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Brain-Skin Connection: Stress, Inflammation and Skin Aging

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Abstract: The intricate relationship between stress and skin conditions has been documented since ancient times. Recent clinical observations also link psychological stress to the onset or aggravation of multiple skin diseases. However, the exact underlying mechanisms have only been studied and partially revealed in the past 20 years or so. In this review, the authors will discuss the recent discoveries in the field of "Brain-Skin Connection", summarizing findings from the overlapping fields of psychology, endocrinology, skin neurobiology, skin inflammation, immunology, and pharmacology.

Keywords: Inflammation, skin aging, stress response.

INTRODUCTION

Psychological stress arises when people are under mental, physical, or emotional pressure. It arises when the individual perceives that the pressure exceeds his adaptive power. It is perceived by the brain and stress hormones such as corticotropin-releasing hormone (CRH), glucocorticoids, and epinephrine are released. This triggers a wide range of physiological and behavior changes and responses that try to adapt the body to the stress [1]. However, if the stress responses are inadequate or excess, they may trigger adverse physiological events [2]. It has been shown that stress can trigger and/or exacerbate multiple conditions, including cardiovascular disease [3, 4], migraine [5], multiple sclerosis [6], epileptic seizures [7], and neurodegeneration [8].

Recent research has confirmed skin both as an immediate stress perceiver and as a target of stress responses. As the largest organ of the body, skin plays important barrier and immune functions, maintaining homeostasis between external environment and internal tissues. It is composed of two major layers: epidermis and dermis. The epidermis is a continuously renewing layer where basal proliferating keratinocytes gradually differentiate, move up and eventually slough off the surface. The outermost layer of the skin epidermis, the stratum corneum (SC), is composed of dead and flattened corneocytes embedded in a matrix of lipids. Corneocytes contain numerous keratin filaments bound to a peripheral cornified envelope composed of cross-linked proteins. While the flattening of the secreted lipids vesicles form intercellular lamellar disks, which then disperse and join together to form multiple, continuous membrane sheets [9, 10]. The dermis is composed of fibroblasts and extracellular matrix which provides elasticity and tensile strength [11].

In this review, we will summarize the recent findings on how brain and skin communicate with each other, how the skin reacts to the stress by activating the endocrine and immune systems, and the negative impact of chronic stress on skin health.

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STRESS MEDIATORS AND EFFECTOR CELLS

Skin is the primary sensing organ for external stressors, including heat, cold, pain, and mechanical tension. Three classes of receptors (thermoreceptors for heat and cold, nociceptor for pain and mechanoreceptors for mechanical changes) are responsible for transmitting the outside signals to the spinal cord, and then to the brain [12]. The cutaneous sensory fibers also convey changes in temperature, pH, and inflammatory mediators to the central nervous system (CNS). The nerve terminals are often associated with receptors indicating close interaction [13]. The brain responds to these signals, which in turn influence the stress responses in the skin.

Skin and its appendages are not only targets of key stress mediators, they are also a local source for these factors which induce various immune and inflammation responses. In this section we will discuss key players in mediating the stress response from both the central nervous system as well as the resident skin cells.

Central HPA Axis

Stress conditions exert their effects to skin mainly through the hypothalamic-pituitary-adrenal (HPA) axis. Upon sensing stress, neurons in the hypothalamus secrete corticotropin-releasing hormone (CRH), which is transported to the pituitary gland, where it binds to the CRH receptor type-1 (CRH-R1) and stimulates the secretion of proopiomelanocortin (POMC)-derived neuropeptides, including α - melanocyte stimulating hormone (α-MSH), β-endorphin, and adrenocorticotropin (ACTH). In turn, ACTH travels to the outer layer of adrenal cortex through the bloodstream, binds to the MC2 receptors (MC2-R), and stimulates production of glucocorticoids (GC) including cortisol and corticosterone. Cortisol is the primary stress hormone in human that regulates a wide range of stress responses [14]. Cortisol works by binding to the glucocorticoids receptor (GR), which undergoes conformation change, dissociates from the heat shock protein binding complex, translocates to the nucleus, and affects gene expression through binding domains on gene promoter regions or direct interactions with

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transcription factors like Activating Protein 1 (AP-1) and nuclear factor-κB (NF-κB) [15, 16].

Normally cortisol levels undergo daily oscillation regulated by the internal circadian clock system, with peak level at early morning and lowest point around midnight [17, 18]. Stress can significantly disrupt cortisol level and oscillation curve. It was shown that in mice under restraint stress, there is diurnal dysregulation of HPA-axis activation resulting in a 4-fold increase in plasma corticosterone [19]. Under stress conditions, significantly up-regulated cortisol can have a major impact on the immune system (mainly being immunosuppressive), including antigen presentation, lymphocyte proliferation and traffic, secretion of cytokines and antibodies, and shift of the T helper (Th)1 towards Th2 responses [20].

