Review Article

The interplay between neuroendocrine activity and psychological stress-induced exacerbation of allergic asthma

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Abstract

Psychological stress is recognized as a key factor in the exacerbation of allergic asthma, whereby brain responses to stress act as immunomodulators for asthma. In particular, stress-induced enhanced type 2 T-helper (Th2)-type lung inflammation is strongly associated with asthma pathogenesis. Psychological stress leads to eosinophilic airway inflammation through activation of the hypothalamic-pituitary-adrenal pathway and autonomic nervous system. This is followed by the secretion of stress hormones into the blood, including glucocorticoids, epinephrine, and norepinephrine, which enhance Th2 and type 17 T-helper (Th17)-type asthma profiles in humans and rodents. Recent evidence has shown that a defect of the μ-opioid receptor in the brain along with a defect of the peripheral glucocorticoid receptor signaling completely disrupted stress-induced airway inflammation in mice. This suggests that the stress response facilitates events in the central nervous and endocrine systems, thus exacerbating asthma. In this review, we outline the recent findings on the interplay between stress and neuroendocrine activities followed by stress-induced enhanced Th2 and Th17 immune responses and attenuated regulatory T (Treg) cell responses that are closely linked with asthma exacerbation. We will place a special focus on our own data that has emphasized the continuity from central sensing of psychological stress to enhanced eosinophilic airway inflammation. The mechanism that modulates psychological stress-induced exacerbation of allergic asthma through neuroendocrine activities is thought to involve a series of consecutive pathological events from the brain to the lung, which implies there to be a "neuro-psychiatry phenotype" in asthma.

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Introduction

Bronchial asthma is a disease characterized by chronic airway inflammation, which is associated with the accumulation and activation of inflammatory cells such as type 2 T-helper (Th2) cells, eosinophils, and mast cells within the bronchial mucosa. Airway inflammation frequently causes narrowing and remodeling of the airways and bronchial hyper-responsiveness to inhaled allergens. Despite advances in our understanding of the immune mechanisms involved in the development of asthma and in the use of short-relief or long-term control medications, severe asthma cases due to inappropriate risk management of avoidable factors for exacerbation are reported in clinical settings. Increasing evidence has indicated that asthma is a heterogeneous disorder. Therefore, researchers have proposed asthma phenotypes based on pathological and clinical features to identify more effective asthma therapies specific to each phenotype.

Early results from the US Centers for Disease Control and Prevention (CDC)'s January—September 2015 National Health Interview Survey showed that 3.5% of adults had experienced serious psychological distress recently; there has been a steady increase from 2.7% in 2007. Stress and emotional factors have been strongly implicated in morbidity and mortality from several types of inflammatory diseases. A possible mechanism for this, proposed by one meta-analysis, is that stress elicited simultaneous enhancement and suppression of the immune response via the effects of stress hormones by altering patterns of cytokine secretion, such as the Th1-to-Th2 shift. Specifically, the Th2-dominant profile generates a family of Th2 cytokines; levels of these cytokines in the lungs are correlated with the severity of asthma. In addition, cytokine imbalance among regulatory T (Treg), type 1 T-helper (Th1), and Th2 cells causes airway inflammation in patients with asthma.

Although the precise path from the experience of psychological stress to the enhanced Th2-predominant immune response in asthma exacerbation has been studied, therapeutic interventions to control psychological stress-induced asthma exacerbation have yet to be developed. The major part of this review is focused on the critical role of psychological stress in neuroendocrine activity followed by asthma exacerbation through cytokine imbalance. In particular, we describe recent research developments that have examined the interplay among μ-opioid receptors (MORs) in the central nervous system (CNS), the release of glucocorticoids, and enhanced Th2-type immune responses, with emphasis on our data from a murine model of stress-induced exacerbation of asthma.

Search strategy and selection criteria

We searched the literature in PubMed. We also included highly relevant literature from CDC reports. In view of the clinical research studies, we assigned priority to meta-analyses or systematic reviews. According to the quality criteria for assessment of observational studies to assess the links between exposures and outcome or prognosis of disease, articles in which the results should be interpreted with caution were excluded. This review covered articles written between 1980 and 2016.

