Acta Derm Venereol 2013; 93: 387–393

REVIEW ARTICLE

Expression of Hypothalamic–Pituitary–Adrenal Axis in Common Skin Diseases: Evidence of its Association with Stress-related Disease Activity

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Hypothalamic–pituitary–adrenal (HPA) axis hormones and their receptors expressed in the skin are known to function locally, but how these hormones affect the maintenance of skin homeostasis or the pathogenesis of skin diseases is not fully understood. We comprehensively reviewed the distribution and function of the central and peripheral HPA axis in various stress-related skin diseases. Previous studies have shown altered expression of central and peripheral HPA axis hormones in chronic inflammatory skin diseases and skin tumours, and that hyper-active lesional HPA axis hormones may negatively feedback to the central HPA axis and interact with some cytokines and neuropeptides, leading to symptom deterioration. This provides an evidence-based understanding of the expression of the central and peripheral HPA axis in common skin diseases and its association with disease activity. ***Key words: stress hormone; hypothalamic–pituitary–adrenal axis; atopic dermatitis; psoriasis; alopecia areata; skin tumour; skin disease.***

Accepted Nov 7, 2012; Epub ahead of print Mar 5, 2013

Acta Derm Venereol 2013; 93: 387–393.

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Stressors activate two major neuroendocrine systems; the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. An activated HPA axis leads to a series of hormonal cascades and is regulated by a feedback mechanism. Corticotrophin-releasing hormone (CRH) is the principal component of the HPA axis. CRH is produced in the paraventricular nuclei of the hypothalamus in response to stress. CRH controls the release of pro-opiomelanocortin (POMC) and POMC-derived peptides (adrenocorticotrophin (ACTH), α-melanocyte-stimulating hormone (α-MSH) and β-endorphin) from the anterior pituitary gland (1–4). CRH activates pituitary ACTH secretion, which in turn stimulates the production of adrenal cortisol and glucocorticoids to regulate homeostasis. CRH is also involved in activating the sympathetic nervous system by stimulating the locus coeruleus of the brain stem (5). Glucocorticoids are key effector molecules of the HPA axis, and are essential for tissue homeostasis. In the resting state, glucocorticoids are secreted with circadian variation and regulate the activity of the HPA axis by feedback inhibition (6). Acute stressors induce temporary activation of the HPA axis, but it returns to normal levels due to the phenomenon of adaptation (7). Chronic exposure to stress enhances the central tone of the HPA axis and interferes with the normal function of the HPA axis. Chronic repeated stress enhances the central tone of the HPA axis, responsiveness of which normalizes with time. On the other hand, glucocorticoids positively feedback to the HPA axis under chronic exposure to acute novel stressors. Persistent exposure of tissues to elevated glucocorticoid levels may be damaging (7). CRH induces arginine vasopressin (AVP) secretion, which produces a synergistic effect with CRH, particularly under the state of chronic stress (1–4).

There have been several hypotheses to explain how a chronically activated HPA axis aggravates inflammation. One hypothesis is that a chronically activated HPA axis could diminish the anti-inflammatory effects of glucocorticoids at the target tissue, which may result from exhausted glucocorticoid levels or tissue receptor resistance. Recurrent infection, interactions between the HPA axis and disease-specific immune response, and the proinflammatory effect of HPA axis hormones have been suggested as additional hypotheses (8).

HPA AXIS EXPRESSION IN THE SKIN

The skin senses the environment and reacts immediately against various stressors to restore tissue homeostasis. Stress influences the immune response by altering HPA axis hormones and the secretion of stress-related neuropeptides as well as cytokine profiles (9). The existence of a peripheral HPA axis equivalent to the central HPA axis has been identified in the skin (2, 3, 10–12). CRH, urocortin, ACTH, α-MSH, β-endorphin and their receptors can be generated in normal skin cells. Epidermal