Skin Peripheral HPA Axis

The skin also developed a fully functional peripheral HPA system where CRH, ACTH, and their receptors are produced in skin cells [21, 22]. CRH is produced by epidermal and hair follicle keratinocytes, melanocytes, sebocytes, and mast cells upon stress, including immune cytokines, UV irradiation, and cutaneous pathology [23, 24]. In human, CRH receptor (CRH-R) 1 was expressed in all major cellular populations of epidermis, dermis, and subcutis layers, while CRH-R2 was only expressed in hair follicle keratinocytes and papilla fibroblasts [25, 26]. Human melanocytes and dermal fibroblasts respond to CRH signaling *via* the cAMP pathway, leading to ACTH and corticosterone production [27, 28]. ACTH has also been detected in keratinocytes, Langerhan cells, monocytes, and macrophages [29].

The function of CRH in skin is very diverse and cell-type specific. In epidermal keratinocytes, CRH inhibits proliferation by arresting cells at the G0/1 cycle, and induces differentiation by calcium influx and AP-1 transcription pathway [30, 31]. MAPK pathway and VEGF down-regulation was proposed to be a possible mechanism [32]. In dermal fibroblasts and melanocytes CRH acts as growth factor stimulating proliferation. It also inhibits apoptosis in the same cells induced by starvation stress [33]. In mast cells, CRH induces degranulation and increases vascular permeability, demonstrating pro-inflammatory functions [34]. It also leads to selective secretion of vascular endothelial growth factor (VEGF) to promote angiogenesis [35]. In keratinocytes, it stimulates the pro-inflammatory IL6 production [36]. However, in melanocytes CRH inhibits NF-κB signaling, possibly to self-inhibit the inflammation response [37]. In a human sebocyte model, CRH stimulates lipid production through up-regulation of key lipogenesis enzymes [38].

ACTH stimulates IL-18 production in skin keratinocytes. IL-18 is a pro-inflammatory cytokine that enhances T-cell activity and promotes T helper type 2 (Th2) cytokines production [39]. Since CRH down-regulates IL-18 in keratinocytes [40], IL-18 may participate in the negative feedback loop to regulate HPA axis activity. In melanocytes ACTH stimulates proliferation and melanogenesis with a similar effect of α-MSH [41, 42]. Endogenous ACTH can stimulate hair growth in mouse model [43]. In sebocytes, ACTH can work through the MC5R receptor and induce sebocytes differentiation [44].

SAM Axis

Stress also induces the release of catecholamines through the sympathetic- adrenal medullary (SAM) axes. The inner layer of the adrenal medulla releases epinephrine (adrenaline) and norepinephrine (nonadrenaline) upon activation by stress. They are the critical components of the "fight or flight response": acceleration of heart rate and respiration, constriction of blood vessels except in the muscles, increased perspiration, and dilation of pupil. Epinephrine acts by binding to a variety of adrenergic receptors, leading to decreased skin blood flow, and altered immune and inflammation functions, including lymphocyte trafficking, circulation, proliferation, and cytokine production [45-47]. In monocytes and dendritic cells, adrenergic signaling can inhibit IL-12 production *via* increasing cAMP, thus blunting TH1 response and promoting TH2 differentiation [48]. It also has an impact on the production of various cytokines in dendritic cells [49].

The skin also holds a peripheral catecholamine system where epinephrine is synthesized in keratinocytes while the adrenergic receptors are present in both epidermal keratinocytes and melanocytes [50]. In keratinocytes, after epinephrine activates the β2-adrenoceptor, it induces a major increase in cAMP, which in turn increases calcium concentration through protein kinase C (PKC) activation [51, 52]. Since calcium level can regulate both epidermal proliferation and differentiation, it is possible that epinephrine can affect epidermal health. In melanocytes, the epinepherine produced by surrounding keratinocytes can promote melanogenesis [53]. Fibroblasts functions are also impacted by epinephrine, including migration and collagen production, both being important steps in wound healing [54]. For a detailed review of epinephrine's effect on wound healing, please refer to the third section.

Neurotrophins, Substance P, and Prolactin

The skin is highly innervated so peripheral nerves can also impact skin health through secreted factors like neuropeptides (ex: substance P or SP) and neurotrophins (NT). They serve as local stress responders that mediate neurogenic inflammation [55]. NGF contributes to stress-induced cutaneous hyperinnervation and affects all hallmarks of allergic inflammation and cutaneous stress responsiveness upstream of SP [56].

NGF (Nerve growth factor) is one of four NT family members. It binds to the high affinity tyrosine kinase receptor (TrkA, TrkB, and TrkC) and low affinity p75 NT receptor, and promotes neurogenic inflammation by stimulating cytokine releases from skin mast cells [57]. In keratinocytes NGF promotes proliferation and protects cells from UV-induced apoptosis [58-60]. In fibroblasts, NGF induces proliferation, migration and differentiation into myofibroblasts, which could play a vital role in cutaneous wound healing [61]. In melanocytes, NGF receptors are induced by UV irradiation and they can induce migration and dendricity [62, 63]. In a stress-induced hair loss mouse model, sonic stress induced rapid increase of NGF and p75

