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REVIEW ARTICLE

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

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Atopic dermatitis 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 neuropeptide mediators in the brain, endocrine organs, and peripheral nervous system directly affect immune and resident cells in the skin. Lesional and non-lesional skin of patients with atopic dermatitis demonstrates increased mast cells and mast cell-nerve fiber contacts. In the setting of stress, sensory nerves release neuromediators that regulate inflammatory and immune responses, as well as barrier function. Progress towards elucidating these neuroimmune connections will refine our understanding of how emotional stress influences atopic dermatitis. Moreover, psychopharmacologic agents that modulate neuronal receptors or the amplification circuits of inflammation are attractive options for the treatment of not only atopic dermatitis, but also other stress-mediated inflammatory skin diseases. ***Key words: atopic dermatitis; eczema; psychological stress; neurogenic inflammation; psychoneuroimmunology.***

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Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease characterized by eczematous skin lesions, xerosis, lichenification, and severe pruritus (1, 2). AD affects 10–20% of children worldwide and persists into adulthood in a minority of cases, affecting approximately 2–3% of the adult population, with an increased prevalence over the past decades in urbanized societies (3–5). While the exact etiology of AD is undefined, laboratory and clinical data point to a multifactorial pathogenesis comprised of both genetic and environmental factors (6, 7). Stress is a well-established trigger and aggravator of AD (8). While the term "stress" includes both physiological and psychological stress, for the purposes of this review, we will focus on psychological stress and its role in AD.

Skin is the largest body organ and is equipped with metabolic and endocrine capabilities that facilitate homeostatic control between internal and external environments (9–12). A hallmark feature of AD is failure of the epithelial barrier, as evidenced by increased susceptibility to skin infections, increased transepidermal water loss, hyper-irritability, and altered sweat delivery to the epidermal surface (13). Innervated by an extensive cutaneous network of sensory fibers, skin expresses many of the same neurotransmitters and neuropeptide receptors as the central nervous system, including corticotrophin-releasing hormone (CRH), serotonin, prolactin, and substance P (SP) (9). Furthermore, skin is involved in the communication between immune, nervous, and endocrine systems, with bi-directional crosstalk occurring between these systems through various biochemical mediators (10, 14–16). Dysregulation of these mediators in both the central nervous system (CNS) and in the skin uniquely contribute to the pathophysiology of AD (17, 18).

Psychoneuroimmunology is an interdisciplinary field that specifically examines the biochemical cross talk between brain, behavior, and the immune system. This review will provide a comprehensive discussion on the contributions of psychoneuroimmunological mechanisms to AD. We will first examine the systemic response to stress and its effects on immune function and, specifically, the effects of stress in AD on T cells and mast cells. We then review those studies examining the hypothalamic-pituitary-adrenal (HPA) axis response in chronically stressed patients with AD, and its affect on cutaneous immune responses. Lastly, we will discuss novel findings regarding peptide mediators of neurogenic inflammation in AD and review the known neurogenic inflammatory mechanisms of epidermal barrier dysfunction. We devote particular attention to the use of pharmacologic agents that target these neuroimmunologic mechanisms as therapeutic stress interventions in AD.

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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, neurogenic inflammation, cortisol, corticotrophin releasing hormone, mast cell, serotonin, neuropeptide, norepinephrine, nerve, nerve growth factor, 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 with upregulation of CRH, adrenocorticotropic hormone (ACTH), neuropeptides (e.g. pituitary adenylate cyclase-activating protein), and glucocorticoids (GCs) (20, 21), as well as activation of the sympathetic and brainstem serotonergic nervous systems (Fig. 1) (20–22). Subsequently, increased levels of GCs and catecholamines (CAs) suppress antigen-presenting cell production of interleukin (IL)-12, the principal cytokine inducer of T helper 1 (Th1)-mediated humoral immune responses via induction of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) (23–25). Thus, GCs inhibit the production of IL-12, IFN-γ, IFN-α, and TNF-α in both antigen-presenting cells and Th1 cells, and upregulate cytokines involved in T helper 2 (Th2)-mediated antibody production responses, such as IL-4, IL-10, and IL-13 (24). Dendritic cells (DCs) are specialized antigen-presenting cells of the skin and mucosal surfaces. These cells are thought to have an important role in the generation and regulation of immune responses, and likely represent the link between antigen uptake and clinical features of inflammatory skin diseases, such as AD (26).

