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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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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.

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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

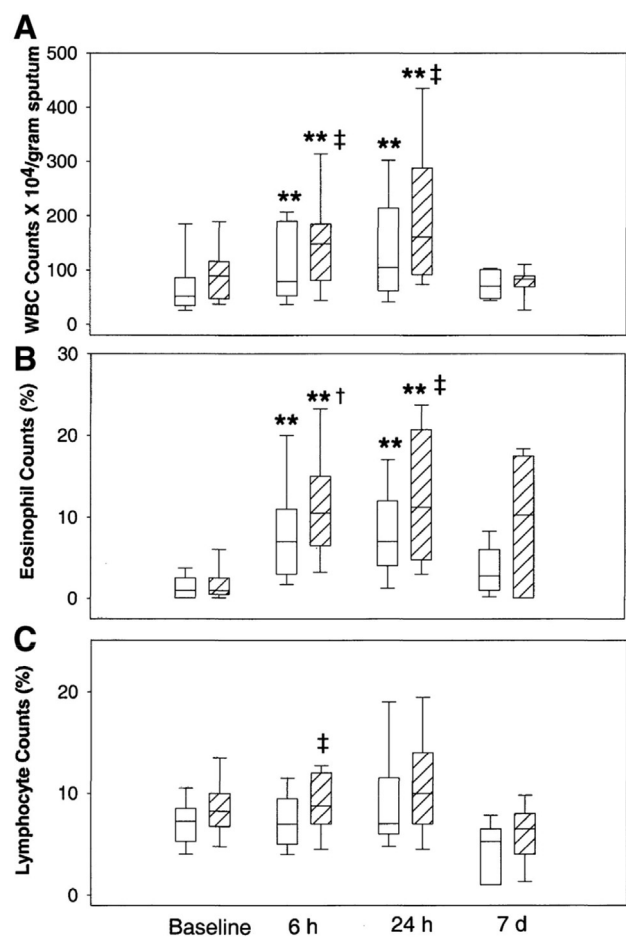


Fig. 1. School examinations enhance airway inflammation following antigen challenge. In college students with mild asthma ($n = 20$), the number of sputum white blood cells (A), the percentages of sputum eosinophils (B), and the percentages of sputum lymphocytes (C) were counted before, 24 h after, and 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; † $p < 0.05$, ‡ $p < 0.01$, stress versus low-stress. This figure is adapted from the Reference⁷ with permission.

significant increase in the number of total mononuclear cells and eosinophils and enhanced airway hyperresponsiveness compared to those in control mice.²¹ Interestingly, pretreatment with a glucocorticoid receptor antagonist inhibited physical stress-induced augmentation of airway inflammation. This result suggests that the endocrine system is involved in the pathway from the receptiveness of psychological stress to the enhanced Th2 immune responses in asthma.²¹

Brain activity in response to stress and asthma pathophysiology

Stress-induced enhanced Th2-type immune responses originate from stress-induced brain activity. Rosenkranz *et al.* reported that the emotional response associated with a greater change of functional magnetic resonance imaging (fMRI) signal in the anterior cingulate cortex (ACC) and insula, which are major components of an emotional circuitry in the cognitive processes of psychological stress, was negatively correlated with pulmonary function, and resulted in increased numbers of eosinophils and tumor necrosis factor- α (TNF- α) production in patients with asthma (Fig. 2).²² Furthermore, greater activation of the anterior insula in response to increased inflammatory signals in the lungs induced by asthma-

relevant psychological stimuli and was associated with disease severity.²³ Acute psychological stress induced the exacerbation of airway inflammation in chronically stressed asthmatic patients, which was associated with signal cross-interaction between the ACC and insula in response to psychological stress.²⁴ Furthermore, increased mid-cingulate cortex and ACC activation during the induction of psychosocial stress was associated with a larger increase in *IL23A* mRNA expression and increased *IL1R1* mRNA expression in sputum cells from the baseline levels following stress in patients with asthma.²⁴ These brain activities caused by psychological stress exert type 17 T helper (Th17)-type immune responses such as the increase of neutrophils in individuals with asthma,²⁴ which contribute to the refractory asthma characteristic of glucocorticoid resistance.^{8,14,15} These results suggest that neural activation in specific areas of the brain in response to psychological stimuli leads to immune responses that may result in increased asthma severity.