Table 1. Major Stress Mediators in Skin

Stress Mediator	Source	Effector Cell	Functions in Skin
CRH	Hypothalamus; Skin keratinocytes, sebacytes, and mast cells	CRH-R1 is expressed in epidermis, dermis and subcutis layer; CRH-R2 is expressed in in hair follicle keratinocytes and papilla fibroblasts	Stimulation of downstream ACTH and cortisol production; Proliferation, differentiation, apoptosis, inflammation, and angiogenesis.
ACTH	Pituitary gland; Skin melanocytes, epidermal and hair follicle keratinocytes and dermal fibroblasts; Langerhan cells, monocytes, and macrophages	MC2-R is expressed in skin melanocytes, hair follicles, epidermal keratinocytes, sebaceous and eccrine glands, as well as dermal fibroblasts, sebaceous and eccrine glands, muscle and dermal blood vessels	Stimulation of cortisol and cortocosterone production; Melanogenesis, cytokine production, cell proliferation, dendritic formation, hair growth, immune and inflammation regulation.
Cortisol	Adrenal cortex; Skin hair follicles, melanocytes, and fibroblasts	glucocorticoids receptor (GR) is ubiquitous expressed in all skin cells	Major impact on the immune and inflammation system; Cell proliferation and survival *via* the PI3K/Akt pathway; Hair follicle proliferation and differentiation; Epidermal barrier formation.
Neurotrophins	Central nervous system; Skin sympathetic neurons, mast cells, T-cells and B-cells, keratinocytes, fibroblasts, and melanocytes	Two receptors TrK and p75 are expressed in mast cells, immune cells, keratinocytes, fibroblasts and melanocytes	Promote skin innervations; Promote survival and differentiation of mast cells, and modify inflammatory cytokines expressions; Promote proliferation of keratinocytes; Important for melanocytes migration, viability and differentiation and protect them from oxidative stress and apoptosis; Promote fibroblast differentiation and migration, and possibly contraction and MMP secretion.
Substance P	Sensory nerve fibers	Mast cells, macrophages, T-cells	Cytokine release to induce inflammation, activate mast cells, and induce lymphocyte proliferation Induce vascular permeability.
Prolactin	Pituitary gland; Skin hair follicle and epidermal keratinocytes, fibroblasts, adipocytes, sweat glands, and sebaceous glands	Prolactin receptor (PRLR) is ubiquitous expressed except in fibroblasts	Autocrine hair growth modulator by promoting catagen (hair regression); Stimulate keratinocytes growth and keratin production in keratinocytes; Sebum production in sebaceous glands; Immuno-modulation.
Catecholamines (epinephrine and norepinephrine)	Adrenal medulla; Skin nerve fibers, keratinocytes	adrenergic receptors are expressed by natural killer cells, monocytes, and T cells, keratinocytes and melanocytes	Regulate keratinocytes proliferation, differentiation, and migration; Promote melanogenesis in melanocytes; Decrease fibroblasts migration and collagen secretion and impair wound healing; Suppress IL-12 in dendritic cells leading to blunted Th1 and increased Th2 differentiation; Important for lymphocyte trafficking, circulation, proliferation, and cytokine production.

NTR, which in turn significantly increased the number of Substance P-positive sensory neurons, and eventually caused premature hair growth termination [64].

Substance P (SP) is a stress-related pro-inflammatory neuropeptide which is released from cutaneous peripheral nerve terminals. During repeated sonic stress, SP+ nerve fibers are significantly increased [64]. It is the key mediator in connecting the brain to the hair follicle by stimulating mast cells degranulation and increasing macrophage infiltration. SP receptor antagonist can indeed normalize stress-induced phenotypes [65]. Substance P participates in the effect of CRH on mast cell degranulation during stress, an important process in neuroinflammation [66]. It also induces neutrophil and inflammatory cell infiltrates [67]. SP can induce a variety of cytokines release from monocytes