Psychological stress-related increases in inflammatory proteins activate an inflammatory reflex that triggers actions potentials, via the vagus nerve, to the brainstem nuclei that control efferent action potentials transmitted back to the periphery. Relayed to the spleen, signal transduction via the nicotinic α7-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 neuropeptides SP, calcitonin gene related peptide (CGRP), and nerve growth factor (NGF) (31, 32). In the local environment of the skin, these mediators are released in response to various stimuli, including cytokines and proteases, thereby activating sensory neurons, which affect local immune responses and modulate immune defense mechanisms (33–35). In close association with unmyelinated C-fibers in the skin are resident skin mast cells, which are crucially important for many local inflammatory outcomes, including vasodilatation (erythema), plasma extravasation (edema), vascular endothelial molecule expression, cytokine release, and nerve growth factor production or chemo-attraction (36, 37). Activated by several stress hormone mediators, (38,

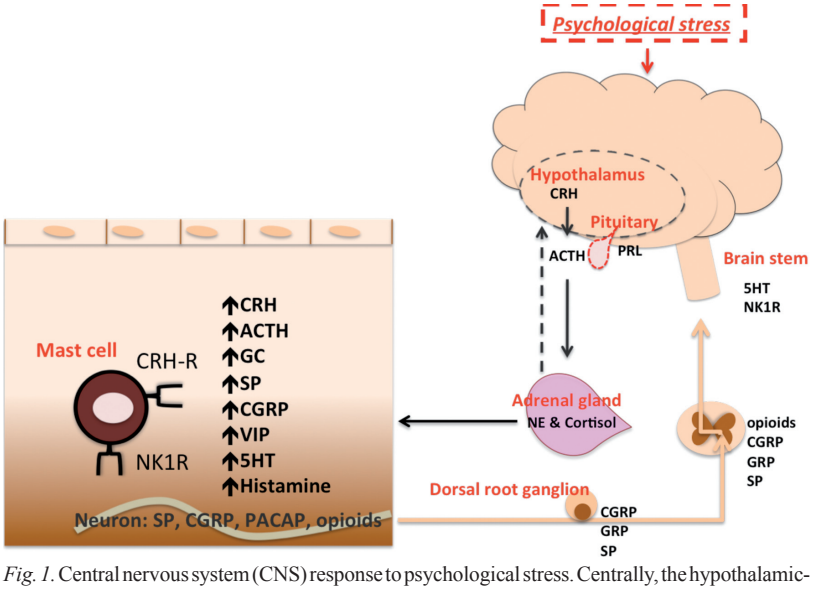

Fig. 1. Central nervous system (CNS) response to psychological stress. Centrally, the hypothalamic-pituitary-adrenal axis (HPA) responds to psychological stress by upregulating the stress hormones corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) (20, 21). Pituitary prolactin (PRL) increases and it abrogates stress-induced inhibition of lymphocyte proliferation (155). CRH and ACTH stimulate norepinephrine (NE) and cortisol release from the adrenal glands, and directly stimulate immune cells in the blood and periphery via their respective receptors. This outcome is regulated by negative feedback of cortisol (*dashed arrow*) on further CRH and ACTH release by the hypothalamus and pituitary hypophysis. Brainstem serotonin (5HT) production increases (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 cytokines, chemokines, and neuropeptides that modulate local inflammatory responses. Sensory nerves release neuromediators that modulate cutaneous inflammation, pain, and pruritus, and transmit sensory stimuli via dorsal root ganglia and the spinal cord to specific areas of the CNS (10). Cutaneous mast cells are in close association with substance P (SP), CGRP, pituitary adenylate cyclase-activating protein (PACAP), and opioid-releasing neurons, and are receptive to these respective neuromediators (157). They synthesize and secrete many inflammatory mediators in response to various physical 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).