Psychological stress and asthma exacerbation

The role of physiological stress and emotional factors in asthma exacerbation has garnered much attention. Physiological stress was recognized as a potential immune system modulator for asthma by the end of the 19th century. According to the 2001–2007 US National Health Interview Survey, the prevalence of serious psychological distress was 7.5% among adults with asthma, more than double that of the overall US population. Recently, Chida et al. conducted a systematic review and clarified that psychosocial factors were positively associated with the prevalence of atopic disorders including asthma. Chronic exposure to high levels of psychosocial stress has been shown to increase the risk of attacks in children with chronic asthma. Furthermore, exposure to physiological stress in both children and adults has been found to strongly correlate with poor prognoses for asthma. In college students with mild allergic asthma, school examinations exacerbated eosinophilic airway inflammation and enhanced IL-5 production by sputum cells due to increased anxiety and depression. In addition, work-exacerbated asthma has been attributed to exposure to emotional and socio-economic stress. Thus, psychological stress from living conditions is associated with the exacerbation of asthma symptoms.

The relationship between lower socio-economic status and asthma exacerbation has also been demonstrated. For instance, Chen et al. found that lower socio-economic status was associated with higher chronic stress and increased IL-5 and IL-13 levels, and eosinophil counts in children with asthma when families rented rather than owned their home. In their study, the production of IL-13 in children with asthma was inversely correlated with family savings and annual family incomes. Similarly, children whose families have contact with the welfare system have been identified as a high-risk group for the exacerbation of asthma symptoms compared with children in families who have not. In addition, the risk of hospitalization and death for children with asthma was found to be higher in lower-income neighborhoods. Poverty may be a contributing factor to asthma exacerbation because families living at or below the poverty level usually have poor housing conditions and may not be able to afford to heat their houses.

Psychological problems caused by domestic and neighborhood circumstances, such as bereavement and violence, are frequently responsible for stress-induced asthma exacerbation. Similarly, psychological stress due to a lack of family support has been related to poorer pulmonary function and increased biological markers of asthma in youths. Finally, inner-city schoolchildren whose primary caregivers perceived the neighborhood to be unsafe had a greater likelihood of increased rescue medication use and worse nighttime asthma symptoms than those living in neighborhoods considered to be safe.

Animal studies have verified the effects of stress on asthma exacerbation. The induction of psychological stress in asthmatic mice has been used for research into the pathophysiology of stress-induced asthma exacerbation. These studies have shown similar pathological features and overlapping clinical signs to those found in observational studies of asthma patients exposed to...
stressful situations, such as an increased production of stress hormones and enhanced Th2 immune responses.

Psychological interventions in the treatment of asthma contribute to the prevention of attacks and can alleviate symptoms. Relaxation approaches used as complementary therapies have been shown to result in improvements in the quality of life of patients with asthma. Data from larger and prospective studies are needed to confirm the effectiveness of psychological interventions in the treatment of stress-induced asthma exacerbation; nevertheless, stress reduction techniques can reduce anxiety, help control breathing, and relieve signs of asthma.

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### Brain activity in response to stress and asthma exacerbation

#### Receptiveness of psychological stress

The anterior cingulate cortex (ACC) and insula are major components of an emotional circuitry that plays a pivotal role in the cognitive processes of psychological stress during asthma exacerbation. Rosenkranz et al. reported that the emotional response associated with greater signal change in the ACC and insula correlated negatively with pulmonary function and induced the recruitment of eosinophil and TNF-α production in patients with asthma (Fig. 1). Furthermore, greater activation in the anterior insula in response to asthma-relevant psychological stimuli induced greater inflammatory signals in the lungs and was complicit in disease severity. These results suggest that neural activation in specific areas of the brain in response to psychological stimuli affect symptom expression and asthma severity.

