Psychoneuroimmunology of Psychological Stress and Atopic Dermatitis: Pathophysiological and Therapeutic Updates

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by impaired epidermal barrier function, inflammatory infiltration, extensive pruritus and a clinical course defined by symptomatic flares and remissions. The mechanisms of disease exacerbation are still poorly understood. Clinical occurrence of atopic dermatitis is often associated with psychological stress. In response to stress, upregulation of neuromediators that modulate cutaneous immunity and biochemical stimuli (158). Local production of neurohormones and neuropeptides, with sprouting of SP+ nerve fibers, occurs in the skin in response to stress (9).

Psychoneuroimmunology is an interdisciplinary field that specifically examines the biochemical cross talk between nervous, immune, and endocrine systems. We will focus on the role of psychological stress in the pathogenesis of AD and review the known neurogenic inflammatory mechanisms of epidermal barrier dysfunction.

METHODS

We conducted a search of PubMed’s Medline database of articles in English for the years 1965–2010 (19). Abstracts containing the keywords “atopic dermatitis” or “eczema”, and one of the following terms were reviewed: stress, psychological stress, neuromediators, mast cell, serotonin, neuropeptide, substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and antidepressant.

RESULTS

Stress and immunity: general background

Centrally, the HPA-axis responds to psychological stress by upregulation of CRH, adrenocorticotrophic hormone (ACTH), and interleukin-6 (IL-6). This induces the hypothalamic-pituitary-adrenal axis (HPA-axis) response in chronically stressed patients with AD. Its effects on immune function are multifaceted (20, 22, 156). Substance P (SP), gastrin-releasing peptide (GRP), and calcitonin gene-related peptide (CGRP) in the dorsal root ganglia also increase (10). In the skin, immune cells release neuromediators, which modulate neuroimmune inflammation. Cutaneous mast cells are in close association with substance P (SP), calcitonin gene-related peptide (CGRP), and mast cell-nerve fiber contacts are targets for stress-related inflammatory mediators (157). They synthesize and secrete many inflammatory mediators in response to various psychological stressors, including corticotrophin-releasing hormone (CRH) and neuropeptides that modulate cutaneous immunity and inflammation.

Psychological stress-related increases in inflammatory mediators can activate inflammatory reflexes that trigger actions potentially via the vagus nerve, to the brainstem nuclei that control effector actions potentially transmitted back to the periphery. Relayed to the spleen, signal transduction via the nicotinic a7-acetylcholine receptor subunit inhibits
cytokine expression, serving as a cholinergic anti-inflammatory "brake" system to the damaging effects of over-active innate immunity (27). In addition, psychological stress and stress-related hormones increase serotonin synthesis, a neurotransmitter with receptors on keratinocytes, melanocytes, and dermal fibroblasts (28, 29). Local cutaneous effects of serotonin include proinflammatory responses, such as edema or vasodilation, as well as pruritus induction (30, 31).

Sensory cutaneous afferent nerve fibers conduct pain and itch signals to the CNS from the skin and release the neurotransmitters SP, calcitonin gene related peptide (CGRP), and growth-related peptide (80). In the presence of pruritus, sensory nerves release SP and CGRP, which may sensitize dorsal horn neurons to itch stimuli (80). Histamine and NPY, via their respective receptors on sensory nerves, mediate pruritus and induce itch sensitivity (80). Sensory nerves modulate itch intensity and provide an "on-off" character to itch in health volunteers (52, 53). Histamine-induced itch intensity with a delayed peak in intensity following cold induction in lesional and non-lesional AD skin compared with healthy controls (54). Compared with healthy controls, total mean itch intensity was perceived as more intense in lesional skin and slightly less intense in non-lesional skin. The Eppendorf Itch Questionnaire (EIQ), a validated instrument to quantitate and subjective assessment of itch intensity was assessed in patients with AD compared with healthy controls (54). The subjective manifestation of inflammatory skin disease is itch: an unpleasant sensation that provokes the desire to scratch. Patients with inflammatory skin diseases feel severe itch, particularly in the setting of stress, they have difficulty refraining from scratching, which subsequently worsens their dermatitis and causes more itch (46). Corticotropin-releasing factor (CRF) is a hypothalamic-hypophysial-thyroid cycle that produces a state of high anxiety, leading to decreased quality of life (17–19). Neuropeptide Y (NPY) and noradrenaline are released from sympathetic nerve terminals and function synergistically as a cholinergic anti-inflammatory system to the damaging effects of over-active innate immunity (30, 31).

