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Pathogenesis of Stress-Associated Skin Disorders: Exploring the Brain-Skin Axis

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Abstract

The association between psychological stress and skin diseases is well known from clinical practice and the literature. Stress – a complex adaptive response – acts on different levels of the nervous system and affects many organ systems. We review here the available knowledge regarding the possible mechanisms underlying stress actions in the pathogenesis and course of skin diseases.

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It is well acknowledged that psychological stress plays an important role in the pathophysiology of numerous skin disorders [1, 2]. However, the strength of association between stress responses and the onset, recurrence or exacerbation of various skin diseases varies [1, 2] (table 1). The skin disease best known as stress associated and by far the most intensively studied for this association is psoriasis, with 40–60% of cases triggered by stress [3–7]. Moreover, psychological distress has a detrimental effect on treatment outcome in patients with psoriasis [8]. Interestingly, among pediatric patients with psoriasis, stress has an even more important role in disease exacerbation compared to adults [9]. Another common inflammatory skin disease, known to be associated with psychological stress is atopic dermatitis (AD) – a common pruritic skin disorder. Both children and adults with AD have higher anxiety levels than those without, and it is well known that psychological stress brings on attacks or exacerbates skin symptoms [10–14]. In patients with c1 esterase inhibitor deficiency, suffering from urticaria and angioedema, stress has been shown to be an important triggering factor [15]. Moreover, adrenergic urticaria, a separate rare clinical entity, appears during periods of emotional stress or exercise [16, 17]. Stress is often cited as

Table 1. Stress-associated skin disorders

Disease	Association	References
Psoriasis	well established	[3–7]
AD	well established	[10–14]
AA	well established	[2, 24]
Urticaria	indicated but not proven	[16, 17]
HSV	indicated but not proven	[19, 20]
Vitiligo	indicated but not proven	[2, 55, 56]
Lichen planus	weak	[2, 57]
Pemphigus vulgaris	weak	[2, 58, 59]
Acne	weak	[18]

playing a role in acne vulgaris flares [18], as well as in reactivation of latent herpes simplex infection [19, 20]. Although the association between stress and skin diseases has been well known for decades, the mechanisms underlying stress-induced dermatopathologies are not fully understood. Here, we will review the up-to-date knowledge of mechanisms proposed to underlie stress-induced skin disease, from stress perception by the brain's cerebral cortex to the appearance of skin lesions. Since the brain and the skin communicate in both directions through the immune and the neuroendocrine systems, stress effects on skin disease must be mediated through these systems. All skin diseases mentioned here are inflammatory disorders, except herpes simplex infection, which is a latent infectious disease, and for the activation of HSV some attenuation of the immune system needed. Thus, when searching for understanding of the mechanism underlying the role of stress action in skin diseases, we should understand the role of stress-induced activation of the neuroendocrine system in the inflammatory cascade and the skin immune system (fig. 1).

Hypothalamic-Pituitary-Adrenal Axis

During acute stress response, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing hormone (CRH). CRH then acts on the pituitary gland to induce a release of adrenocorticotrophic hormone (ACTH), which in turn causes the adrenal cortex to release cortisol. How elevated cortisol levels protect the organism under stress is not completely understood, but in conditions of cortisol deficiency, stressful events like trauma or infection result in hypotension, shock, and death. Moreover, cortisol is a very potent

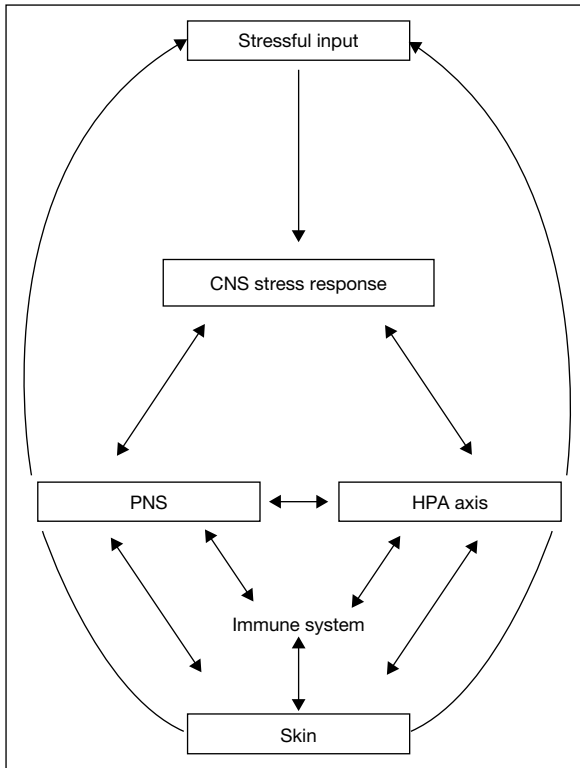


Fig. 1. Schematic presentation of the brain-skin axis. Stressful input perceived by the cerebral cortex leads to CNS stress response and activation of the HPA axis and PNS which may affect the skin directly or through modulation of the immune system (see text for details).