39) skin mast cells express various neuropeptide or neurohormone receptor isoforms, including CRH, (40) and thus are themselves a rich source of CRH (41). In addition, the mast cell synthesizes and secretes over 50 biologically active molecules, including cytokines, SP, serotonin, TNF-α, NGF, tryptases and chymases, which all are mediators of neurogenic inflammation (15, 42–44). Likely potentiation of neurogenic inflammation occurs perhaps via a feed-forward mechanism, as these mediators excite and stimulate surrounding neuropeptide-containing C-fibers, with proinflammatory cytokines and chemokines released from mast cells (45).

The subjective manifestation of inflammatory skin disease is itch: an unpleasant sensation that provokes the desire to scratch. When 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 creates more itch (46). This contributes to an itch-scratch cycle that perpetuates a state of high anxiety, leading to decreased quality of life. (17, 47). Histamine and acetylcholine (ACh) instigate itch by binding to c-fiber related sensory receptors, neuropeptides, proteases, and/or cytokines (18, 48–51). Short-term alternating temperature modulation of histamine-induced itch provides an "on-off" character to itch in health volunteers (52, 53).

In a comparison of itch intensity in the skin of patients with AD vs. healthy controls, there was a delayed increase of 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 for qualitative and quantitative itch assessment of pruritus, was completed by each subject to allow for assessment of descriptive and emotional items associated with itch (55). EIQ ratings following induction of itch were significantly higher for lesional, as well as non-lesional, AD skin compared with healthy controls. Histamine-induced itch in non-lesional skin at 25°C stimulation was accompanied by deactivation of brain structures, including primary and secondary somatosensory, insular, cingulated, and prefrontal cortex, as well as supplementary motor area, premotor areas, and basal ganglia, and were less pronounced in the later course of the 25°C stimulation with a parallel activation increase in the basal ganglia. Histamine-induced itch in lesional skin at 25°C was associated with activation of the basal ganglia, insular cortex, prefrontal areas and parietal cortex, with deactivations observed in the parietal, temporal, primary and secondary somatosensory, cingulated cortex, premotor and prefrontal areas, but to a lesser degree than 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 can be observed compared with healthy controls (56). 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 neurodermatitis or allergic or atopic eczema in their child (59). 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 allergen-specific proliferative responses in children predisposed to atopy (60). Higher stress levels were also associated with increased TNF-α and reduced IFN-γ levels from peripheral blood lymphocytes stimulated *in vitro*. When stressed, patients with AD with high baseline serum IgE levels had an *in vitro* increase in IL-4 levels from stimulated peripheral blood lymphocytes compared with both healthy controls and patients with AD with low baseline serum IgE (61). In addition, high trait anxiety, as determined by the state-trait anxiety inventory, was positively correlated with serum IgE levels, but inversely correlated with Th1/Th2 ratios in patients with AD compared with healthy controls without a history of allergic disorders (62).

Crosstalk between mast cells, nerves, and keratinocytes is thought to play a role in exacerbation of inflammatory conditions by stress. In addition to activating the HPA axis in the setting of stress, corticotropin-releasing factor (CRF) also has peripheral pro-inflammatory effects. In a recent study, DCs from patients with AD were analyzed for IL-6, IL-18, chemokine (C-C motif) ligand (CCL)17, CCL22, and CCL18 expression after exposure to CRF. Following exposure to CRF, a prominent decrease in expression of IL-18 was detected in patients with AD compared with non-atopic healthy controls (63). However, CRF did not alter the expression of IL-6, CCL17, CCL18, and CCL22 (63). This is the first report demonstrating decreased IL-18 expression in DCs upon exposure to CRF.

