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Invited review article

Neuropsychiatry phenotype in asthma: Psychological stress-induced alterations of the neuroendocrine-immune system in allergic airway inflammation

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Abbreviations:
ACC, anterior cingulate cortex; BAL, bronchoalveolar lavage; BLN, bronchial lymph node; CD, cluster of differentiation; CNS, central nervous system; DC, dendritic cell; fMRI, functional magnetic resonance imaging; HPA, hypothalamic-pituitary-adrenal; HR, histamine receptor; IL, interleukin; KO, knockout; MOR, μ-opioid receptor; NK, natural killer; PNS, parasympathetic nervous system; PTSD, posttraumatic stress disorder; SNS, sympathetic nervous system; Th1, type 1 T helper; Th2, type 2 T helper; Th17, type 17 T helper; TNF-α, tumor necrosis factor-α; Treg, regulatory T; WT, wild type

ABSTRACT

Since the recognition of asthma as a syndrome with complex pathophysiological signs and symptoms, recent research has sought to classify asthma phenotypes based on its clinical and molecular pathological features. Psychological stress was first recognized as a potential immune system modulator of asthma at the end of the 19th century. The activation of the central nervous system (CNS) upon exposure to psychological stress is integral for the initiation of signal transduction processes. The stress hormones, including glucocorticoids, epinephrine, and norepinephrine, which are secreted following CNS activation, are involved in the immunological alterations involved in psychological stress-induced asthma exacerbation. The mechanisms underlying this process may involve a pathological series of events from the brain to the lungs, which is attracting attention as a conceptually advanced phenotype in asthma pathogenesis. This review presents insights into the critical role of psychological stress in the development and exacerbation of allergic asthma, with a special focus on our own data that emphasizes on the continuity from the central sensing of psychological stress to enhanced eosinophilic airway inflammation.

Receptiveness of psychological stress in living conditions

Mental illnesses were recognized in Greece in the 3rd to 4th centuries BCE. The Greek physician Hippocrates, one of the first scholars to recognize the notion of neuropsychiatry, first proposed the concept that mental illnesses were of natural origins rather than due to the possession of evil spirits or punishment sent from the gods. In the 19th century, Wilhelm Griesinger, a German neurologist, suggested that mental illnesses are actually illnesses of the nerves and brain. Around the same time, in the field of allergy pathophysiology, physiological stress was recognized as a potential immune system modulator for asthma, although the mechanisms leading to asthma pathogenesis were not yet clearly understood. In the 20th century, the importance of the signal transduction pathway from the brain in response to psychological stimuli to the peripheral organs, in concert with the development of psychopharmacology, was becoming clear. Recently, stress and emotional factors are increasingly recognized as stimuli that disturb the

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homeostasis of the brain, and which have been strongly implicated in morbidity and mortality from several types of inflammatory diseases, including allergic asthma.[1]

Early results from the National Health Interview Survey, conducted by the US Centers for Disease Control and Prevention (CDC), showed that 3.5% of adults had recently experienced serious psychological distress, a marked increase from the reported 2.7% in 2007.[2] The results of the CDC survey indicate that mundane stressful life events may become acute or chronic psychological stressors. Stressful life events such as lower socioeconomic status in families renting homes, contact with the welfare system, and lower levels of savings and annual incomes may lead to psychologically stressful conditions in children.[3,4] This observation is supported by Maxmen, who provided scientific evidence for the concept that deprivation leads to stress, which may, in turn, lead to poor health.[5] In addition, domestic circumstances such as bereavement, violence, and lack of family support are also associated with psychological stress in parents and their children.[6] Similarly, dwelling environments such as areas with lower-income neighborhoods or with caregivers who perceive the neighborhood as unsafe may also act as psychological stimuli in children.[4] School examinations in college students with mild allergic asthma increased their anxiety and depression.[7] In addition, more than half of the individuals with occupational asthma felt clinically significant levels of psychological distress.[8] Thus, psychological stress from several types of life events and living conditions may become psychological stimuli and stressors.