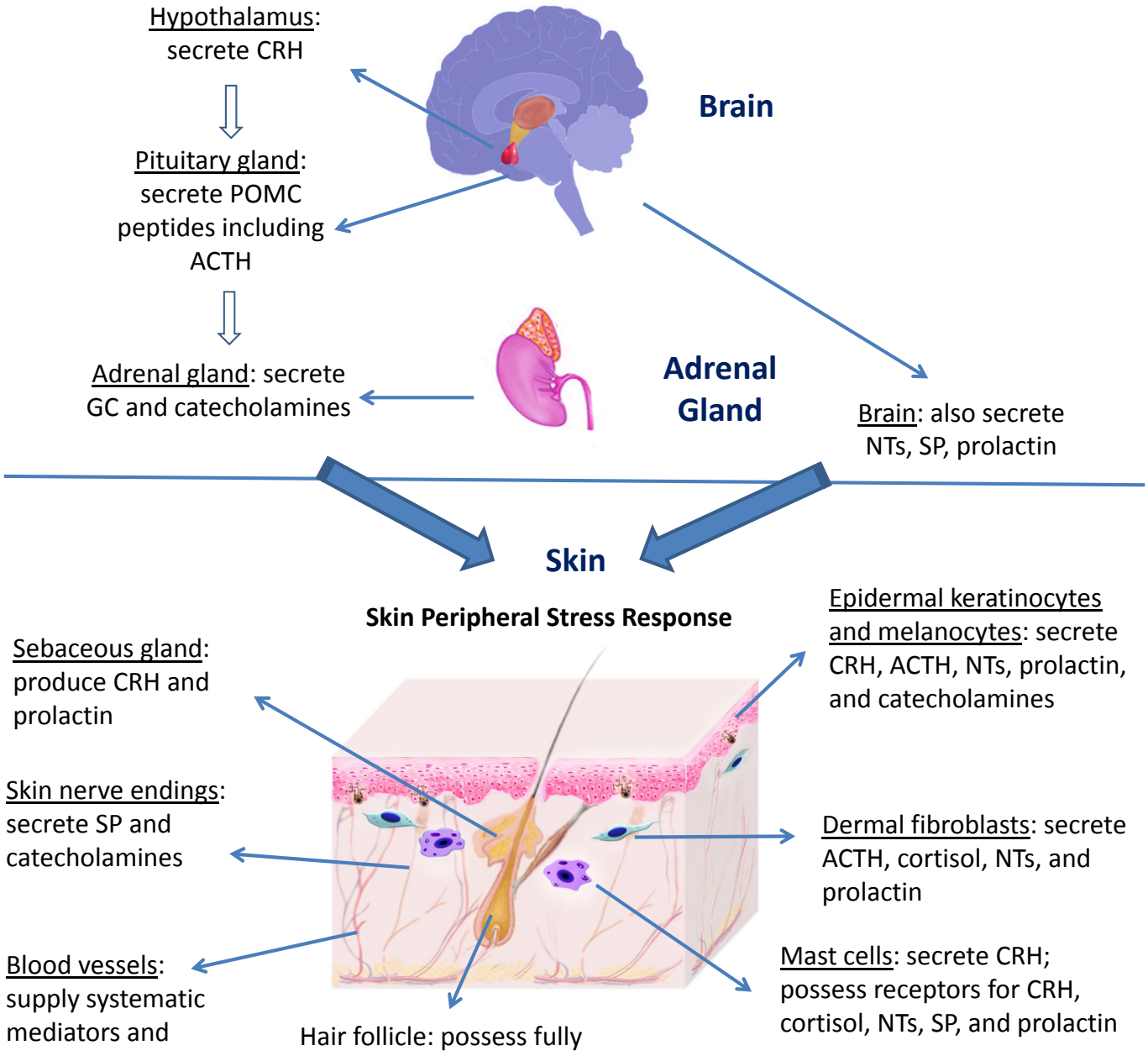

Fig. (1). Central stress response and skin peripheral stress response.

and T-cells, including IL-1, IL-6, and IL-12, leading to T-cell proliferation and inflammation [68, 69]. Very interestingly, SP can increase the virulence of multiple skin microflora by increasing caspase and altering the actin cytoskeleton. This could be another mechanism contributing to its role in neurogenic inflammation [70].

Prolactin is the hormone best known for its function in lactation and reproduction. It also has a global effect on body weight and adipose tissue [71, 72]. It is also immediately induced by psychological stress [73]. Recent research has revealed its function and implication in the brain-skin connection [74]. Prolactin stimulates keratinocytes proliferation and regulates keratin expression in keratinocytes [75, 76]. It stimulates sebum production in sebaceous glands [77]. In human monocytes/macrophages, prolactin stimulates heme oxygenase-1 production and VEGF production, contributing to angiogenesis [78]. Prolactin was proposed to have immunoprotection functions during stress because it can antagonize glucocorticoids function and maintain survival and function of T lymphocytes and macrophages [79, 80].

Mast Cells

Skin mast cells have emerged as a central player of the skin stress responses. It was proposed as the "central switchboards" of neurogenic inflammation [81]. In skin they

are located near SP+ nerve endings and blood vessels, where they are the first-line defense of the innate immune system. All the major stress pathways discussed above can affect various aspects of mast cell functions, including survival, activation, and downstream effectors secretion (See above for details). These include various vasodilatory and proinflammatory mediators, ex: histamine, VEGF, cytokines, nitric oxide (NO), and proteases. In turn, they serve as central players in the skin neurogenic immune response activated by stress.

SKIN NEUROGENIC INFLAMMATION DURING STRESS RESPONSES

Stress is known to affect various diseases and conditions, for example, asthma, arthritis, migraines, and multiple sclerosis [82-85]. Specifically in skin, multiple neuroinflammatory conditions can be triggered or aggravated by stress, such as: psoriasis, atopic dermatitis, acne, contact dermatitis [86, 87], alopecia areata [88-91], itch or Pruritus [92], and erythema. This section will only focus on several skin conditions.

Psoriasis

Psoriasis is a chronic skin inflammatory disease, affecting about 2% of populations worldwide. It is characterized by overproliferation of keratinocytes and inflammation, which lead to epidermal hyperplasia, a hallmark of lesional psoriatic skin. The psoriatic plaques are most seen over the elbows, knees and scalp. Other pathological signatures include dysregulated angiogenesis, skin infiltrating T lymphocyte, and expression of proinflammatory T helper (Th) 1 cytokines [93-95]. Although recent research has revealed parts of the pathogenesis and the intricate crosstalk between nerves, immune system, endocrine system, and skin cells, there is still no cure for psoriasis.