#### Efflux of neuropeptides

The signals that project to the amygdala and hypothalamus from the ACC, and the receptivity to emotional stress of limbic structures in the brain that link the amygdala, hypothalamus, and bed nucleus of the stria terminalis, are associated with an increased efflux of neuropeptides, including substance P, histamine, endogenous opioids, and neuropeptide Y (NPY). In a study of asthmatic guinea pigs exposed to stress, Tohda et al. demonstrated that stress increased levels of substance P in plasma and bronchoalveolar lavage (BAL) fluid, resulted in enhanced airway hypersensitivity to histamine, and raised eosinophil counts in BAL fluid. Furthermore, Joachim et al. demonstrated that signaling via neurokinin-1 receptor, which has a high affinity for substance P, mediated the

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**Fig. 1.** Anterior cingulate cortex activity is associated with peripheral measures of asthmatic immune responses. (a) The increase in the percentage of sputum eosinophils and (b) TNF-α production by peripheral blood leukocytes (% of production relative to no dexamethasone) during late phase antigen relative to methacholine challenge [Ag-Meth] were significantly and positively correlated with percent signal change in the anterior cingulate cortex in response to asthma words (e.g., wheeze) compared with neutral words (e.g., curtains) that is not directly associated with an asthmatic episode [As-Ne]. Adapted from Ref. 45 with permission. Copyright (2005) National Academy of Sciences, U.S.A.
increase of inflammatory cells in sound-stressed asthmatic mice. In stress-induced asthma exacerbation, mast cell activation induced by substance P and the increased percentage of TNF-α-positive T cells by substance P in allergic airway inflammation may augment the inflammatory response.65

Recently, we demonstrated that intracerebroventricular administration of histamine receptor 1 (H1R) antagonist or H2R antagonist in stressed asthmatic mice attenuated the asthmatic airway inflammation response to psychological stress. This suggests that psychological stress activates the histamine receptor in the CNS through neuropeptide receptor-mediated mechanisms that transmit a stress signal to peripheral organs.60 Furthermore, exposure to emotional stress has been found to increase histamine turnover in the nucleus accumbens and striatum, which prolongs the stimulation of endogenous transmitters in rats.61 In addition, emotional stress exposure increases locomotor activity and endogenous opioid release in specific brain areas that play a critical role in psychological stress-induced asthma exacerbation. This is described in more detail in Section Stress-Induced Endogenous Opioids and MORs, below.

Results of a clinical study and one using a stress-exacerbated asthmatic mouse model are suggestive of a possible link between stress-induced NPY production and asthma exacerbation.52,53 Namely, NPY levels mediated the association between high perceived stress levels and IL-4 overexpression in patients with asthma.52 Also, the concentration of NPY was positively correlated with the total leukocyte count (ρ < 0.05) and eosinophil (ρ = 0.053) in stressed asthmatic mice.53 Although the underlying mechanisms of signal transduction pathway of NPY from the CNS to the lungs in stress-induced asthma exacerbation remain unclear, NPY may directly exert pro-inflammatory effects in peripheral organs through the recruitment of immature dendritic cells (DCs), and may confer a Th2 polarizing profile to DCs through the up-regulation of IL-6.54

Transduction of psychological stress signals: hypothalamic-pituitary-adrenal axis activation

The hypothalamic-pituitary-adrenal (HPA) axis is a well-known route by which external psychological factors elicit a peripheral stress response. Corticotrophin-releasing hormone (CRH) and arginine vasopressin from the hypothalamic paraventricular nucleus (PVN), α-melanocyte-stimulating hormone and β-endorphin (β-END), and adrenocorticotropic hormone (ACTH) production from the pituitary gland all have profound effects on the stress response in the brain; they function as neurotransmitters at the beginning of the signal transduction processes via the HPA axis.55,56 These are strongly linked to the severity of allergic inflammatory responses.57 Ippoliti et al. showed that neuroendocrine hormones such as prolactin, cortisol, and ACTH were significantly more concentrated in stressed than non-stressed patients with asthma; they also found that symptom score, peak expiratory flow, and eosinophil cationic protein showed a significantly greater improvement in non-stressed patients than stressed patients after sublingual immunotherapy (SLIT).58 Although SLIT improved clinical parameters and eosinophil cationic protein concentration in both stressed and non-stressed patients with asthma, psychological stress negatively affected the response to SLIT.