In an immunohistochemical analysis of patients with stress-associated AD, there was increased positive staining for mast cells, serotonin receptor subtypes 5-HT1A and 5-HT2A, and serotonin transporter protein (SERT) observed 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). Pretreatment of patients with TC significantly inhibited foot shock stress-induced degranulation of murine dermal mast cells (66). In a double-blind clinical trial of 37 patients with AD randomized to receive either 30 mg/day TC or placebo for 4 weeks, there was a significant improvement in Profile of Mood States (POMS) scores for tension-anxiety and SCORAD (SCORing Atopic Dermatitis) indices for skin disease severity in the treatment arm, but did not in the placebo arm (67). Of note, 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 (68). In several case series and two randomized controlled trials, the selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, and fluoxetine improved pruritus secondary to a variety of medical conditions (69–74), in addition to improving psychogenic itch (75). In an open label two-armed proof of concept study examining the SSRIs paroxetine and fluvoxamine in chronic pruritus patients, there was healing of chronic scratch lesions and decreased pruritus, as measured by evaluation of visual analog scores and maximum percentage reduction in pruritus (76). Of the subgroups examined in this study, patients with AD responded with considerable reduction in pruritus. There was no statistical difference in anti-pruritic effect in patients with psychological co-factors.

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 that, atopic patients with seasonal allergic rhinitis showed attenuated cortisol responses to a standardized laboratory stressor test (Trier Social Stress Test) during an acute pollen season, but not during a pollen-free season (80). Moreover, infants of mothers who were stressed prenatally had exaggerated cortisol responses to stress (81). Increased HPA response to heel stick was observed in neonates with increased cord blood IgE or a positive family history of atopy. In addition, 9–12-year-old children with AD had a blunted cortisol response compared with age-matched controls when subjected to the psychological stress of public speaking (82).

Activation of the HPA axis by perceived stress and increased stress hormone levels has been reported to downregulate progesterone levels (83). An inverse relationship was shown between maternal progesterone levels during early pregnancy and subsequent risk for AD in the child (84). This association was exclusive to girls, as low levels of maternal progesterone were not associated with an altered risk for AD in boys. Maternal levels of estradiol during pregnancy were not associated with an altered risk for AD. A parental history of atopic disease further augmented the risk of AD in all children (84).

The autonomic nervous system, consisting of the parasympathetic and sympathetic subdivisions, affects physiologic parameters, such as heart rate in digestion, in the settings of stress vs. calmness. Variations in beat-to-beat intervals of the heart rate are measured to assess the state of sympathetic (stress, anxiety) or parasympathetic (relaxation, calmness) in an individual subject. Heart rate is consistently elevated in patients with AD, compared with healthy controls, even in the absence of stress (85). Histamine and ACh instigate itch, and histamine is the best-known pruritogen in humans (86). However, both patients with either chronic pain or chronic itch responded to a histamine stimulus with burning pain, rather than pure itch (87–89). ACh induced pain in healthy controls, whereas patients with acute AD, mixtures of pain and itch, or patients newly free of AD respond to ACh with pure pruritus (90). Histamine-induced itch, scratching, and psychological stress induced an increase in very low frequency heart rate variability (a measure of sympathetic tone) in patients with AD (91). Increase in very low frequency heart rate variability amongst healthy controls was only statistically significant following psychological stress. Healthy controls demonstrated an increase in high-frequency heart rate variability (a measure of parasympathetic tone) after histamine-induced itch, which promptly decreased with scratching. Patients with AD, in comparison, presented an elevated high-frequency heart rate at rest, which remained elevated with histamine-induced itch, scratching, and psychological stress (91).

Biofeedback training is a therapeutic technique in which patients are trained to consciously alter the autonomic response, in an effort to establish a new habit pattern and influence immunoreactivity to positively affect symptom severity (92, 93). Integrative body-mind training (IBMT) incorporates aspects of mindfulness and meditation and is accompanied by physiological changes, including oxygen consumption, heart rate, skin conductance/resistance, and respiratory rate. Chinese undergraduates randomized to undergo IBMT showed significant increases in frontal midline brain theta rhythms, associated with the parasympathetic component of the autonomic nervous system, when compared with subjects randomized to relaxation therapy alone (94). In combination with the increased parasympathetic activity, lower heart rate and skin conductance response, increased belly respiratory amplitude, and high frequency heart rate variability were observed with IBMT compared with relaxation training alone controls (94).