Stress is both a consequence of living with psoriasis, and a cause for psoriasis exacerbation [96, 97]. The pro-inflammatory cytokines that are highly expressed in psoriasis are potent activators of the HPA axis. This could lead to a vicious cycle and amplify the negative effects [98]. Stress leads to a hyporesponsive central HPA axis with blunted cortisol response and upregulation of inflammatory cytokines [99, 100]. In psoriasis stress also has an impact on the skin peripheral HPA axis, and the SAM axis. However, the exact role and mechanism still need to be elucidated by further research due to conflicting data from different research groups [101].

The role of NGF and substance P in psoriasis has been extensively studied. It was discovered that psoriatic tissues express high levels of NGF compared to the controls [102, 103]. NGF can contribute to keratinocytes proliferation [58, 59] and mast cell activation [57, 104], both being early events of psoriatic lesion formation. NGF also contributes to inflammation, by activating T lymphocytes [105] and inducing chemokine expression from keratinocytes [106]. The critical role of NGF in psoriasis development is further confirmed when blocker of TrkA, the high affinity NGF receptor, can significantly improve transplanted psoriatic plaques in a mouse model [107]. Substance P and SP-positive cutaneous sensory nerves are both increased in psoriasis skin [108, 109]. This could be downstream of NGF signaling since NGF and its receptors play a crucial role in regulating innervation and upregulating neuropeptides [110]. In fact, cutaneous denervation can improve inflammation and reduce T-cell numbers, which is prevented by restoration of SP signaling [111].

It was recently discovered that in keratinocytes prolactin enhances interferon-gamma-induced production of (C-X-C motif) ligand 9 (CXCL9), CXCL10, and CXCL11. Thus prolactin may promote type 1 T cell infiltration into psoriatic lesions *via* these chemokines [112]. It can also stimulate keratinocytes proliferation [75], potentially promoting the development of psoriatic plaques.

Acne

Acne vulgaris (or simply acne) is a very common skin disease affecting a majority of the population at some point in their life. It affects skin with the densest population of sebaceous follicles, including the face, the upper part of the chest, and the back. Acne pathogenesis is characterized by increased colonization of P. acne anaerobic bacteria, increased sebum production from the sebaceous glands, inflammation, and hyper-keratinization [113].

Stress has long been suspected to induce acne flares by clinical experiences and anecdotal observations [114, 115], but it was only confirmed 10 years ago by a well controlled study. In a student examination stress study, increased acne severity is significantly associated with stress levels [116].

The role of skin peripheral HPA axis has been studied in the pathogenesis of acne. CRH and its receptors have been detected on sebocytes [23, 38]. It was shown that CRH promotes lipogenesis in sebocytes through up-regulation of a key enzyme [38]. In addition, it induces cytokines (IL-6 and IL-11) productions in keratinocytes [36], contributing to inflammation. ACTH and α-MSH also contribute to sebum production and possibly worsen the acne phenotype [117, 118]. The role of neuropeptide, specifically substance P in ance has been studied extensively [119]. Facial skin from acne patients show marked increase of SP-positive nerve fibers around the sebaceous glands and around acne lesions [120]. SP can promote both proliferation and differentiation of sebaceous glands [121]. SP induces gene expression of PPAR-γ, which plays a unique role in stimulating sebocyte lipogenesis. It also stimulates various pro-inflammatory cytokines release from sebocytes, including IL-1, IL-6, and TNF-α [122]. In addition, SP can activate mast cells, adding another player to the neurogenic inflammation [66].

Atopic Dermatitis

Atopic dermatitis or AD, is a chronic and relapsing inflammatory skin disease often associated with eczema and itch [123]. A complex interaction of genetic, environmental, and immunological factors is manifested in AD. Skin barrier function defect is a key feature of AD because null mutations in the filaggrin gene are an important predisposing factor for AD. Filaggrin protein is essential for the final cell compacting process to form the terminally differentiated stratum corneum [124-126]. Environmental factors such as allergens or microbial organisms are critical triggers or complications in the disease [127]. And Toll-like receptor 2

(TLR-2) has emerged as another important player. It recognizes cell wall components of bacteria and its gene polymorphism has been associated with AD [128]. AD is also characterized by an acute phase with predominant TH2 response (IL-4, IL-13, and IL-31) and a chronic phase towards a TH1 (IL-5, IL-12, and IFN-γ) feature [129].

Similar to psoriasis, AD symptoms and psychological stress seem to form a vicious cycle. AD patients have been reported to have anxiety and depression, while psychological stress in turn can exacerbate AD pathology [130-132].

Stress can impact AD symptoms through different mechanisms. First of all, stress can negatively affect skin's permeability barrier function and homeostasis. In AD patients, barrier dysfunction could lead to increased sensitization to allergens and microbial organisms, increased transepidermal water loss, and lowered threshold for itch [133]. For a detailed review of how stress impact barrier function, please refer to the next section.