and hair follicle keratinocytes, sebocytes and mast cells can secrete CRH in response to stress (10–12). The action of CRH is mediated via CRH receptors (CRH-R1 and CRH-R2) belonging to G protein-coupled receptors (12). CRH-R1 is the predominant receptor of major cellular constituents in the epidermis, dermis, and subcutis. CRH-R2 is expressed mainly in pilosebaceous units, eccrine glands and blood vessels (3, 12). However, CRH-binding protein has not been detected in the skin; this is the reason for the debate about whether the major source of CRH in the skin is centrally originated or locally produced (13). POMC and POMC-derived peptides act through melanocortin receptors (MC1R and MC2R) in the skin, which are members of the rhodopsin family of 7 transmembrane receptors. MC1R is the predominant receptor type in the skin and is expressed in keratinocytes, melanocytes and adipocytes (14). α-MSH exhibits its anti-inflammatory effect and induces pigmentation through MC1R. ACTH is involved in the regulation of the anagen period of the hair cycle and in melanin production. ACTH produces cortisol, which is stimulated by CRH and fully functionally exerts in skin HPA axis. MC2R is a specific receptor for ACTH and its presence has been demonstrated in the skin, but the exact location is unknown (15). β-endorphin enhances the epidermal turnover rate and has a protective effect on the skin barrier (16).

PLEIOTROPIC EFFECT OF CORTICOTROPHIN-RELEASING HORMONE ON THE SKIN

Among the skin HPA axis components, CRH is the most studied substance with regard to its function. CRH has various effects in the skin according to the cell type and experimental microenvironment. CRH affects proliferation (17), differentiation (18, 19), and apoptosis (17) of skin cells via CRH-R1 activation. Whereas CRH stimulates fibroblast proliferation, it shows inhibitory effects on the growth of keratinocytes and melanocytes (17). Furthermore, CRH promotes the differentiation of keratinocytes and inhibits proliferation through G0/1 arrest in a dose-dependent manner (18, 19). CRH prolongs the survival of melanocytes by inhibiting apoptosis (17). It also acts as a pro-inflammatory peptide by stimulating mast cells. Mast cells, a key player of inflammatory skin diseases, express CRH-R1 and degranulate in response to CRH stimuli, then released histamine increases vascular permeability (20). CRH stimulates IL-6 release by keratinocytes and may potentiate an acute phase stress response (21). In contrast, CRH shows its anti-inflammatory effects by modulating angiogenesis, vascular permeability and cytokine production (21–24). CRH decreases vascular endothelial growth factor (VEGF) expression in keratinocytes through CRH-R1 and MAPK signalling pathways (22). The peptide inhibits NF-kappa B signalling, which induces a high level of pro-inflammatory cytokine production in human melanocytes (24). CRH also inhibits the pro-inflammatory cytokine IL-1β and stimulates the anti-inflammatory cytokine IL-11 from keratinocytes (21).

INTERACTION BETWEEN HPA AXIS HORMONES AND PROINFLAMMATORY CYTOKINES

Many studies have found evidence of interaction between HPA axis hormones and pro-inflammatory cytokines (25–28). IL-18 is a proinflammatory cytokine that is believed to play an important role during stress. IL-18 levels are elevated by activation of the HPA axis in a tissue-specific fashion. IL-18 produced in the adrenal and pituitary glands modulates the HPA axis during stress. IL-18 production by keratinocytes is known to induce severe cutaneous inflammation. The skin HPA axis may have its own regulatory feedback mechanism through interaction with inflammatory cytokines.

We have shown previously that ACTH upregulates IL-18 secretion from HaCaT cells through caspase-1 activation, melanocortin receptor and p38 and ERK MAPK pathways in a dose-dependent manner (27), whereas CRH downregulates IL-18 expression in HaCaT cells through activation of the p38 MAPK pathway (28). IL-18 may contribute to the negative feedback loop of CRH control. On the other hand, HPA axis hormones may be involved in the regulation of pro-inflammatory cytokine IL-18 expression.

HPA AXIS IN SKIN DISEASES

Several studies have shown aberrant central and peripheral HPA expression in some skin diseases under both basal and stress circumstances (11, 29–34). In this context, we focused on summarizing the distribution and function of HPA axis hormones in some common stress-related skin diseases (Table I and Fig. 1).