Transduction of psychological stress signal: autonomic nervous system activation

The hypothalamus regulates stress-induced activation of the autonomic nervous system (ANS), which includes both the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). PNS activation prompts the release of acetylcholine from efferent cholinergic nerve endings, which promotes airway inflammation and mucus secretion, bronchoconstriction, and remodeling via the muscarinic M3 receptors.69 The cholinergic pathway has been found to underlie airway constriction in patients with asthma in response to perceived psychological triggers in daily life.60 This involves a highly uniform activation pattern that contributes to airway constriction at an early phase after stimulus.70 Stress-induced SNS activation releases norepinephrine from the adrenal medulla through the sympathetic-adrenal-medullary (SAM) axis; surface expression of MCH, cluster of differentiation (CD)80, and CD86 on DCs is enhanced, followed by an over-production of IL-4 and IL-17A by CD4+ T cells in a β2-adrenergic receptor (β2AR)-dependent manner.62 Although treatment with the β2AR agonist is used currently in asthma management, the epinephrine activation of the β2AR may, paradoxically, be necessary for the development of the phenotype for stress-induced asthma exacerbation. This is described in more detail in Section Stress-induced Endocrine Secretion and Asthma Exacerbation. Thus, perceived psychological stress critically induces brain activity and the secretion of endogenous neurotransmitters.

Stress-induced endogenous opioids and MORs

Opioid receptors are a group of G protein-coupled receptors with four major subtypes: MORs, κ-, δ-, and opioid receptor-like-1 receptors. They are widely distributed in the brain, peripheral sensory neurons, and different types of immune cells.63,64 Stress-induced endogenous opioids, which bind to opioid receptors, are released in the locus coeruleus, hippocampus, pons, and nucleus accumbens. Earlier animal studies found that endogenous opioid peptides were released under several physiological stress conditions.51,65,66 In response to stress, endogenous opioids such as endorphin, enkephalin, dynorphin, and nociceptin, are released; these bind preferentially to opioid receptors, but have been found to exhibit different affinities for different opioid receptor subtypes.67,68 Previous research has devoted much attention to the role of two endogenous opioids – β-endorphin and endomorphin (EM) — that have high affinities for MORs in stress responses for the exacerbation of asthma.

β-endorphin

The β-END, derived from enzymatic cleavage of the precursor molecule pro-opiomelanocortin (POMC), binds equally to both δ- opioid receptors and MORs, and has a much lower affinity for κ-opioid receptors.67 Plasma β-END levels have been found to increase after exposure to psychological stress.69-71 Furthermore, Alexandra et al. demonstrated that traumatic foot-shock stress was associated with a reduction in the β-END degradation rate, which suggests that catabolism of β-END in the brain is an integral part of the stress response.72 β-END induces the release of epinephrine, norepinephrine, and dopamine from the adrenal medulla or sympathetic nerve endings.73 Pre-treatment of β-END before antigen challenge has been found to induce an increase of histamine and albumin levels in nasal lavage fluid during the allergic reaction in asymptomatic allergic subjects, which suggests that β-END induces nasal congestion through direct neuroendocrine receptor activation.74 Furthermore, MOR activation was found to evoke the activation of endocrine systems such as secretion of ACTH from the pituitary gland and CRH from the hypothalamus via HPA axis activation. Indeed, morphine, a MOR agonist, exacerbated stress-induced increments in levels of hypothalamic CRH and pituitary and plasma ACTH, while systemic administration of naloxone, a MOR-selective antagonist, significantly attenuated plasma glucocorticoid levels.75
Endomorphin

Coventry et al. reported that acute restraint stress did not change EM immunoreactivity significantly, but induced an increase in plasma levels of corticosterone, ACTH, and β-ENDOR. In addition, a central injection of EM did not affect plasma corticosterone levels, mRNA expression of CRH in the PVN, or POMC levels in the anterior pituitary gland. EM thus appears to make a limited contribution to stress-induced activation of the endocrine systems, although further studies are required to clarify its role in stress-induced asthma exacerbation.

Stress-induced endocrine secretion and asthma exacerbation

Psychological stress induces the secretion of the following stress hormones: (1) epinephrine and norepinephrine release from the adrenal medulla via the SNS73,74; and (2) glucocorticoid release from the adrenal cortex via the HPA axis.77,78 Glucocorticoids, epinephrine, and norepinephrine disrupt airway immune homeostasis, which exacerbates asthmatic symptoms.75 While inhaled glucocorticoids and β2AR agonists have been widely used in the treatment of asthma for over half a century, we and other investigators have accumulated evidence indicating that stress-mediated β2AR activation and endogenous glucocorticoid secretions can also contribute to the exacerbation of asthma.

