin and reduced hemoglobin in skin blood 3. The thickness of the relationship and the scattering optical factor of the relationship on skin surface[41]. Melanin is the main substance affecting skin color. Melanin is synthesized in epidermal melanocytes, and the synthesis process includes some enzymatic reactions and chemical reactions.

Chronic stress can show up in the skin as pigmentation. Under UV stimulation, skin cells synthesize CRF and POMC. POMC generates different POMC neuropeptide hormones (such as ACTH, α -MSH, β -MSH and β -endorphin) through the action of prohormone convertase (PC1 or PC2). Skin pigmentation is mainly regulated by melanotropin α -MSH and adrenal sebum hormone (ACTH)[42]. Experiments have shown that increasing the expression levels of ACTH and α -MSH can induce human pigmentation [43], which is mainly mediated by melanocortin receptors (MCRs). Melanocortin receptor 1 (MC1R) is a receptor on the cell surface of melanocytes. In the process of melanin synthesis, ACTH and α -MSH bind to melanocortin receptor 1 (MC1R) and activate cyclic adenosine phosphate signaling pathway (cAMP) to stimulate the generation of melanin [44].

As a precursor of ACTH, promelanocortin (POMC) mutations have been found to cause whitening of type 1 skin and redness of hair [45], thereby changing skin pigmentation. In addition, another study [46] evaluated the expression of CRH and POMC peptides in skin biopsies from vitiligo and reported that POMC expression was significantly reduced in damaged skin.

2.4 Stress and skin immunity and inflammation

Skin is an important part of the body's immune defense system, which can produce a variety of immune-related cells and immune molecules to participate in immune response. The skin also responds positively to psychological stress. In response to psychological stress, the HPA axis and other neurostress mediators (such as ACTH, CRH, cortisol, catecholamines, prolactin, substance P, and nerve growth factor) are released[47, 48] and these stress mediators act on cells of the skin immune system (keratinocytes, Langerhans cells, T lymphocytes, etc.) regulate various skin immune responses and inflammatory responses by releasing various cytokines and chemokines[49].

POMC activated by the hypothalamic-pituitary-adrenal (HPA) axis and its generated CRH, ACTH, and cortisol can induce various skin immune responses[50]. In healthy skin, POMC peptide levels are low, while POMC peptide levels are found to be increased in various skin diseases (such as inflammation)[51]. Keratinocytes produce IL-18 in response to ACTH

stimulation. IL-18 can act as a proinflammatory factor to promote the production of T-helper type 2 (Th2)[52], while CRF has been shown to stimulate the formation of IL-1 β , IL-6, and TNF- α in HaCaT keratinocytes[53]. Psychological stress response affects the release of catecholamines and cortisol, the latter two have a strong influence on the immune system, mediating the differentiation of T-helper (Th) cells into Th2 cells, impairing the development of Th1 cells, and thus increasing allergic inflammatory reactions[54].

Continuously increased CRH in patients with chronic stress or depression can directly act on CRHR1 receptors in skin mast cells, leading to their degranulation, and then induce itching[55]. The nerve terminals around the skin secrete proinflammatory neuropeptide Substance P, which further aggravates the effect of CRH on mast cell degranulation and increases macrophage infiltration, which is an important process of neuroinflammation [56]. Substance P can also induce monocytes and T cells to release various cytokines (such as IL-1, IL-6, and IL-12), leading to inflammation[57].

2.5 Stress and skin aging

The skin of the human body will gradually age from 25 to 30 years old, with the manifestation of flabby skin without elasticity, wrinkles, accompanied by dry skin, desquamation, pigmentation, repair function decline., etc. Long-term exposure to physical stress (such as ultraviolet radiation and environmental pollution) increases the generation of free radicals in the skin, thereby promoting the expression of inflammatory mediators and matrix metalloprotein (MMP-1), which specifically degrades extracellular matrix and inhibits collagen synthesis, ultimately leading to aging[58].

UV stimulation also causes the skin's HPA axis to secrete CRH, POMC, ACTH, cortisol, and β -endorphin [59], which may also be related to aging. It has been reported that long-term use of glucocorticoids (GC) in the treatment of inflammatory skin diseases will lead to epidermal thinning and destruction of the intercellular matrix in the dermis [60], and it has also been reported that glucocorticoids can cause cell dysplasia and delay wound healing by interfering with the function of keratinocytes and fibroblasts[61].

Similarly, the increase of catecholamines released by chronic psychological stress through the SAM axis of skin sympathetic nerve and adrenal medulla is also an important external factor affecting the aging process [62]. In mouse skin experiments, high concentration of epinephrine increased the generation of reactive oxygen species (ROS) and reactive nitrogen (RNS) free radicals in mouse dermal fibroblasts, and decreased the expression level of type I collagen[63], accelerating the aging of mouse skin. Epinephrine and norepinephrine have also been found to increase DNA damage and affect cellular transcriptional regulation [64]. Previous studies have shown that stress can induce DNA damage through the β 2-adrenal receptor (β 2AR) pathway[65]. When β 2-adrenal receptor (β 2AR) blockers are used, DNA damage accumulation does not increase [66].

3. Discussion

The symptoms discussed above are not the only skin problems caused by stress. Research results confirm that various diseases (such as psoriasis, atopic dermatitis, pruritus or alopecia areata) under high psychological stress are associated with stress to a greater or lesser extent [67-70]. With the increasing pressure of modern society, how to deal with the " Stressed-Skin" is a problem worth thinking about for the current cosmetic researchers.

Traditional efficacy products are designed to improve the condition of the skin, for example, cosmetic formulators will think about "Skin-Molecular Biology"information about acne products to control lipase activity, reduce inflammatory cytokines produced by immune cells, or to reduce the excessive proliferation of *Propionibacterium acnes* (*P.acnes*) by targeting the balance between skin and microorganisms from the perspective of "Skin-Ecology". However, skin is still an endocrine organ. In the face of skin problems caused by pressure, "Skin-Neurology"analysis is needed to reduce the generation of stress to change its impact on the skin. synergistic effects can be achieved through these several discipline. Therefore, by summarizing the epigenetic effects of stress on skin, this review hopes to generate a series of new methods and concepts to promote the improvement of skin problems caused by psychological stress, so as to provide cosmetics practitioners with another solution when dealing with these skin apparent problems.

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