Neurogenic inflammatory mediators in atopic dermatitis

Neuropeptide Y (NPY) and noradrenaline are released from sympathetic nerve terminals and function synergistically as adrenergic agonists. NGF-reactive cells were more abundant in the epidermis and dermis and the number of NPY-positive cells were significantly greater in the epidermis of AD-involved skin compared with healthy controls (95). In this study, the affected skin of patients with AD with high trait anxiety and state anxiety scores stained more intensely for NPY and NGF compared with healthy controls and patients with AD with lower anxiety scores. However, the statistical significance of these differences was undetermined due to limited specimen number.

Compared with healthy controls, an increased density of cutaneous nerves in atopic skin was demonstrated by immunochemistry (96, 97). AD lesional and non-lesional skin had increased SP-positive and CGRP-positive fibers associated with increased mast cell-nerve fiber contacts (24, 98). Plasma levels of CGRP were not significantly different in patients with AD compared with healthy controls, but levels of CGRP were higher in severely pruritic patients with AD compared with non-pruritic patients (99). Increased levels of NGF and SP were detected in the plasma of patients with AD, and there was a positive correlation with these levels and disease severity (100–102). SP plasma levels remained elevated in patients following AD remission (99). In mouse models, stress-induced worsening of AD occurred in an SP-dependent fashion and was almost abolished in mice lacking the neurokinin-1 SP receptor (NK1R) (103). In NK1R knockout mice, mast cell degranulation in AD skin was significantly reduced compared with wild-type controls (103). Upon exposure to additional stress, there was a significant reduction in stress-induced eosinophil infiltration and epidermal thickening, with complete block of mast cell degranulation (103). In addition, SP-induced scratch in mice is also mediated by NK1R activation (104–106).

In accordance with these findings, intradermal injection of SP is known to provoke itch, with direct inhibition by antihistamine (10). Olopatadine (Patanol™) is an anti-allergic drug with selective histamine H1 receptor antagonist activity. In comparison with standard topical therapy alone, a randomized controlled trial of patients with AD randomized to receive standard therapy plus oral olopatadine for 4 weeks, resulted in a more dramatic improvement of SCORAD index of disease severity, itch behavior, and plasma SP levels (107). The NK1R antagonist BIIF 1139 CL decreased scratching behavior in mouse models (108). These studies with olopatadine and B11F 1139 CL did not test a role for psychological stress in outcome measures.

Aprepitant (Emend™) is a selective high-affinity neurokinin receptor 1 (NKR1)-antagonist that crosses the blood-brain barrier and was originally developed and approved for the prevention of chemotherapy-induced emesis (109). Upon treatment with aprepitant a rapid and pronounced improvement in chronic pruritus was observed in patients with chronic pruritus secondary to a variety of dermatologic conditions, including AD (110, 111). Cases of pruritus associated with erlotinib treatment in cancer patients have also been reported as responsive to aprepitant (112, 113). In a prospective, open-label study of five primary cutaneous T-cell lymphoma (CTCL) patients whose primary symptom was pruritus, not controlled by conventional anti-pruritic treatments, four of the five patients responded following aprepitant treatment with a $>50\%$ reduction in pruritus severity, as determined by a visual analogue scale (114). In mouse models of AD, systematic aprepitant administration decreased serum IgE levels, as well as the density of SP+ nerve fibers in AD-like skin lesions, as determined by immunohistochemistry (115).

Bupropion (Wellbutrin™) is an antidepressant whose mechanism of action is thought to occur via inhibition of both noradrenaline and dopamine re-uptake. Case reports have shown that patients with AD can have symptomatic improvement with oral bupropion treatment (116). A pilot study was conducted to determine if oral bupropion portended skin benefits in non-depressed patients with AD and psoriasis. Six of the ten subjects with AD had a reduction in affected body surface area at the end of 6 weeks of bupropion treatment, without a sustained response upon discontinuation of bupropion (117). Case reports of patients with Crohn's disease, an inflammatory bowel disease, underwent remission when treated with bupropion for depression or smoking cessation (118, 119), suggesting a role for bupropion in lowering TNF-α levels (120). *In vivo* mouse models of inflammation showed a significant lowering of serum TNF-α, IFN-γ, and IL-1β following bupropion treatment. Together, *in vivo* studies in both humans and mice indicate a role of neuropeptides and other neuromediators in the context of stress-induced AD and atopy.