β2-adrenergic receptor-mediated asthma exacerbation

Norepinephrine, released following SNS activation under stressful conditions, stimulates β2ARs on B cells; this regulates the expression of immunoglobulin (Ig) E production from IL-4-primed B cells through a p38 MAPK activation-dependent process.82 Since IgE levels are an important factor that predicts the severity of asthma,83 β2AR-mediated immune cell activation is directly related to asthma pathogenesis. Similarly, Thanawalla et al. demonstrated that activation of the β2AR by epinephrine was paradoxically required for the development of the asthma; the authors found that mice lacking the enzyme for the synthesis of epinephrine (PNMTfl/fl-mice) had complete attenuation of the cellular features of asthma.81 Furthermore, chronic intraperitoneal administration of formetol, a β2AR agonist, to PNMTfl/fl-mice before and during antigen inhalation augmented the number of eosinophils, mucus production, and airway reactivity and sensitivity to methacholine.83 Moreover, stress-derived epinephrine generated a dominant Th2/Th17 phenotype in DCs.82,84 Pretreatment of DCs with β2AR agonist enhanced pattern recognition receptor-mediated expression of CD86 and MHC-II, or cytokine production. In particular, activation of β2ARs on DCs increased IL-6 production from DCs stimulated with the nucleotide-binding oligomerization domain 2 (NOD2) agonist82,84. In addition, stimulation of β2ARs enhanced IL-23p19 gene expression in DCs stimulated with the agonist for NOD2 and TLR2, or TLR4.82,84 Since both IL-6 and IL-23 play a central role for Th17 cell differentiation,85,86 stress-induced catecholamine production may exert a Th17-type immune response, which potentially induces insensitivity to exogenous corticosteroid therapy in asthma.87 Thus, the unintended role of β2AR in asthma caused by stress is beginning to become clear.

In contrast, Brehm et al. reported that stress-induced down-regulation of the β2AR caused a reduced bronchodilator response in asthmatic children.88 This down-regulation was found in CD4⁺ lymphocytes, and was associated with polymorphism of the pituitary adenylate cyclase-activating polypeptide 1 receptor 1 (ADCYAP1R1), a susceptibility gene for post-traumatic stress disorder and anxiety.89 Furthermore, methylation of a CpG site, cg11218385, in the promoter of ADCYAP1R1, and the C allele of the single nucleotide polymorphism, rs2267735, in ADCYAP1R1 has been associated with asthma in Puerto Rican children.90 Although no association between the single nucleotide polymorphism of rs2267735 in ADCYAP1R1 and bronchodilator response has yet been found,91 this suggests that stress-induced epigenetic regulation of gene expression also affects asthma exacerbation. Indeed, physiological stress has been found to induce epigenetic plasticity in the hippocampus in terms of transient up- and down-regulation, which regulates P300-driven histone H3 lysine 27 acetylation.92 Thus, differences in sensitivity to psychological stress based on transcriptional control of gene expression may affect asthma exacerbation.

Endogenous glucocorticoid-mediated asthma exacerbation

Lim et al. reported that stress-triggered glucocorticoids during pregnancy in mice caused a rapid, large increase in plasma corticosterone levels in the fetuses of stressed mothers, which increased airway inflammation and airway responses to methacholine.93 These effects on offspring were blocked with metyrapone pretreatment of pregnant mice. In another animal study using early-life psychologically stressed mice, treatment with a glucocorticoid receptor (GR) antagonist before allergen exposure completely inhibited adult asthma exacerbation.94 Together, this suggests that release of endogenous glucocorticoids and its binding with GRs cause asthma exacerbation.