Stress also contributes to the immune and inflammation dysfunction in AD patients. HPA response after stress was found to be impaired in AD patients. This hyporesponsiveness was linked to severity of inflammation [134]. The blunted HPA response was proposed to lead to immune function dysregulation, allergic inflammation, and exacerbation of disease [135]. On the other hand, the SAM axis is over-reactive. Both basal and stress-induced levels of catecholamines are higher in AD patients compared to control [134]. However, the adrenergic receptor mutation or polymorphisms have been discovered in AD. A point mutation in the β2-adrenoceptor gene could alter the structure and function of the receptor, thereby leading to a low density of receptors on both keratinocytes and peripheral blood lymphocytes [136]. Receptor mutation or polymorphism is also associated with AD [13, 136]. So the catecholamines signaling is probably still dysfunctional even with upregulated ligand. It was discovered that adrenoceptor signaling defect with TLR activation can shift the recall memory response to the Th1 type, releasing multiple cytokines. This could be a mechanism where SAM axis can contribute to chronic AD pathogenesis [137]. Further research is warranted to elucidate the role of SAM axis in AD pathogenesis.

In a mouse model for atopic dermatitis, it was discovered that stress increased cutaneous but not serum or hypothalamic NGF. Treatment with NGF neutralizing antibody can partially recover the skin inflammation phenotype by reducing epidermal thickening, decreasing pro-inflammatory cytokines induction, and attenuating allergy-characteristic cellular infiltration [138]. However, there are conflicting data on NGF expression in AD patients. Some research showed increased NGF [132, 139-141], while others demonstrated no significant difference or even decreased NGF level [142, 143]. Further research is needed in this area to elucidate the differences. Substance P was also involved in the neurogenic inflammation that worsens dermatitis because the exacerbation was not seen in mice lacking the SP receptor [144]. It was shown that SP receptor expression is much higher in AD patients' peripheral blood mononuclear cells (PBMCs) than in healthy control. SP can increase PBMCs proliferation rate and TNF-α and IL-10 production [12]. However, in an atopic dermatitis mouse model, the SP+ nerve fibers in skin are decreased in stressed animals [145]. The exact role of SP in AD remains to be clarified. Mast cells also play a role in AD neurogenic inflammation. Mast cell numbers are increased in lesional AD skin, as well as mast cell-nerve contacts [146, 147]. Recently it was discovered that oxytocin (OXT), a neuropeptide playing a major role in behavior regulation, is down-regulated in lesional AD skin. Both oxytocin and its receptor are detected in keratinocytes and fibroblasts, and it affects cell proliferation, inflammatory cytokines release and oxidative stress responses [148].

IMPACT OF STRESS ON SKIN BARRIER FUNCTION AND WOUND HEALING

The stratum corneum (SC) plays important barrier functions by regulating epidermal permeability and homeostasis. This protein/lipid barrier creates a surface seal essential for maintenance of hydration and protection against microbial infection. Disruption of the skin barrier function can lead to flaky or dry skin [127]. Alternation of the lipids composition has also been linked to skin diseases like atopic dermatisis and psoriasis [149, 150].

Stress can cause detrimental physiological and functional consequences in the skin. Overcrowding stress in mice caused higher transepidermal water loss, lower water retention property and impaired barrier function, leading to moderate exfoliation and slight wrinkle formation. The exact mechanism is still unclear, but a decrease in ceramide and pyrrolidone carboxylic acid was observed [151, 152]. Other studies have corroborated the result and further confirmed the involvement of stress by demonstrating that treatment of glucocorticoid receptor antagonist or CRH receptor antagonist can block the adverse events [153, 154]. A study using topical glucocorticoid-treated mice proposed that lipid synthesis inhibition is key for the stress-induced abnormalities [155]. In a later insomnia study, the authors discovered that stress can significantly impair epidermal proliferation and differentiation, decrease size and density of corneodesmosomes, and decrease lipid synthesis and lamellar body production. It also confirmed the critical role of lipids because topical application of physiological lipids including ceramides and free fatty acids can restore barrier homeostasis and stratum corneum integrity [156].

Similar effects were also observed in human subjects. For example, final exam stress on students caused a decline in permeability barrier recovery kinetics [157]. Interview stress caused barrier function recovery delay, increased plasma cortisol level, and activated several inflammation and immune players, including interleukin-1β, interleukin-10, tumor necrosis factor α, and circulating natural killer cells [158]. Stress due to marital disruption significantly delayed skin barrier recovery after tape stripping [159].

One of skin's major functions is physical protection and wound repair upon injury. Wound healing is an intricate process that involves resident skin cells, skin extracellular matrix and systematic factors. Mechanosensing and mechanotransduction also play vital roles in wound closure [160]. It is divided into three major yet overlapping phases: inflammation, proliferation, and remodeling. During inflammation, cytokines and chemokines including IL-1α,

IL-1β, IL8, transforming growth factor-β, vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF-α) play important roles. They protect against infection, attract phagocytes, and recruit fibroblasts. In proliferation, new granulation tissue is rebuilt with collagen, blood vessel, and other ECM proteins. Finally, in remodeling collagen is remodeled and realigned and apoptosis remove unnecessary cells, which may take weeks or months [161].

An extensive literature search has revealed that chronic systemic corticosteroids have a negative impact on all three phases of wound healing [162]. A meta-analysis also concluded that stress was associated with impaired healing or dysregulation of healing biomarkers [163].

The negative impact of stress on wound healing was first observed clinically in human when caregivers of demented relatives needs 20% more time for complete dermal wound healing [164]. Anxiety and depression are also associated with delayed healing in chronic wounds [165]. It was found that perceived stress and elevated cortisol level are among the contributing factors [166].