Central and peripheral nervous system responses to stress

Atopic patients, including those with AD, respond to stress with suboptimal cortisol production (77–79). In accordance with pathologic studies, the selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, and fluoxetine improved anxiety and SCORAD (SCORing Atopic Dermatitis) indices for skin disease severity in the treatment arm, but did not provide an "on-off" character to itch in health volunteers (52, 53).

Painful cutaneous and mucosal itch is relieved by the cholinergic agonist Tandospirone citrate (TC) (Sediel™) (83). Local cutaneous and mucosal itch is relieved by the cholinergic agonist Tandospirone citrate (TC) (Sediel™) (83). Histamine-induced itch in non-lesional skin at 25°C stimulation was accompanied by decreased expression of brain structures, including primary and secondary sensory areas, insular, and prefrontal areas, but to a lesser degree than that was observed for non-lesional skin (54).

Peripheral and cutaneous inflammatory cells in stressed patients with atopic dermatitis

In both lesional and non-lesional skin of the AD patient an increased number of TH2 cells and levels of IL-4, IL-5, and IL-13 was observed compared with healthy controls (65). Increased numbers of blood eosinophils are also found in atopic patients, with eosinophil counts and IgE production rising in response to stress (57, 58). A German prospective birth cohort study demonstrated a positive association with stress-related maternal factors during pregnancy and the presence of childhood eczema in the first 2 years of life, as determined by parental report of a physician’s diagnosis of neonatal eczema or atopic eczema in their child (95). Moreover, higher caregiver stress in the first 2 years of life, as measured by the Perceived Stress Scale, was associated with increased total IgE expression and enhanced allergic, IgE-mediated proinflammatory responses in children (96). Higher stress levels were also correlated with increased disease severity, with patients with AD scoring significantly worse than healthy controls (97, 98). In addition, infants of mothers who were stressed prenatally had exaggerated cortisol responses to stress (81). Moreover, infants of mothers who were stressed prenatally had exaggerated cortisol responses to stress (81). Histamine-induced itch in lesional compared with non-involved skin (64). In this study, low cortisol ratios were an indicator of chronic stress, and correlated with the degree of serotonin receptor positive staining in the papillary dermis of involved skin. Tandospirone citrate (TC) (Sediel™) is a serotonin agonist and is effective both as an antidepressant and anxiolytic agent (65). Pre-treatment of patients with TC significantly inhibited foot shock stress-induced degradation of murine dermatitis genes (64). In a double-blind clinical trial of 37 patients with AD randomized to receive either 30 mg/d TC or placebo for 4 weeks, there was a significant improvement in Profile of Mood States (POMS) scores for tension- and depression-related variables at 8 weeks. In the total study population, patients randomized to TC showed significant improvement in POMS compared with placebo. A significant positive correlation between changes in the POMS scores and SCORAD index was determined. Patients with AD often report a close relationship between emotional distress, pruritus, and scratching, and 81% of patients report that psychological stress aggravates their pruritus (65). In several case series and two randomized controlled trials, the selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, and fluoxetine improved itch, scratching, and fatigue in children with AD who were 3.5 years old (89). However, infants of mothers who were stressed prenatally had exaggerated cortisol responses to stress (81). Increased HR to foot shock was observed in normals with increased cord blood IgG or a positive family history of AD (81). Activation of the HP axis by perceived stress and increased stress hormone levels has been reported to downregulate proinflammatory genes (66). An inverse relationship was shown between maternal progesterone levels during early pregnancy and subsequent risk for AD in the child (94). This relationship was observed to be significant in late gestation, compared with age-matched controls when subjected to the psychological stress of public speaking (94).

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A total of 203 patients with AD were included, and the median age was 20 years (range: 4–63). A total of 98 patients with AD were included, and the median age was 20 years (range: 4–63). The main findings of the study were:

1. Psychological stress and epidermal barrier dysfunction
2. Stress hormone CRF
3. Psychological interventions
4. Psychological stress and atopy
5. Psychological stress and cytokines
6. Psychological stress and pain
7. Psychological stress and psychosis
8. Psychological stress and depression
9. Psychological stress and anxiety
10. Psychological stress and sleep

The study concluded that psychological stress plays a significant role in the development and exacerbation of AD. The results support the need for further research and the development of effective interventions to manage psychological stress in patients with AD.
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response from Th1 (cell-mediated) to Th2 (humoral) [70]. Furthermore, the effect of CRF on decreased IL-18 production in DCs is of special consideration, given that IL-18 functions primarily as an IFN-γ inducer and promoter of Th1 responses in T cells. Thus, these findings support that stress down-regulates cellular immunity, and suggest that CRF may modulate immune responses by directly acting on DCs [39]. Mast cell progenitors can be isolated from human umbilical cord blood and cultured in the presence of stem cell factor, IL-6, IL-7, and other cytokines to yield distinct mast cell populations. The use of live cell array to rapidly uncover mast cell biology at the cellular level provides a unique opportunity for further study of mast cell triggers and inhibitors, and their contribution to stress-induced exacerbation of AD [147].