In contrast, stress-induced down-regulation of GRs in children with asthma was reported by Miller et al., who showed that stressful life experiences induced a 5.5-fold reduction in GR mRNA and a 9.5-fold reduction in β2AR mRNA.95 Similarly, Bailey et al. reported that GR mRNA and protein expression were markedly reduced in the lungs of mice with stress and allergen exposure compared with mice exposed to only stress, only allergen exposure, and naive mice.92 This reduced GR expression suggests that the binding of GRs with glucocorticoid response elements in nuclear fractions is attenuated in allergic airway inflammation under conditions of stress. This is supported by Quan et al., who showed that nuclear translocation of the GR in macrophages was impaired in socially stressed mice.93 Decreased DNA-binding capability of the GR-glucocorticoid complex may result in diminished efficacy of anti-inflammatory therapy.96 Indeed, transcriptional suppression by glucocorticoids is reportedly absent in conditions of psychological stress, which is the same as the molecular mechanisms observed in glucocorticoid insensitivity.97,98 Thus, psychological stress increases the release of endogenous glucocorticoids, whereas stress induces insensitivity to the anti-inflammatory properties of exogenous glucocorticoids, followed by resistance to relief medication (such as inhaled glucocorticoids and β2-agonists) during chronically stressed patients’ asthma attacks.94

To date, the discrepancy between the effects of endogenous and exogenous glucocorticoids on allergic inflammation has not been resolved. It also remains unclear as to whether higher doses of inhaled corticosteroids (with or without β2-agonists) are required to relieve bronchoconstriction in highly stressed patients with asthma. However, the quantity and timing of the appearance of glucocorticoids in response to psychological stress may play an important role in the enhancement of Th2 immune responses in stress-induced asthma exacerbation, which is described more fully in Section Psychological Stress-induced Modulation of the Immune Response in Asthma Exacerbation. Meanwhile, there may be a need for a novel strategy for stress-induced asthma exacerbation mediated by endogenous glucocorticoids, given the variations in patients’ stress susceptibility gene and its epigenetic modifications.
Psychological stress-induced modulation of the immune response in asthma exacerbation

Stress-induced enhancement of Th2 cell-mediated immunity

Allergic asthma has been recognized as a Th2 cytokine-mediated allergic airway inflammation in the lungs, accompanied by elevated levels of cytokines such as IL-4, IL-5, and IL-13. IL-4 directly promotes the polarization of naïve CD4+ T cell differentiation towards the Th2 phenotype and is a necessary prerequisite for class switching to IgE in B lymphocytes. In addition, IL-4 induces greater expression levels of vascular cell adhesion molecule 1 on endothelial cells, which results in the accumulation of eosinophils at the airway inflammation site. IL-5 plays an important role in eosinophil expansion, priming, and recruitment, as well as prolonged tissue survival in response to allergic stimuli. Furthermore, IL-13 acts directly on airway smooth muscle cells and tissue fibrosis, promoting the development of bronchial hyper-responsiveness. These immune responses caused by overproduction of Th2 cytokines are strongly associated with the development of asthmatic symptoms. In Th cell differentiation toward a Th1 or Th2 phenotype, corticosteroids inhibit the capacity to produce IL-12 in monocytes and macrophages, which enhances Th2 cytokine production in CD4+ T cells. Furthermore, in vitro experiments have revealed that glucocorticoids directly enhance mRNA levels of Th2 cytokines in CD4+ T cells. In addition, corticotosterone has been found to dose-dependently enhance the differentiation of thymocytes into IL-4-producing cells and to suppress their differentiation into interferon-γ-producing cells. In contrast, Wiley et al. reported that the administration of local corticosteroid during concomitant mucosal allergic sensitization amplified allergen-specific IgE in sera and Th2 cytokine production in lymphoid tissues after re-exposure to allergens; however, corticosteroid treatment during re-exposure attenuated the severity of subsequent peribronchial and perivascular inflammation and reduced goblet cell hyperplasia. Together, these results suggest that exogenous glucocorticoid administration during ongoing inflammation is effective in the treatment of asthma attacks and in symptom control, while endogenous glucocorticoid secretion during primary stimulation risks increasing the magnitude of inflammation triggered by secondary allergen exposure. Thus, the quantity of glucocorticoids secreted by the adrenal gland and the timing of their appearance in response to psychological stress, which affect cytokine production in antigen presenting cells and T cells, can be proposed to enhance Th2-type immune responses to stress-induced asthma exacerbation.