When brain sites such as the ACC, insula, and limbic structures that link the amygdala, hypothalamus, and bed nucleus of the stria terminalis perceive emotional stress signals, they induce signal transduction processes through the efflux of neuropeptides, including substance P, histamine, endogenous opioids, and neuropeptide Y.^{25,26} Our previous investigations have demonstrated the critical role of μ -opioid receptors (MORs) and histamine receptors

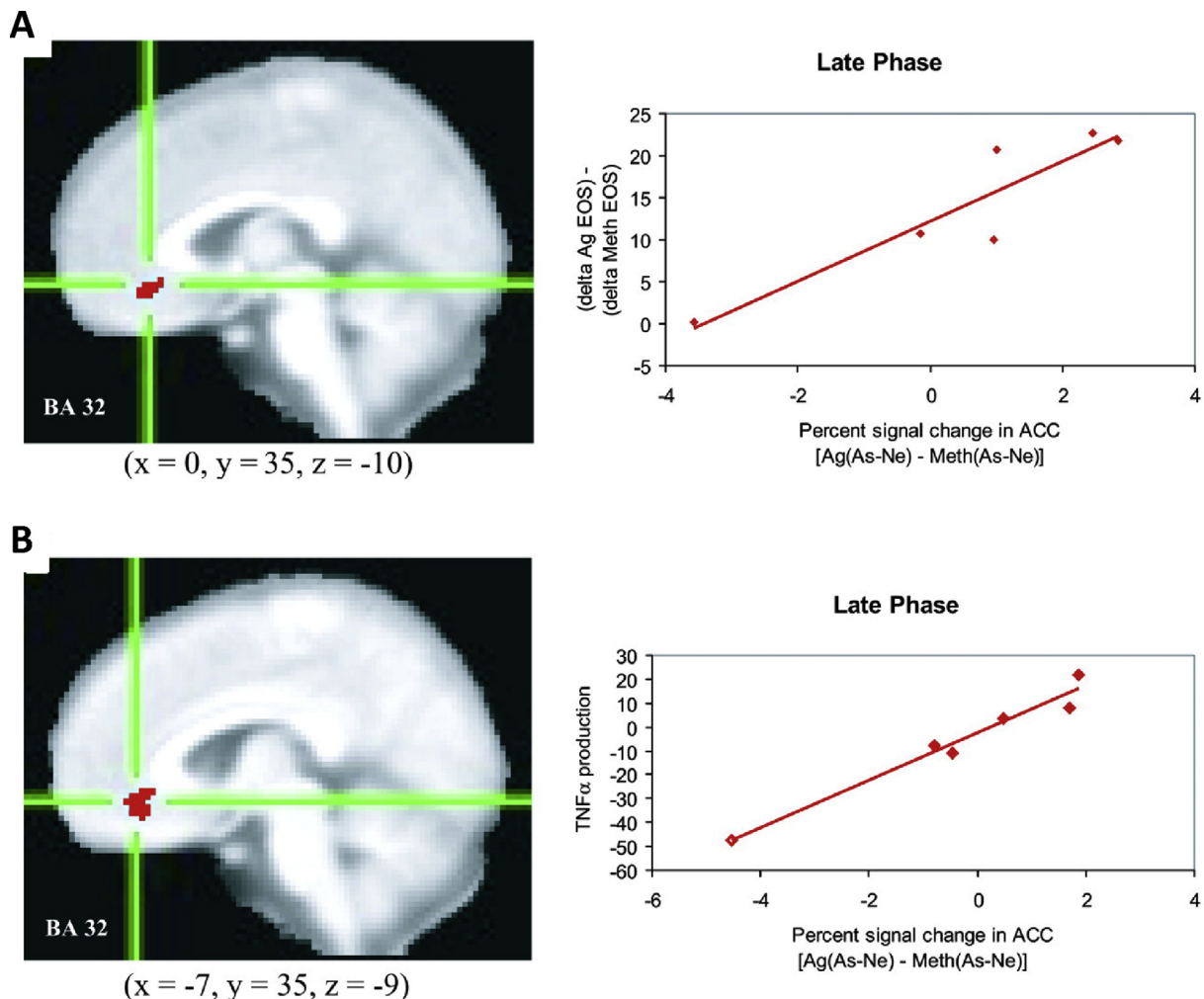


Fig. 2. Anterior cingulate cortex activity is associated with increased eosinophil counts and tumor necrosis factor (TNF)- α production. The correlation was evaluated between eosinophils (A) or TNF- α production by peripheral blood leukocytes (% of production relative to no dexamethasone) (B), and the percent change of functional magnetic resonance imaging (fMRI) signal in the anterior cingulate cortex in response to words related to asthma (e.g., wheeze) compared with neutral words (e.g., curtains) [As-Ne] during late phase after antigen relative to methacholine challenge [Ag-Meth]. This figure is adapted from the Reference²² with permission.