Table I. *Suggested role of corticotrophin-releasing hormone in common stress-related skin diseases*

Atopic dermatitis
IL-18: Th2 response
Mast cell-mediated inflammation
Psoriasis
Altered keratinocyte proliferation/differentiation
Mast cell-mediated inflammation
Alopecia areata
Premature catagen development
Prolongation of inflammation
Skin tumours
Tumour cell growth/invasion
Contact dermatitis/urticaria
Increased severity of delayed type IV hypersensitivity
Suppressed development of delayed type IV hypersensitivity
Vascular permeability/vasodilation
Acne/seborrhoea
Altered infundibular keratinocyte differentiation
Lipogenesis
Inflammation

Atopic dermatitis

Atopic dermatitis (AD) is caused by the imbalance between T-helper type 1 (Th1) and T-helper type 2 (Th2) immune responses. Chronic stress has been known to result in the blockade of the HPA axis and to aggravate allergic diseases due to the lack of immunosuppressive effects of low cortisol levels and enhanced Th2 response (25, 26). A blunted HPA axis response to various experimental stressors has been reported in a number of clinical studies involving children, and adolescent and adult AD patients, whereas basal cortisol concentrations are not different between AD patients and their age-matched healthy counterparts in all age groups (29–34). AD patients frequently use topical glucocorticoids to control disease activity. Decreased responsiveness of the HPA axis is shown only in patients with severe AD, and is recovered as their symptoms improve. Thus, decreased responsiveness of the HPA axis is thought to result from disease activity rather than from the use of topical glucocorticoids (35, 36). A chronic Th2-predominant cytokine profile acts as a negative feedback loop and blunt HPA axis response in AD. IL-4, a Th2 cytokine, showed a direct inhibitory effect on the POMC expression in the anterior pituitary gland in a dose-dependent manner (37).

Psychological stress delays skin barrier recovery in humans and mice. Psychological stress induces endogenous glucocorticoid production, which subsequently inhibits epidermal lipid synthesis and lamellar body secretion in the stratum corneum (38–40). Itch-scratch behaviour may accelerate and prolong the altered integrity of the skin barrier in AD as acute stressors (41). In animal models, stress has shown to inhibit antimicrobial peptide production and increased susceptibility to severe skin infection. Inhibition of CRH and glucocorticoids returned antimicrobial peptide level to normal and improved the severity of infection (42).

Several inflammatory cells seem to promote Th2 inflammatory activity in response to CRH stimulation via CRH-R. Dendritic cells (DCs) play an important role in Th2-tilted cell differentiation. Mononuclear cell-derived DCs express CRH-R and inhibit the release of IL-18, which is stimulated by CRH, resulting in naïve T helper cells toward Th2-tilted differentiation in AD patients (43). CRH stimulates mast cells through CRH-R. With the aid of stem cell factor (SCF) and IL-4, CRH-activated mast cells secrete Th2 cytokines and various neuropeptides, which potentiate Th2 differentiation in AD (44). Mast cells have an anatomical association with nerve fibres in AD lesions and promote neurogenic inflammation. During psychological stress, contact between mast cells and nerves are increased in number in AD lesions (45, 46). CRH induces the release of IL-4, IL-6, IL-10, and IL-13 from keratinocytes and mast cells (47). During chronic stress, enhanced serotonin receptor expression was shown in AD lesions (48). Pretreatment with tandospirone citrate, a serotonin agonist anxiolytic, prior to stress blocked mast cell degranulation in rat skin (49, 50), suggesting that relaxation therapy may be helpful in controlling mast cell-related inflammatory skin diseases such as AD.