anti-inflammatory molecule, and is widely used in pharmacy for this property, especially in dermatology, as a fundamental ingredient in local and systemic remedies. So, how may the activation of the HPA axis harm the skin? Recent studies in rats, demonstrated the involvement of CRH receptors (CRHR) in stress-induced exacerbation of chronic contact dermatitis [21]. In this study, the authors induced chronic contact dermatitis in rats by local exposure to 2,4,6-trinitro-1-chlorobenzene. In addition, rats were exposed to a 1-hour period of electric foot-shock following intraperitoneal administration of CRA1000, selective CRHR type 1 (CRHR1) antagonist, or vehicle everyday for 9 days. Histological examination of the skin showed that the epidermis significantly thickened and the number of mast cells in the dermis significantly increased by repeated exposure to stress, and that these changes were blocked by CRA1000.

These results suggest that CRHR1 located in the brain, skin or both is involved in the stress-induced exacerbation of chronic contact dermatitis in this animal model. A recent clinical study by Richards et al. [22] support the notion that disturbances in the HPA axis are involved in skin diseases. In their study, 40 patients with chronic plaque psoriasis and 40 age-matched healthy controls experienced three randomly presented acute psychological stressors (cognitive, emotional and social). While in healthy subjects there was a significant correlation between pulse rate and serum cortisol level following the social performance stressor, no such correlation was found in the psoriasis group. Moreover, patients who believed that their psoriasis was highly stress responsive had significantly lower salivary cortisol levels at baseline and lower serum cortisol levels following the social performance stressor than patients who believed that stress had no impact on their disease. In contrast, the pulse rate response to the stressors was similar in the two groups. This study suggested that patients with psoriasis, and in particular those whose disease appears to be stress-associated, exhibit an altered HPA response to acute social stress. The implication is that such patients may perhaps be primed to flares of their psoriasis. Whether this is genetically predetermined and/or a consequence of the distress of living with psoriasis remains to be determined. Recently, a fully functional peripheral equivalent of the HPA axis was demonstrated [23]; normal human scalp hair follicles directly respond to CRH stimulation in a strikingly similar manner to what is seen in the classical HPA axis, including synthesis and secretion of cortisol and activation of prototypic neuroendocrine feedback loops, as demonstrated by the downregulation of follicular CRH expression with the glucocorticoid receptor agonist, hydrocortisone. Moreover, the influence of a local HPA axis or rather CRH-proopiomelanocortin axis in alopecia areata (AA) was recently investigated [24]. In this study, the immunohistochemical analysis of the expression levels of CRH and proopiomelanocortin peptides, including the ACTH and α -melanocyte-stimulating hormone, in a number of AA lesions and normal scalp (as control) showed that the epidermis and pilosebaceous units of normal scalp stained weakly with CRH, ACTH and α -melanocyte-stimulating hormone, whereas those from the affected sites of the AA group showed intense expression of the peptides.

Hypothalamic-Pituitary-Adrenal Axis and Immune System

So far, we discussed the direct effect of HPA activation during stress on skin disease. However, HPA axis activation modulates the function of the immune system as well [for review, see 25]; for example, in a recent study a correlation between the degree of stress and the levels of IgE and Th2 was found in patients with AD [26].

Long-Term Effects of Stress

Studies in animals and humans suggest that stress is associated with long-term alterations in brain function and structure. Studies in animals showed long-term dysregulation in stress-responsive systems, including the norepinephrine (NE) and HPA axis systems. The HPA axis and cortisol systems have been shown to be dysregulated in posttraumatic stress disorder, and glucocorticoids, which are released during stress, were shown in animal studies to be associated with reduced number of neurons in the hippocampus, a brain area that plays an important role in learning and memory. More studies are awaited to reveal the mechanism underlying altered HPA response in psoriatic patients and its possible relation to dysregulation of the HPA axis in posttraumatic stress disorder patients.

Peripheral Nervous System

Sympathetic System

This major arm of the stress response within the peripheral nervous system (PNS) originates from the 'locus coeruleus/norepinephrine system' within the central nervous system (CNS). Its activation causes central sympathetic discharge and peripheral sympathetic outflow, resulting in secretion of NE from nerve fibers terminals, and adrenalin (or epinephrine), which is secreted from the adrenal medulla. During the stress response, both molecules are invariably present in the circulation. What effect has sympathetic activation on the skin and how may it be related to skin diseases? Sympathetic activation via its actions on cutaneous blood vessels is important for thermoregulation and response to heat and cold stress. When core temperature is reduced, NE is released and acts to constrict cutaneous vessels. However, during a rise in core temperature (such as may occur with environmental stress), the control of cutaneous blood flow becomes more complicated [27]. The main mechanism involved in response to heat stress in nonacral regions of skin is sympathetically mediated active vasodilatation. Details regarding neurotransmitters responsible for this vasodilatation are not completely understood, but the best evidence existing now points to sympathetically released cholinergic co-transmitter [28] and nitric oxide [29]. Case reports showing that injury to cutaneous nerves result in complete remission of psoriasis at the distal site support an important role for nerve terminals at the PNS in the pathogenesis of psoriasis. In one such case report [30], a complete unilateral remission was observed in a patient with chronic plaque psoriasis after acute accidental injury of the ipsilateral brachial plexus. The psoriasis reappeared as the nerve plexus recovered. Substance P (SP) was proposed as one potential neural mediator in psoriasis and psoriatic arthritis [31]. Emotional stress was shown to cause a release of SP from neurons [32]. Notably, cutaneous