Stress-induced enhancement of Th17 cell-mediated immunity

Several studies have emphasized the functional role of IL-17 in insensitivity to glucocorticoid therapy. Recent data show a common denominator between psychological stress-induced asthma exacerbation and IL-17-induced asthma phenotype in terms of neutrophil-associated airway inflammation. Namely, psychological stress induces changes in the distribution of peripheral leukocyte populations, including neutrophils, by increasing the trafficking of leukocytes to sites of immune activation. Indeed, in occupational asthma cases, more than half of which showed clinically significant levels of psychological distress, an increase in neutrophils was observed in 20%–30% of patients, which was negatively related to lung function. These stress-induced Th17-type immune responses originate from stress-induced brain activity.

Recently, Melissa et al. showed that greater mid-cingulate cortex activation during the induction of psychosocial stress, was associated with a larger increase in IL23A mRNA expression in the sputum of patients with asthma. A similar tendency has been observed in the relationship between activation of the perigenual ACC and the increase of IL1R1 mRNA expression from baseline levels following stress in patients with asthma. Furthermore, social stress has been found to up-regulate inflammatory gene expression such as IL1 and Myd88 in peripheral blood monocytes via β-adrenergic dependent myelopoesis. In addition, stress-induced SNS activation has been found to enhance catecholamine production, which induces IL-6 and IL-23 production from DCs. Since IL-23- and IL-1-dependent stimulation of T cells induces IL-17 production, they potentially contribute to the recruitment of eosinophils and neutrophils into the airway and steroid insensitivity in asthma. Thus, brain activation caused by psychological stress exerts Th17-type immune responses in asthma via β-adrenergic receptor-dependent stimulation, which is a candidate mechanism in stress-induced asthma exacerbation.

Stress-induced suppression of Treg cell-mediated immunity

Stress-induced glucocorticoid release in asthma aggravates the Th2-type immune response by reducing Treg cell quantity and activity. In a clinical study, Freier et al. demonstrated that acute psychological stress decreased the expression of Treg-related effector molecules, as well as the proportion of CD4+ Foxp3+ Treg cells in the lymphocytes of subjects experiencing mental stress. In vitro experiments suggest that this glucocorticoid-mediated reduction of Treg cell number depends on the level of glucocorticoid. Corticosterone at concentrations of 0.01–0.1 μM have been found to suppress naïve T-cell differentiation into Treg cells, defined as IL-10-producing T cells, in vitro, whereas treatment with 1 μM of corticosterone was found to enhance IL-10-producing T-cell differentiation. Similarly, exogenous glucocorticoid also suppressed T cell differentiation through thymic atrophy, which decreased the number of Treg cells in the lungs and lymphoid organs of allergic mice. Furthermore, Stock et al. showed that treatment with dexamethasone during delivery of respiratory antigens eliminated the development of IL-10-secreting DCs, which impair allergen-specific respiratory tolerance and Treg cell development.

Our previous investigations have demonstrated the critical role of MORs in stress-induced exacerbation of asthma. Inflammatory responses and serum corticosterone levels in stressed asthmatic MOR-knockout (MORKO) mice diminished to the same levels as non-stressed asthmatic wild-type (WT) mice. Moreover, the number of total cells and eosinophils in BAL fluids increased significantly in stressed asthmatic MORKO/Tg mice that express MORs only on noradrenergic and adrenergic neurons, compared with those in stressed asthmatic MORKO mice. In addition, plasma corticosterone levels were significantly lower in stressed MORKO mice, but not in stressed MORKO/Tg mice, compared with stressed WT mice. Thus, MOR expression in the CNS assumes a central role in the stress response with the release of glucocorticoids in peripheral blood. Furthermore, treatment with the GR antagonist miltepristone or the glucocorticoid synthesis inhibitor metyrapone, which block glucocorticoid signal transduction under stress, reduced inflammatory cell counts in the BAL fluid of stressed asthmatic WT mice to the same levels as non-stressed asthmatic mice. We suggest that stress-induced glucocorticoids are strongly associated with a transient airway inflammation in the stress-induced exacerbation of asthma.