Subsequent mouse and human studies have revealed some important molecular mechanisms. The HPA axis plays a vital role because glucocorticoid receptor antagonist treatment can restore proper healing rate [19]. Inflammatory markers (including IL1α and IL1β) kinetics are disrupted [167]. Two key cytokines (IL1α and IL8) were found to be significantly lower at wound site in stressed patients [168]. MMP2 expression in blister wound was found to be negatively correlated with plasma cortisol level [169]. Rotational stress in mice can delay wound closure by delaying immune cell infiltration, lowering TNF-α level at wound site, and reducing MMP activity [170]. Bacterial infections during early stages of wound healing are also more prominent due to compromised skin immune function [171]. Antimicrobial peptide expression was also decreased by stress leading to increased severity of infection at wound site [172]. Furthermore, myofibroblasts differentiation is delayed, leading to severely impaired wound contraction [173]. TGF-β signaling could also be involved since it was shown that endogenous glucocorticoids plays an important part in wound healing by altering TGF-β expression which affects fibroblast proliferation, migration, and differentiation [174, 175].

Alternatively, stress can also work through the SAM - epinephrine pathway to negatively impact keratinocyte motility and wound re-epithelialization. Epinephrine can be induced by stress systematically and can also be produced locally by wound site. Epinephrine binds to the β2-adrenergic receptor (β2AR) in keratinocytes, and decreases downstream PI3K/AKT signaling. This leads to stabilization of actin cytoskeleton and increased focal adhesion formation, both inhibiting migration and proper wound healing. β2AR antagonist was shown to be effective at reversing this impairment [176]. Antagonist can also accelerate skin barrier recovery and reduce epidermal hyperplasia [177]. Epinephrine was found to decrease fibroblast migration and MMP2 secretion *in vitro* [170]. It can also reduce collagen deposition by fibroblasts [54]. A recent research discovered that neutrophil trafficking alternation and IL-6 up-regulation were induced by epinephrine and inflammatory responses are impaired in wound healing [178]. Stress activated SAM pathway can alter blood flow. Peripheral vasoconstriction can limit the blood and oxygen supply at the wounding site, which limit the rate of healing by increasing the production of nitrix oxide (NO). Hyperbaric oxygen therapy was shown to effectively correct stress-impaired wound healing in mouse [179]. In human, emotional disclosure intervention was shown to significantly improve wound healing after skin biopsy [180].

LONG TERM SKIN DAMAGE OF CHRONIC STRESS

Under short term acute stress, the HPA axis is tightly regulated through feedback mechanisms. Increased cortisol level can keep the HPA activity in check through both a slow genomic and a fast non-genomic negative feedback mechanism [181]. Acute stress can induce a significant re-distribution of lymphocytes from the blood to the skin, leading to enhanced skin immunity and successful stress adaptation [182]. In a mouse restraint stress study, both innate and adaptive immunity are involved: dendritic cells mature and traffick from skin to the lymph nodes, macrophages are activated, and surveillance T cells are recruited to the skin [183]. Acute stress also suppresses ROS production [184].

In contrast to acute stress, which may augment innate and adaptive immune responses, chronic stress usually suppresses immunoprotection, increases susceptibility to infections, and exacerbates some allergic and inflammatory diseases [185]. This is due to altered stress responses after repeated or prolonged stress termed stress habituation, which reduces HPA axis activation, but also sensitizes reactivity to new stimuli [186]. Aging also has a negative effect on the feedback system, as shown in both rats and human [187, 188].

In a mouse study, chronic stress induced by fox urine can significantly accelerate UV-induced skin neoplasma development. Stressed group starts to develop skin tumor much earlier than the control group and the survival rate is significantly lower [189]. It was later discovered that chronic stress caused a significant decrease in T-cell infiltration in the skin and cell-mediated immunity was greatly compromised. Several important skin immune markers are decreased by stress, including IL12 (Th-1 response promotion and cellular immunity mediator), IFN-γ (tumor recognition and elimination), and CCL27 (skin homing T-cell attraction) [190].

Skin aging is characterized by formation of lines and wrinkles, increased pigmentation, loss of elasticity and firmness, and dull skin. It is a consequence of both intrinsic factors and extrinsic factors. There are two major theories for aging: the programmatic theory which focuses on reduced cellular life span, decreased responsiveness and functionality, and dysfunctional immune responses; while the stochastic theory points towards environmental damages, focusing on DNA damage, inflammation and free radical formation [191-193].

The exact mechanism of how stress impacts skin aging is still quite elusive. However, recent research has provided evidence of possible pathways that might contribute to skin aging [194]. UV irradiation is one of the major extrinsic stressors responsible for premature skin aging, thus the term

"photoaging". UV irradiation is one of the major stimulants of skin HPA axis. It induces expression of CRH, POMC peptides, ACTH, cortisol, and β-endorphin [195]. Considering that skin is under daily UV stress, the repeated activation of the HPA axis can have detrimental effects on the skin. Long term glucocorticoids (GC) therapy for treating skin inflammatory disease has severe skin atrophy side effect, including decreased epidermal thickness, flat dermal-epidermal junction, reduced number of fibroblasts, and disruption of the dermal fibrous network, which are also hallmarks of skin aging. Several extracellular matrix proteins are negatively impacted by GC, including collagen I, collagen III, proteoglycans, and elastin [196].