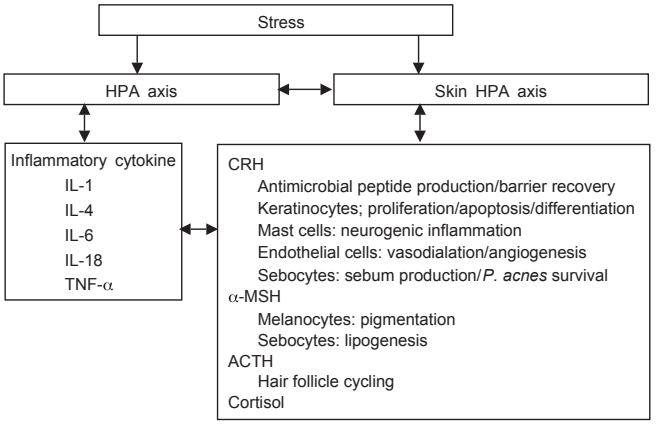

Fig. 1. Function of skin hypothalamic–pituitary–adrenal (HPA) axis hormones and its interactions between central and skin HPA axis.

There have been few studies of local HPA axis expression in AD lesions. No difference in CRH expression has been shown between AD lesions and healthy control skin (51).

Stress contributes to the initiation of AD lesions as well as lesional aggravation. Psychiatric stress alone has been shown to be sufficient to form AD-like lesions in mice, and lesional occurrence could be blocked with CRH-antagonist treatment (52).

Interestingly, infants with a familial history of AD showed an exaggerated HPA axis response to heel prick stress, which may be derived from abnormal maternal stress hormonal response (53). Such altered responsiveness may trigger the onset of AD in later life. Infants of mothers with severe psychosocial stress during pregnancy exhibited enhanced responsiveness of the HPA axis and altered Th1/Th2 cytokine profiles (54). Patients with a history of sexual abuse in their early lives showed a higher prevalence of persistent low cortisol levels in their adult lives (55). Infants who experienced chronic stress from their caregivers developed more AD than those without chronic stress (56). These findings suggest that stress in the early years of life may increase vulnerability to AD development by persistent sensitization of the HPA axis and by affecting the immune response.

The immunomodulatory effect of POMC-related hormones differs depending on the concentrations of hormones and the levels of stress. An increased serum level of β-endorphin had been regarded to correlate with severe AD symptoms, which is thought to be secreted from lesional chronic inflammatory cells and released into the systemic circulation. This increased β-endorphin level is also associated with stress-aggravated pruritus (57–59). Meanwhile, the physiological plasma level of β-endorphin is maintained by mild exercise stress, and seems to upregulate the natural immunity and control AD-like lesions in NC/Nga mice (60).

Plasma α-MSH expression was increased by strong exercise stress in the same animal model and was proportionate to the severity of AD symptoms (60). Increased plasma α-MSH levels and its receptor expression in the skin also affect the formation of post-inflammatory hyperpigmentation in NC/Nga mice (61). CRH and POMC-related peptides seem to contribute to the development and aggravation of AD in some susceptible patients by modulating Th2 immune and inflammatory responses.

Psoriasis

It is widely accepted that chronic stress suppresses HPA axis responsiveness and activates Th2 immune response. Psoriasis and AD are representative stress-exacerbating chronic inflammatory skin diseases. The former is associated with Th1- and Th17-tilted immune responses, whereas the latter is a Th2-related disease. Thus, it is difficult to fully understand how to stress-induced HPA axis alteration paradoxically aggravates both Th1- and Th2-predominant diseases.

Earlier studies have reported that patients with psoriasis often experience symptom aggravation weeks to months after a stressful event (62–64). It has been suggested that these might be related to attenuated HPA axis responsiveness and increased neuropeptides after stress. This idea was recently supported by Verhoeven et al. (65) through a prospective observation. They found that daily stressors were followed by increased Psoriasis Area and Severity Index (PASI) and itch 4 weeks later (65). The highest level of stressors was well correlated with low serum cortisol levels as a result of blunted HPA axis responsiveness (66), which was consistent with prior studies. The proinflammatory cytokine IL-1, 6, and tumour necrosis factor (TNF)-α are upregulated in psoriatic lesions and are well-known activators of the HPA axis (4). One may speculate that a prolonged sensitization of the HPA axis by these specific cytokines negatively feedback and diminish the suppressive effect of cortisol. However, others have found that HPA responsiveness of psoriatic patients were not different from that of healthy controls when exposed to stress (67, 68). Buske-Kirschbaum et al. (67) detected a blunted HPA axis responsiveness to stress in patients with AD, but normal HPA axis responsiveness in psoriatic patients. They suggested that this difference resulted from different pathogenic pathways between Th1- and Th2-predominant immune responses.