Psychological stress in asthma development and exacerbation

The role of psychological stress and emotional factors in the development and exacerbation of asthma has garnered much attention.[1,9] Sandberg *et al.* demonstrated that high levels of chronic stress increased the risk of new asthma attacks three-fold in children aged 6–13 years within the first fortnight, but not the subsequent third to sixth weeks.[10] Similarly, lower levels of family support and higher levels of neighborhood problems, but not a lack of peer support, were associated with increased symptoms and poorer pulmonary function in children and adolescents with asthma, although family and neighborhood factors and peer support were not associated with asthma outcomes in youths.[6] In Japan, Koyanagi and colleagues surveyed factors contributing to asthma exacerbation in 3085 adult patients, reporting that emotional stress caused 10%–15% of the asthma exacerbation. In their study, the percentage of patients who had asthma exacerbation caused by psychological stress were gradually increased dependent on asthma severity.[9] Furthermore, psychological stress during pregnancy increased the risk of the development of childhood wheezing and asthma through the effect of stress on epigenetic modulations such as genome-wide alterations in DNA methylation in both mothers and their children.[11] In addition, Lim *et al.* reported that stress-triggered glucocorticoid release 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 in the adult offspring.[12] These results suggest that psychological stress signals are transferred from the mothers to their offspring, which become a risk factor for new asthma attacks. This risk is reflected in the Japanese guidelines for the definition, evaluation, and treatment of severe asthma.[13] The results from other studies also show that psychological stress is an important factor for asthma severity.[14,15] Childhood and adult exposures to physiological stress are strongly correlated with attacks and poor asthma prognoses,[16] with which living conditions such as lower socioeconomic status and problems in domestic and neighborhood circumstances are deeply associated.[3,17,18]

Enhancement of Th2-type immune responses in response to psychological stress

School examinations exacerbated eosinophilic airway inflammation in college students with mild allergic asthma (Fig. 1) and enhanced interleukin (IL)-5 production by sputum cells in association with increased anxiety and depression.[7] Furthermore, examination stress skewed the type 1 T helper (Th1)/type 2 T helper (Th2) ratio to Th2-dominant, and reduced natural killer (NK) cell numbers in atopic students.[19] Chen *et al.* found that lower socioeconomic status such as that in families who rented rather than owned their homes was associated with higher levels of chronic stress, which increased IL-5 and IL-13 levels and eosinophil counts in children with asthma.[17] Furthermore, the production of IL-13 in children with asthma was inversely correlated with family savings and annual family incomes.[17] Wolf *et al.* demonstrated that perceived stress levels in parents, as evaluated by the Perceived Stress Scale, a self-report questionnaire of globally perceived stress, is associated with increased levels over time of asthma-relevant inflammatory markers such as eosinophil cationic protein and IL-4 in children with asthma.[20] These relationships are supported by studies using animal mouse models by Chida *et al.*, who demonstrated that mice exposed to psychological stress exhibited a

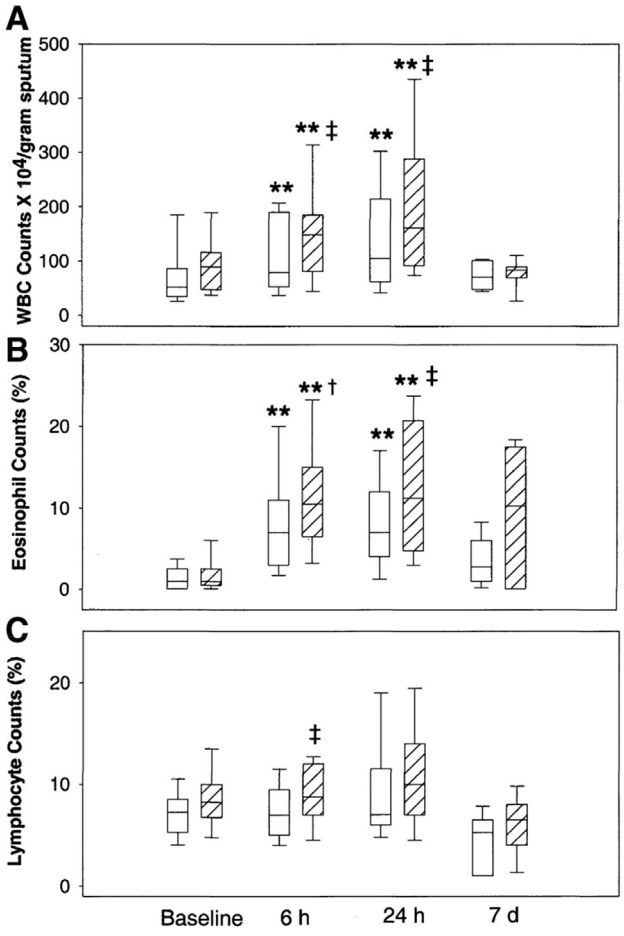

Fig. 1. School examinations enhance airway inflammation following antigen challenge. In college students with mild asthma (n = 20), the number of sputum white blood cells **(A)**, the percentages of sputum eosinophils **(B)**, and the percentages of sputum lymphocytes **(C)** were counted before, 24 h after, and seven days after antigen challenge. The boxes represent medians with 25 and 75% quartiles; the vertical lines represent the 10th and 90th percentiles. $^{**}p < 0.01$, versus baseline; $\dagger p < 0.05$, $\ddagger p < 0.01$, stress versus low-stress. This figure is adapted from the Reference[7] with permission.