Epinephrine, norepinephrine and cortisol were found to increase DNA damage, interfere with DNA repair, and alter transcriptional regulation of the cell cycle [197]. It has been demonstrated that stress can induce DNA damage through the β2-adrenoreceptor (β2AR) pathway. Chronic catecholamine stimulation leads to p53 degradation and accumulation of DNA damage [198]. Furthermore, blockage of the β2AR pathway can prevent DNA damage accumulation [199]. Thus, stress-induced SAM axis can also contribute to skin aging by compromising genome integrity.

Reactive oxygen species (ROS) was recently discovered to also play a role in the stress-SP-mast cell pathway. In chronic restraint stress mice, oxidative stress pathway has two-way crosstalks with the SP pathway and antioxidantant Tempol was shown to be also effective at normalizing hair growth [200]. Repeated short term stress can induce ROS production by up-regulation of NF-κB in the skin induced by toxicant and UVB. Stress augmenting depletion of cellular anti-oxidant machinery is shown by significant loss of GSH (Glutathione and GSH dependant enzymes), superoxide dismutase and catalase activity [201]. It was also discovered that in the brain, stress leads to increased oxidative stress and mitochondria dysfunction [202, 203]. Considering ROS production in the mitochondria is the major determinant of aging and life span [204], stress can have a major impact on skin aging through the ROS pathway.

Smoking and air pollution have been confirmed as critical chronic stressors that impact skin aging significantly. In photoprotected area, years of smoking and packs smoked per day are strong indicators of premature skin aging [205]. In an identical twin study, it was observed that 5-year difference in smoking history led to noticeable changes in skin aging [134]. Significant increase in temperature and decrease in oxygen content were observed in skin after smoking [69]. ROS production and arylhydrocarbon receptor (AhR) signaling pathway lead to dermal matrix breakdown and wrinkle formation [206]. Air born particles exposure from traffic was associated with significant increase in pigment spots and facial wrinkles [207]. ROS production is the major underlying mechanism. It can induce Vitamin E depletion and lipid peroxidation, as well as MMP induction [208, 209]. Direct mitochondria damage, and AhR pathway have also been proposed as possible mechanisms [210-212].

Recently, telomere shortening has emerged as another possible cellular mechanism linking chronic psychological stress and aging. Telomeres are DNA repeats at the ends of chromosomes and it shortens with each cell division, eventually leading to replicative senescence and premature cellular aging. Various chronic stress situations have been associated with shorter telomere length, including caregiving for sick child with chronic conditions or elderly dementia patients, major depression, childhood adversity, and exposure to intimate partner violence [120, 122, 140, 213]. Although the exact mechanism of how stress induces telomere shortening is still under debate, cortisol and epigenetic modulation have been proposed as possible routes [119, 214]. Telomere shortening can lead to the downregulation of mitochondria biogenesis and ROS production [113, 215]. This could constitute a vicious cycle where stress from lifestyle or habits further exacerbate the skin damage and signs of aging.

A recent study established the negative effect of sleep deprivation on skin aging [121]. It was found that poor quality sleepers showed increased signs of intrinsic skin aging including fine lines, uneven pigmentation and reduced elasticity. They also recover much slower after skin barrier disruption. Hypoxia stress induced during wound healing can also impact skin aging by disrupting basement membrane involving laminin and integrins [216].

CONCLUSION AND FUTURE PERSPECTIVES

In recent years, emerging research has demonstrated that skin is not only a target of psychological stress signaling modulation, it also actively participates in the stress response by a local HPA axis, peripheral nerve endings, and local skin cells including keratinocytes, mast cells, and immune cells. There are also feedback mechanisms and crosstalk between the brain and the skin, and pro-inflammatory cytokines and neurogenic inflammatory pathways play huge roles in mediating such responses. In this review, we summarized findings that shed light on how the "brain-skin connection" actually works: what are the major pathways and effector cells; how they negatively affect skin functions and diseases; and how chronic stress can have a detrimental effect on skin aging.

As of today there is no proven medical treatment that can either prevent or treat stress-induced or exacerbated skin conditions or skin aging. Several key players have been proposed which might give rise to potential therapeutics. Skin mast cells are activated by stress, and in turn they also produce stress hormones and inflammatory factors. This could lead to a vicious cycle of stress-induced inflammatory events. Indeed mast cells have been implicated in numerous skin diseases including acne, atopic dermatitis, psoriasis and pruritus [217]. Several compounds have been found to be effective in inhibiting cytokine release from mast cells [128]. Dietary supplements combining active flavonoids with proteoglycans could also be helpful in atopic and inflammatory conditions [146]. Specific receptor antagonists against CRH receptors, NGF receptors, or SP receptors could also prove to be effective in relieving stress-induced neurogenic inflammation [218].

In the future, researches should further investigate the HPA axis, proinflammatory hormones and cytokines, and their downstream effectors that mediate the brain-skin connection. Future researches can look into the ways to modulate this connection and discover novel therapeutics for skin diseases and anti-aging treatments.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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