Stress modifies the distribution of leukocyte subsets in psoriasis patients, which is relevant in stress-induced exacerbation of psoriatic plaques. While the number of $CD25^+$ regulatory T cells decrease after stress, the number of activated T cells with a shift towards a Th1-derived cytokine profile, cutaneous lymphocyte-associated antigens-positive T cells and natural killer cells in the circulation increase at the same time (69–71). Moreover, glucocorticoids strengthen a certain cytokine activity at specific concentrations. Some studies reported that glucocorticoids can induce IL-2R mRNA levels in several T-cell lines (72). Glucocorticoids potentiate the biological action of IL-2, IFN-γ, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factors (73). Acute stress activates the HPA axis, and then the effector molecule glucocorticoids might potentiate the effect of Th1 cytokine profile and contribute to aggravation of psoriatic lesions. Both acute and chronic stress can exacerbate the symptoms of psoriasis, but further studies are needed to explain the time lag from peak daily stressors to flare-up.

Patients with actively spreading psoriatic plaques display an increased concentration of serum β-endorphin (74, 75). Because the peptide does not correlate with the presence of stress or itching, chronic inflammatory cells in psoriatic lesions have been suggested as the source of β-endorphin. The anti-nociceptive effect of β-endorphin may explain why the majority of patients with psoriasis are less likely to experience pruritus (74, 75).

There are some debates regarding peripheral HPA axis hormonal expression in psoriasis. Previous studies reported enhanced CRH/CRH-R expression in the psoriatic epidermis (76, 77). Recently, Cemil et al. (13) found that CRH-R1 expression is positively correlated with PASI scores. There have been a few studies that showed increased CRH/CRH-R1 expression in active psoriatic lesions might lead to disoriented proliferation and differentiation of keratinocytes (17–19) and exaggerate the inflammatory response (20, 21). CRH treatment has shown to stimulate HaCaT cell lines to proliferate or differentiate (17–19). Mast cells and CRH and POMC peptides are involved in the inflammatory process of psoriatic plaques in an autocrine and paracrine manner. CRH activates mast cells via CRH-R, causing histamine release and increased vascular permeability (20). α-MSH is also a potent stimulator of mast cells to release histamine (78). CRH and urocortin induce the selective release of VEGF and IL-6 from mast cells through CRH-R1 activation without degranulation, respectively (49, 79, 80). Mast cells secrete the pro-inflammatory cytokine IL-1, 6, and TNF-α in psoriatic skin (4, 81). These cytokines positively potentiate the production of CRH and POMC peptides in the human skin. Moreover, human mast cells can produce CRH and urocortin (82).

In contrast, some recent studies found a depressed expression of CRH/CRH-R1 in psoriatic lesions with increased serum CRH, which may reflect the negative feedback mechanism of central activation of the HPA axis (83, 84).

Increased CRH/CRH-R expression was also observed in psoriatic arthritis. Inflamed synovia of patients with psoriatic arthritis showed upregulated CRH-R1α expression in the endothelial cells and mast cells at both mRNA and peptide levels. CRH potentially acts through angiogenesis or pro-inflammatory effects in psoriatic arthritis (85).

Alopecia areata

Hair follicles have an anagen-specific immune-privilege and express their own local equivalents of HPA

axis hormones, which are involved in the maintenance of immune-privilege and regulation of the hair cycle (86–88). CRH/CRH-R2 is expressed in hair follicle-derived keratinocytes and dermal papilla cells. CRH expression was the highest during anagen IV/VI, and lowest during catagen and telogen in normal mice (89, 90). ACTH is only detected in the outer root sheath of hair follicles (91), whereas α-MSH is detected in the outer root sheath as well as in the hair matrix during the anagen period (88). The POMC peptide and cortisol are produced by CRH stimulation in cultured human hair follicles and the levels are significantly increased during the anagen period (86). The POMC peptide and cortisol have been considered as potent immunosuppressants and their upregulation contribute to the maintenance of the anagen-specific immune-privilege (86).

