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Review Article

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

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Abbreviations:
ACC, anterior cingulate cortex;
β2AR, β2-adrenergic receptor;
ACTH, adrenocorticotropic hormone;
ADCYAP1R1, adenylate cyclase-activating polypeptide 1 receptor 1; ANS, autonomic nervous system; BAL, bronchoalveolar lavage; BLN, bronchial lymph node;
CD, cluster of differentiation; CNS, central nervous system; CRH, corticotrophin-releasing hormone; EM, endomorphin;
β-END, β-endorphin; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; HR, histamine receptor;
Ig, immunoglobulin; IL, interleukin;
MOR, μ-opioid receptor; NPY, neuropeptide Y; NLRP3, nucleotide-binding and leucine-rich repeat-containing family pyrin domain containing 3; NOD2, nucleotide-binding oligomerization domain 2;
PNS, parasympathetic nervous system;
POMC, pro-opiomelanocortin;
PVN, paraventricular nucleus;

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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SAM, sympathetic-adrenal-medullary;
SLIT, sublingual immunotherapy;
SNS, sympathetic nervous system; Th1, type 1 T helper; Th2, type 2 T helper; Th17, type 17 T helper; TLR, toll-like receptor;
TNF-α, tumor necrosis factor-α;
Treg, regulatory T; WT, wild type

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.[1] 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.[2]

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.[3] Stress and emotional factors have been strongly implicated in morbidity and mortality from several types of inflammatory diseases.[4–9] 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.[10] 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.[1] In addition, cytokine imbalance among regulatory T (Treg), type 1 T-helper (Th1), and Th2 cells causes airway inflammation in patients with asthma.[11,12]

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,[13] 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.[9,14–16] 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.[17] Recently, Chida *et al.* conducted a systematic review and clarified that psychosocial factors were positively associated with the prevalence of atopic disorders including asthma.[18] Chronic exposure to high levels of psychosocial stress has been shown to increase the risk of attacks in children with chronic asthma.[19] Furthermore, exposure to physiological stress in both children and adults has been found to strongly correlate with poor prognoses for asthma.[20] 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.[21] In addition, work-exacerbated asthma has been attributed to exposure to emotional and socio-economic stress.[22] 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.[23] In their study, the production of IL-13 in children with asthma was inversely correlated with family savings and annual family incomes.[23] 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.[24] In addition, the risk of hospitalization and death for children with asthma was found to be higher in lower-income neighborhoods.[25] 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.[26–29] 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.[30] 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.[31]

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.[32–38] These studies have shown similar pathological features and overlapping clinical signs to those found in observational studies of asthma patients exposed to

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