Five psychological interventions (autogenic training, cognitive-behavioral therapy, dermatological education and cognitive-behavioral therapy, habit reversal behavioral therapy, and a stress management program) were evaluated in three separate trials for their efficacy on altering itch intensity, as measured using a subjective Likert-type scale (121–123). Of these five interventions, only habit reversal behavioral therapy had no significant decrease in itching (121). As measured using a Likert scale, scratching intensity was significantly improved following autogenic training, cognitive behavioral therapy, dermatological education and cognitive behavioral therapy, and habit reversal behavioral therapy (121–124).

Psychological stress and epidermal barrier dysfunction

Studies investigating the effects of psychological stress on barrier function demonstrate a disruption in the

balance between production and sloughing of corneocytes with stress (125). Short-term GC administration impaired stratum corneum integrity and cohesion in human subjects. The rate of barrier disruption with tape stripping was increased in students stressed while studying for examinations, but improved when the students were unstressed (126). This outcome was reproduced in mouse experiments, and was associated with impaired epidermal lipid synthesis in the mice and in cultured human keratinocytes (127). Mice subjected to 72 h of psychological stress had a more severe cutaneous infection following subcutaneous group A *Streptococcus pyogenes* (GAS) inoculation compared with unstressed controls (128). There was an accompanied increased production of endogenous GCs, which inhibited epidermal lipid synthesis and decreased lamellar body secretion. Pharmacologic blockade of the stress hormone CRF or of peripheral GC action, as well as topical administration of physiologic lipids, normalized epidermal antimicrobial peptides and decreased GAS infection severity. The CRF1 antagonist, antalarmin, as well as RU-486, and adernalectomy enhanced the other low constituitive expression of antimicrobial peptides in these animals (129). In sum, these findings reveal an association with psychological stress, stress hormones and skin barrier dysfunction, with increased susceptibility to skin infection.

DISCUSSION

In patients with AD, Th2-mediated immunologic responses predominate over Th1 responses and there is an associated activation of keratinocytes, Langerhans' cells, dermal dendritic cells, endothelial cells, mast cells, B cells, and eosinophils (130–132). Research conducted over the last decade indicates that GCs, released in response to stress, cultivate Th2 responses while inhibiting Th1 cell responses (24). It has also become clear that patients with AD may have a hyperacute response to stress in terms of T-cell and mast cell activation, HPA dysregulation, neurogenic inflammatory mediator expression and release, and a disruption of normal epidermal barrier function (31, 133, 134). Studies have suggested that psychological stress in AD is at least partially responsible for the above derangement in immune response and that this polarity may be established following stress in early childhood (60, 135). An interplay between genetic and environmental factors is thought to constitute the major driving force in determining AD disease susceptibility (136), with family and twin studies demonstrating the genetic contribution as substantial (137). Most candidate gene studies to date have focused on adaptive and innate immune response genes (138, 139). One explanation for the occurrence in genetic predisposed atopic patients may be a shift towards Th2-mediated humoral immunity might protect against the tissue-damaging potential of pro-inflammatory Th1 cytokines, such as TNF-α and IFN-γ (23).

Psychological stress in early life may also lead to persistent sensitization of the HPA axis, increasing vulnerability to stress later in life (59, 140). Some data have suggested that an underlying HPA axis disturbance in AD may be the result of acute inflammation, rather than of atopic predilection (80). The relationship between genetic predisposition and neuroimmune dysfunction or neurohormonal changes in the body, however, has to await further exploration. The inverse association of low maternal progesterone during pregnancy and increased risk for AD in girls in later life suggests progesterone not only as a potential risk indicator, but also as a possible therapeutic opportunity for primary prevention of AD in girls.