Alopecia areata (AA) is a hair cycling disorder as a consequence of collapse of the anagen-specific immune-privilege. It has been postulated that AA patients are more susceptible to psychiatric illnesses and stress trigger the development of AA. Abnormal expression of HPA axis-hormones has been observed in AA patients and experimental animal models (92–97). Under normal and stressed conditions, hypothalamic AVP and pituitary POMC expressions were increased in AA mice (93). In general, AA mice showed a significantly weakened systemic HPA responsiveness to acute stress and exhibited an imperfect adaptation to chronic psychological stress (93).

We previously reported an enhanced expression of CRH, ACTH and α-MSH peptides in the epidermis and pilosebaceous units of AA lesions (95). Increased CRH/CRH-R2 and ACTH peptide expressions in human AA lesions were supported by others (94, 95), but some studies failed to detect CRH in AA lesions (93). Meanwhile, the affected human skin revealed a decreased level of glucocorticoids, but an increased level of glucocorticoid receptors (96, 97). On the contrary, increased MC2R mRNA expression and a decreased MC2R protein level were demonstrated in AA lesions (96, 97). These findings suggest that AA patients have an activated CRH-CRHR2-ACTH system, which induces MC2R mRNA expression. However, defective post-transcriptional control of MC2R gene expression results in the down-regulated MC2R protein, and subsequent insufficient levels of cortisol in AA lesions, leading to failure of immune-privilege maintenance (96, 97).

CRH induces degranulation of perifollicular human mast cells in the presence of stem cell factors. Degranulation of mast cells play in an important role in catagen development (98). Intriguingly, CRH can induce human hair follicle precursor cells to differentiate into mast cells (99, 100). The effect of CRH on mast cell differentiation and degranulation may contribute to persistent premature catagen development in AA.

A recent study revealed that treatment with corticotrophin-releasing factor (CRF) receptor antagonist prevented hair loss and had a moderate effect on hair re-growth in a CRF-overexpressing mouse model of alopecia associated with chronic stress (101).

Interestingly, Zhang et al. (93) observed a hyperactive HPA axis in the lymph nodes of AA mice. In these lymph nodes, increased levels of POMC mRNA and a decreased number of mineralocorticoid receptors were identified. They hypothesized that there may exist a feedback loop to control the local HPA axis in AA mice. Plasma ACTH levels and skin lesional ACTH-R expression have a positive correlation with pro-inflammatory cytokine TNF-α in AA mice (93). There may be a cross-talk between systemic HPA axis and local HPA axis with Th1 cytokine production in AA skin.

Skin tumours

Much evidence has shown that HPA axis hormones are involved in the carcinogenesis at the development or progression stage. Chronic stress has been shown to suppress cell-mediated immunity in the skin and to decrease the number of circulating leukocytes by activation of the HPA axis (25). Arbiser et al. (102) observed that CRH enhanced tumour cell growth and angiogenesis through endothelial chemotaxis. In an *in vitro* assay, bovine endothelial cell chemotaxis and vascular smooth muscle cell migration were stimulated at CRH concentrations over 10 nM (102). In an *in vivo* assay, CRH-bearing tumours showed a faster growth rate and higher microvessel density than CRH-negative tumours. CRH enhanced murine melanoma cell migration through the ERK1/2 pathway (103). CRH-POMC axis hormones also modulate metalloproteinase expression (104). In line with this observation, we previously reported the results of CRH, ACTH and α-MSH peptide expression in benign and malignant skin tumours (105). All peptides were highly expressed in malignant skin cancer cells compared with precancerous and normal skin cells. Immunoreactivity of CRH was increased in proportion to the malignant potential of skin cancer cells (105).