nerves and SP play an important role in the pathogenesis of AD, another inflammatory skin disease, through altered patterns of cutaneous innervations and abnormal expression of neuropeptides in the lesional skin [33]. SP has been particularly implicated, because increased numbers of nerve fibers containing SP are found concomitantly with a decrease in SP cutaneous levels in lesioned skin of AD patients. Furthermore, the skin of AD patients is hyposensitive to intradermal injection of SP, further supporting its role in inflammatory skin response [34, 35]. Increased plasma levels of SP and nerve growth factor, which modulates the synthesis of SP, were also found in AD patients [36]. These findings suggest that specific neurogenic factors modulate the systemic allergic response in AD. The mechanisms of SP action in these diseases are most probably related to the activation of mast cells to secrete specific cytokines, chemokines and tumor necrosis factor- α [37]. Interactions between the sympathetic nervous system with various components of the immune system have been reported; for example, acute stress was shown to increase migration of dendritic cells as part of delayed type hypersensitivity reaction [38], and animal studies showed that acute stress initially increases trafficking of all major leukocyte subpopulations to a site of immune activation. Tissue damage-, antigen-, or pathogen-driven chemoattractants subsequently determine which subpopulations are recruited more vigorously. Such stress-induced increase in leukocyte trafficking may enhance immunoprotection during surgery, vaccination, or infection, but may also exacerbate immunopathology during inflammatory or autoimmune (psoriasis or arthritis) diseases [39].

Cholinergic System and Other Neurotransmitter Systems

Additional neurotransmitter systems are known to be involved in the stress response. Besides the sympathetic, adrenergic arm, the cholinergic arm originating from the vagal nucleus of the brain stem is crucially involved in stress responses. Furthermore, adrenergic and cholinergic transmitter systems *within* the brain are also activated during stress, thus influencing the PNS. The brain cholinergic system, including both muscarinic and nicotinic subsystems, plays an important role in a variety of cognitive functions including attention, learning and memory [40]. During the past decade, several groups [38–40] showed that following stress, cholinergic stimulation triggers rapid induction of the gene encoding the transcription factor c-Fos. This protein, in turn, serves as a selective regulator for numerous transcriptional changes affecting the levels of proteins, including those involved in acetylcholine metabolism [41]. In addition, mechanisms like alternative splicing involve neuritic replacement of synaptic acetylcholinesterase with the normally rare ‘readthrough’ variant, leading to altered cholinergic balance and structural changes [42]. The skin has abundant cholinergic system with fully developed enzymatic machinery known

to play a central role in blistering skin diseases [for review, see 43]. Interestingly, in a recent, large case control study, smoking was shown to be strongly associated with pustular psoriasis [6]. Thus, a plausible hypothesis would be that in the skin, like in other body organs (e.g. brain [44], blood and bone marrow [45], testis [46]), stress induces changes in local cholinergic system which alter inflammatory responses [47]. It was shown, that vagal stimulation may inhibit inflammatory responses through activation of nicotinic acetylcholine receptors [48]. Other local transmitter systems (e.g. serotonergic) may also be important [49].

Biological Barriers

Animal studies provide evidence that psychological stress can induce blood-brain barrier disruption [50, 51] thus promoting long-term brain dysfunction [52]. Interestingly, stress induced alterations in epidermal permeability barrier homeostasis have been shown in both animals and humans [53], to be mediated by endogenous glucocorticoids. The mechanisms underlying stress-induced increase in epidermal barrier permeability are related to the inhibition of epidermal lipid synthesis, resulting in decreased lamellar body formation and secretion, as well as decreased corneodesmosomes, both compromising permeability barrier homeostasis and stratum corneum integrity [54].

Conclusion

Stress is a complex biological response known to be associated with various skin diseases. Accumulating clinical and experimental data provide evidence for a complex net of cellular and molecular mechanisms involved in the pathogenesis skin disease under stress. Activation of the HPA axis and the sympathetic system are the most studied so far, but other possibilities have to be considered, like involvement of the cholinergic system and impairment of epidermal barrier function. Exploring these pathways will offer new strategies in the treatment of common skin disorders.

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