Previously, we have reported a reduction in CD4+ CD25+ cell populations in bronchial lymph node (BLN) cells in stressed asthmatic mice compared with non-stressed asthmatic mice. Moreover, the significant difference between stressed and non-stressed
mice in the Treg population in BLN cells was completely abrogated in MORKO mice. Thus, a reduction in the number and an increase in the functional defects of Treg cells appear to exacerbate this mechanism during stress-induced activation of the adaptive immune response with a Th2/Treg imbalance. We emphasize that the stress-induced reduction of the Treg population caused by MOR-dependent receptiveness to psychological stress may critically determine Th2-dominated allergic responses in stress-induced asthma exacerbation.

Stress-induced modulation of other cellular functions

Acute stress results in rapid changes in the functional activity of alveolar macrophages and mast cells, accompanied by ACTH, CRH, and corticosterone production. Alveolar macrophages in stress-exposed rats have been found to secrete greater amounts of IL-1β and TNF-α upon stimulation with lipopolysaccharide than non-stressed rats; this may enhance pulmonary immune responses to antigens.125 Busillo et al. showed that glucocorticoids increased nucleotide-binding and leucine-rich repeat-containing family pyrin domain containing 3 (NLRP3) mRNA and protein in macrophages, enhancing adenosine triphosphate-mediated release of mature IL-1β, TNF-α, and IL-6 in cells.126 Recently, Frank et al. found that glucocorticoids induced the synthesis and release of high-mobility group box 1 protein from microglia, inducing NLRP3 expression via TLR2/TLR4 stimulation under stress.127 Meanwhile, cerebral IL-6 expression was found to result in activation of the HPA axis via the adrenal gland.128 Thus, glucocorticoids may mediate NLRP3 inflammasome activation and the processing of cytokine signaling. Stress-induced glucocorticoids released because of neuroendocrine activities critically disturb immune systems in neurocytes as well as at peripheral sites, aggravating Th2 immune responses.

CRH in the lung has been found to activate mast cells, enhance mast cell-derived cytokines, decrease the ability of Treg to produce IL-10, and to upregulate IL-4 production by Th2 cells.129,130 Mast cell activation caused by stress-induced CRH has been found to increase blood-brain-barrier permeability.131 This influences the transport of cytokines such as TNF-α into the brain, which is able to transmit inflammatory signals back to the CNS.132 Thus, peripheral CRH stimulates the immune system, leading to the selective release of pro-inflammatory mediators followed by the activation of Th2 immune responses. Although it remains unclear how psychological stress-induced increases in peripheral pro-inflammatory cytokines affect CNS activation in asthma exacerbation, the actions of IL-6 on the HPA axis and its other brain functions involve the integrated effects of metabolic pathways.133

Concluding remarks

In this review, we have demonstrated how psychological stress is complicit in asthma exacerbation. We have identified the interplay between neuroendocrine activities post-psychological stress and immunological modulation through stress-induced release of neuroendocrine hormones (Fig. 3).

It is becoming increasingly clear that allergic asthma is a syndrome with complex pathophysiological signs and symptoms caused by neuro-psychiatric involvement. In addition, recent research has attempted to classify asthma phenotypes based on both clinical features and molecular pathological features.134 Activation of CNS, such as the HRs- and MORs-mediated activation of...
signal transduction pathways, followed by endogenous glucocorticoid release is involved in the immunological defect of psychological stress-induced asthma exacerbation; this is attracting attention as a conceptually advanced phenotype in asthma pathogenesis. The interplay between stress and aggravation of the Th2-type immune response via MOR-dependent receptiveness to the signal in asthma is suggestive of the existence of a “neuropsychiatry phenotype” in the field of the pathophysiology of allergy.

To date, the modulation of lung function through the release of signal transducers after experiencing psychological stress has been demonstrated conclusively, in concert with the development of the analysis of brain activity in response to environmental stimuli. Therefore, we propose a consecutive pathology from brain to lung in asthma exacerbated by psychological stress. Further pathophysiology research is needed to more fully investigate the “cross-talk” between the brain and the other organs to advance the discovery of pathogenic factors and therapeutic target molecules in the neuropsychiatry phenotype in asthma.

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Conflict of interest

The authors have no conflict of interest to declare.

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