Acne and seborrhoea

Sebocytes express CRH, CRH-R and CRH-binding protein. Sebaceous lipid synthesis can be modulated by CRH (106). In the sebaceous gland cells of acne lesions, immunoreactivity of CRH and CRH-binding protein was increased as well as those of MC1R (107, 108). While CRH is known as a proinflammatory peptide, α-MSH has a lipogenic effect and partially inhibits IL-8 secretion, a primer cytokine of the neutrophilic inflammatory response of pilosebaceous units (108). Increased MC1R may reflect the cytoprotective function of α-MSH to compensate for the inflammatory activities of CRH in acne lesions (108). Membrane fractions of *Propionibacterium acnes* induced CRH activity in the epidermis, but the supernatant of *P. acnes* did not (109). Certain

membrane components of *P. acnes* seem to produce CRH through direct contact with the keratinocyte membrane (109). On the whole, sebotropin, a growth factor, and the CRH/CRH-R system, a proinflammatory peptide, affects infundibular keratinocyte differentiation, lipogenesis and inflammatory reactions, resulting in exacerbation of the manifestations of acne and seborrhoea (108, 109).

Contact dermatitis and urticaria

Acute stress exposure before and after antigenic challenge enhances delayed type hypersensitivity in rats. CRH/CRH-R and mast cells play a pivotal role in the pathogenesis of stress-induced contact dermatitis. CRH exacerbates the severity of type IV delayed hypersensitivity and chronic contact dermatitis by activating CRH-R1-expressing mast cells (26, 110). The epidermal thickness and the number of dermal infiltrating mast cells were increased by repeated TNCB and stress exposure in rats. Treatment with CRF-R1 antagonist reversed the stress-induced histological changes, but did not reverse the increased level of plasma IgE (110). In contrast, when chronic stress was given before contact sensitization, it suppressed the development of delayed type hypersensitivity by down-regulating the density of Langerhans' cells in the epidermis (111, 112). Corticosteroids inhibit antigen-presentation and migration capacity of Langerhans' cells. While the development of allergic contact dermatitis to TNCB or DNFB was modulated by the stress-induced immune response, irritant contact dermatitis caused by sodium lauryl sulphate was not affected by psychological stress in a mice model (113). The role of stress and stress hormones in contact hypersensitivity seem different depending on the experimental settings, which includes the timing or period of stressors, and the type or dose of the sensitizing agent (114).

Increased expression of CRH-R1 was proven in urticarial lesions from patients with chronic urticaria (115). CRH enhanced vascular permeability and vasodilation through CRH-R and a mast cell dependent mechanism, which was inhibited by a CRH-R antagonist, and thus, was absent in mast cell-deficient mice (20, 116). CRH stimulates the NF-kB signalling pathway in keratinocytes, and the subsequent release of inflammatory cytokines from keratinocytes may further activate mast cells, resulting in stress-induced aggravation of urticaria or contact dermatitis. However, studies are needed to confirm this idea (20, 116, 117).

CONCLUSION

Some patients with chronic inflammatory skin disorders showed a hypo-responsive central HPA axis to acute stress and aberrant peripheral HPA axis hormonal expression in involved skin lesions compared with controls. A few studies have indicated that CRH potentiates the effects of main pathogenic inflammatory cells and their mediators, which may explain the stress-related disease flare-up in several skin disorders. There may be a feedback loop between central and peripheral HPA axis hormones. In such case, those hormones may interact with some cytokines and neuropeptides at various levels, leading to deterioration of local inflammation. It is difficult to determine whether the change in the HPA axis is a cause or an effect of chronic stress because comparison of functional changes of the HPA axis before/after stress provocation was unavailable in human skin lesions. Further studies are needed to establish the pathomechanism of stress exacerbating skin disorders, hoping that skin HPA axis hormones may represent a novel class of therapeutic targets in chronic skin diseases.

ACKNOWLEDGEMENTS

This research was supported by Basic Science Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012046972).

The authors declare no conflicts of interest.

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