Higher than average baseline heart rates and increases in very low frequency heart rate variability after patients with AD scratch (91) suggests a significant sympathetic response that differs from healthy controls. Unpleasant emotions associated with itch are perceived in the anterior cingulated cortex, which controls heart rate and the autonomic nervous system. The authors of this study postulate then that the exaggerated sympathetic response observed in patients with AD is suggestive of a central effect on scratching in chronic itch and AD (91). High-frequency variability in heart rate increased after induction of itch and the promptly decreased with scratching in healthy controls, whereas patients with AD slightly decreased after itch and further decreases after scratching, suggesting an impairment in the parasympathetic arm of the autonomic nervous system, with limited ability to adapt to itch and scratching (91).

Chronic itch shares many neural pathways with chronic pain, including peripheral and central sensitization of nerve fibers, and both conditions respond similarly to acute stress (141–143). The altered sympathetic and parasympathetic tone demonstrated in response to itch and scratching as acute stressors in AD (91) was similar to that demonstrated for acute painful stressors in the setting of chronic pain of fibromyalgia and irritable bowel syndrome (91, 144–146). Therefore, further investigations measuring autonomic function in the setting of acute stress will contribute to clarifying the underlying pathophysiology of this stress-responsive condition.

Lower activity of the vagus nerve is an established observation in inflammatory diseases, suggesting enhanced cytokine release and tissue injury as a part of pathogenesis (27). Preclinical studies of controlled vagus nerve electrical modulation show promise for inhibiting cytokine release in diverse models of inflammatory diseases, with the potential for conveying protection against attendant tissue injury (27). Device-based methods to control regional and dysfunctional

neural circuitry might then represent a potential future therapeutic modality for AD. Increased detection of parameters of the parasympathetic arm of the autonomic nervous system with IBMT provide evidence for central and autonomic nervous system influences with meditation and mindfulness training (94). In light of these findings, randomized controlled trials examining the efficacy of this technique on anxiety-provoked exacerbations in pruritus and AD are worth pursuing. Alternative and psychobehavioral therapies, such as biofeedback and cognitive behavioral therapy, show promise for targeting the discrepancy between sympathetic and parasympathetic tone in AD. Relaxation therapies, including autogenic training and hypnosis, are paramount for chronic pain patients and can ameliorate the itch of patients with AD by directly treating stress and anxiety (31). Therefore, their applicability to the management of inflammatory skin disease should be given consideration by clinicians approaching the treatment of stressed patients with AD. However, the current published data strongly suggest that a combination of anti-inflammatory, skin-barrier protecting, itch controlling and disease-specific pharmacological as well as psychopharmacological approaches will result in an optimal long-term treatment with respect to acute control therapy as well as maintenance and prevention therapy, which should be the goal for this chronic-relapsing multi-factorial disease.

In contrast to healthy control and lesional skin, non-lesional AD skin exhibited a profound deactivation pattern in various regions of the brain following itch provocation. These authors propose that the deactivation pattern during itch in non-lesional skin perhaps reflects a neurobiological attempt to suppress the perception of itch via somatosensory areas, as well as the desire to scratch via the premotor and supplementary motor areas (54). They further propose that differences in brain activation between non-lesional and lesional skin could be related to the magnitude of inflammation induced by histamine in each. Thus, central processing may over-ride peripheral signals in terms of itch intensity. Given the close connect between central processing of psychological stress, and attendant peripheral neurocutaneous inflammation, future AD therapeutics should target CNS mechanisms.

In spite of a blunted HPA axis, however, additional peripheral effects and dysregulatory circuits in glucocorticoid and GC receptor function might be involved in stress-induced neuroimmune effects in skin inflammation. Because peripheral leukocytes of patients with AD demonstrate upregulation of GC receptors they may be primed to respond to lower GC levels. Effector cell responses to stress-induced cortisol elevations may accentuate the shift in immune response from Th1 (cell-mediated) to Th2 (humoral) (79). 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 acting directly on DCs (63).