Sustained psychological stress disrupts permeability barrier function, and induces an increase in endogenous SGPs, which subsequently alter permeability homoeostasis and integrity, as well as antinflammatory defences [33, 146]. These regulatory mechanisms may largely be the result of GC-mediated inhibition of epidermal barrier synthesis. Topical lipophilic formulations normalized these functions, despite ongoing psychological stress, and therefore show promise as effective therapy for patients with high levels of psychological stress and unremitting barrier dysfunction. There are currently no published randomized controlled trials comparing the clinical response of stressed vs. non-stressed patients with AD to such therapies aimed at restoring barrier knowledge. However, promising potential differences, attributable to psychological stress, would be of value to a clinician in the time setting and selection of agents, in terms of therapeutic efficacy.

Psychological stress is associated with flare of itching in AD. The itch sensation, with urge to scratch, is a significant source of continued psychological stress for the patient, such that psychiatric/sympathetic interventions may be efficacious [135]. The correlation between high anxiety scores in patients with AD and pruritus and more intense IFN and NGF reactivity suggests that anxiety may up-regulate expression of these neuropeptides, both of which can contribute to pruritus [15]. IFN- and NGF-mediated induction of pruritus in pruritus-prone patients supports the need for therapeutic strategies aimed at anxiety and stress reduction/management.

Stress in patients with AD also had increased numbers of serotoninergic mast cells, and there was improvement in skin disease and pruritus following treatment with serotonin agonists and SSISs respectively. The underlying mechanism of the anti-pruritic effect has yet to be determined. While intracutaneous serotonin administration can induce itch (149, 150), the inhibitory effect of SSISs is predominately in the CNS (151). Thus, the anti-pruritic effect of SSISs is likely due to their central action rather than peripheral effects. The association between mood and itch at the level of the CNS has been shown in mouse models of AD to influence IgE levels and SP+ nerve density, the role of stress in its potential modulation is yet to be determined [152].

Though the mechanism underlying the association of AD with psychological stress has not been fully elucidated, the field of psychoneuroimmunology has provided many new insights and avenues for research into the role of stress in AD. Recently, it has been established via clinical and physiological means that psychological stress is a significant contributor to AD disease course through its direct and indirect effects on immune response, cutaneous neuropeptide expression, and itch sensitivity. As scientific research into these neuroimmunoendocrine functions continues to develop, there is increasing potential for developing new immunome-modulating therapeutic strategies. Such developments will refine and improve the treatment of this chronic and relapsing skin disease, which otherwise presents a significant burden to patients and society.

The authors declare no conflicts of interest.

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Psychoneuroimmunology of Psychological Stress and Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatological disease characterized by dry skin, pruritus, and eczematous lesions. It affects up to 10% of the population worldwide and is associated with significant psychological distress.

Psychological Stress and AD

Psychological stress has been implicated in the exacerbation of AD, with increased scratching behavior and disease severity in response to stressors. The underlying mechanisms are complex and involve interactions between the immune system, the inflammatory mediators, and the psychological stress response.

Neurotransmitters and AD

Neurotransmitters such as serotonin and bradykinin play a role in the regulation of AD. Serotonin levels are increased in AD patients, and treatments targeting serotonin receptors have been shown to improve symptoms.

Cytokines and AD

Cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma, are involved in the immune response in AD. Stress can modulate cytokine production, contributing to disease exacerbation.

Neurokinins and AD

Neurokinins, such as substance P, are implicated in the pathogenesis of AD. They are involved in the modulation of inflammatory responses and are present in high levels in AD lesions.

Neuropeptides and AD

Neuropeptides, such as calcitonin gene-related peptide and vasoactive intestinal peptide, are involved in the modulation of pain and pruritus, which are common symptoms in AD.

Conclusion

Psychological stress and AD are interlinked through complex neurobiological mechanisms. Understanding these interactions can lead to the development of new therapeutic strategies to improve the treatment of AD.

References