Mast cell progenitors can be isolated from human umbilical blood and grown in the presence of stem cell factor, IL-6, IL-4, 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 GCs, which subsequently alter permeability homeostasis and integrity, as well as antimicrobial defenses (35, 148). These negative effects are largely the result of GC-mediated inhibition of epidermal lipid synthesis. Topical lipid formulations normalized these functions, despite ongoing psychological stress, and therefore show promise as effective therapy for patients with AD 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 topical therapies aimed at restoring barrier integrity. Knowledge of such potential differences, attributable to psychological stress, would be of value to a clinician in the timing and selection of such agents, in terms of therapeutic efficacy.

Psychological stress is associated with flares of itching in AD. The itch sensation, with urge to scratch, is a significant source of continued psychological stress for the patient, suggesting that psychopharmacologic interventions may be efficacious (18). The correlation between high anxiety scores in patients with AD with pruritus and more intense NPY and NGF reactivity suggests that anxiety may upregulate expression of these neuropeptides, both of which could contribute to pruritus (95). NGF- and NPY-mediated induction of pruritus due to anxiety supports the need for therapeutic strategies aimed at anxiety and stress reduction/management.

Stressed patients with AD also had increased numbers of serotonin-receptive mast cells, and there was improvement in skin disease and pruritus following treatment with serotonin agonists and SSRIs, respectively. The underlying mechanism of this anti-pruritic effect has yet to be determined. While intradermal serotonin administration can induce itch (149, 150), the inhibitory effect of SSRIs is predominately in the CNS (151). Thus, the anti-pruritic effect of SSRIs is likely due to their central action rather than peripheral effects. The anxiolytic serotonin agonist TC showed promise in the

management of stress-associated aggravation of AD, and data from mouse models suggest that inhibition of stress-induced mast cell degranulation may underlie its clinical efficacy. Alternatively, the improvements observed with bupropion may reflect its capacity as a TNF-lowering anti-inflammatory agent, (152) rather than central inhibition of neurotransmitter re-uptake.

Psychological stress affects skin barrier function, with itch-scratch behaviors further traumatizing epidermal integrity. SP can induce itch, and rising plasma levels were associated with increased stress and worsening AD (10, 100, 101). The addition of oral olopatadine was more effective than topical therapy alone in decreasing disease severity, itch behavior, and SP levels, suggesting a potential role of olopatadine in the reduction of stress-associated rises in SP and thus atopic pruritus. Mouse models demonstrated attenuated cutaneous inflammation and improvement of "itchiness" following administration of NK1R antagonist. Furthermore, histologic features of AD, which are exacerbated by stress, appear to be heavily dependent on the NK1 receptor for SP (103). Thus pharmacologic interference of SP-mediated neurogenic inflammation is an attractive therapeutic target, and compounds that interfere with activation of NK1R show promise in decreasing scratching behavior. However, SP plasma levels remained elevated in patients following AD remission and perhaps the SP-ergic system is not reflective of acute changes in AD (99). The NK1R antagonist aprepitant exerts its antiemetic effects in the CNS, likely within the chemoreceptor trigger zone of the fourth ventricle's area postrema (109). While CNS injections of SP can induce pruritus in animal models, (153) central imaging studies in humans highlight a major role for the somatosensory cortex, mid-cingulate gyrus, and prefrontal areas in pruriception, rather than the fourth ventricle (154). Therefore, the anti-pruritic effects observed with aprepitant may be mediated mostly through the skin rather than through the CNS. While aprepitant shows significant promise for the treatment of refractory pruritus secondary to a variety of dermatologic and medical causes, and has been shown in mouse models of AD to influence IgE levels and SP+ nerve density, the role of stress in its potential efficacy remains to be addressed. In addition, much confusion exits regarding the central and peripheral actions of therapeutics for pruritus and thus research efforts to elucidate the role of neuropeptides in pruritogenic AD will be of paramount importance in refining these potential therapeutic modalities.

CONCLUSIONS

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 for understanding the role of stress in AD. Recently, it has been further 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 skin barrier function. As scientific research into these neurocutaneous interactions continues to develop, there is great potential for identifying new neuroimmune-modulating therapeutic targets. Such developments will refine and improve the treatment of this chronic and relapsing skin disease, which otherwise presents a significant burden to patients' quality of life.

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