(HRs) in the stress-induced exacerbation of asthma.^{27–29} We showed that the stress-induced aggravations of the asthmatic inflammatory responses observed in wild-type (WT) mice were completely abolished in MOR-knockout (MORKO) mice, while the aggravation re-emerged in MORKO mice when MOR was reconstituted only in the central nervous system (CNS, MORKO/Tg mice) (Fig. 3).²⁸ A similar tendency in serum corticosterone levels was observed in WT, MORKO, and MORKO/Tg mice.²⁸ Intracerebroventricular, but not peripheral, administration of MOR antagonists significantly suppressed stress-induced exacerbations of allergic airway inflammation in WT mice. Furthermore, instead of stress exposure, the administration of morphine, a MOR agonist, reproduced the worsening of allergic airway inflammation in WT mice.²⁹ In addition, we demonstrated that intracerebroventricular administration of type 1 or type 2 HR antagonists, but not type 3 HR antagonists, attenuated the stress-induced exacerbations of asthmatic airway responses in a murine model of allergic asthma.²⁷

Stress signals to the hypothalamus regulate the activation of both the parasympathetic and sympathetic nervous systems (PNS and SNS, respectively); PNS activation prompts the release of

acetylcholine from efferent cholinergic nerve endings, while SNS activation releases epinephrine and norepinephrine from the adrenal medulla through the sympathetic-adrenal-medullary axis, which together amplify airway inflammation, mucus secretion, bronchoconstriction, and remodeling.^{30,31} Thus, brain activity followed by the efflux of neuropeptides could be involved in asthma exacerbation.

The linkage between stress stimuli in the brain and inflammation in the lungs: stress-induced secretion of endocrine hormones

Psychological stress induces the secretion of stress hormones such as epinephrine, norepinephrine, and glucocorticoids.^{32,33} In these stress hormones, glucocorticoid released through the activation of the hypothalamic–pituitary–adrenal (HPA) axis is a well-known mediator that elicits peripheral stress responses to external psychological factors. Administration of psychological stress to impregnated mice was found to increase the plasma corticosterone levels in fetuses, which was associated with increased airway inflammation and airway responses to methacholine in the offspring.¹² The role of glucocorticoids in stress-related asthma exacerbations is supported by Chida *et al.*, who showed that mice exposed to psychological stress in early life exhibited enhanced asthmatic responses in adulthood, which was abrogated by treatment with a glucocorticoid receptor antagonist before allergen exposure.²¹ We demonstrated that treatment with a glucocorticoid receptor antagonist, mifepristone, or a glucocorticoid synthesis inhibitor, metyrapone, prior to the stress exposure, reduced inflammatory cell counts in the bronchoalveolar lavage fluid of stressed-asthmatic mice to the same levels as those in non-stressed asthmatic mice (Fig. 4).³⁴

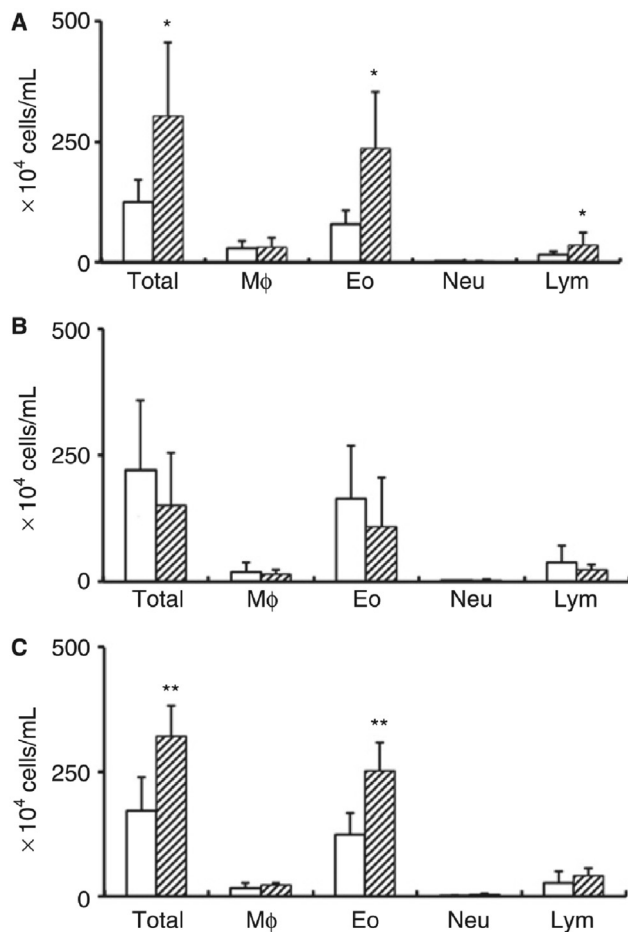


Fig. 3. μ -opioid receptors in the central nervous system (CNS) are involved in the stress-induced increase in inflammatory cells in the bronchoalveolar lavage (BAL) fluid of asthmatic mice. Mice were sensitized with two intraperitoneal injections of ovalbumin and aluminum hydroxide on days 0 and 5. On days 30 and 37, the mice were challenged with aerosolized ovalbumin for 1 h. Psychological stressors were applied from days 30–36. The numbers of total cells (Total), macrophages (Mφ), eosinophils (Eo), neutrophils (Neu), and lymphocytes (Lym) in BAL fluids were counted, for non-stressed (open bars) and stressed (hatched bars) wild-type (A), μ -opioid receptor knock-out (MORKO) (B), and MORKO/Tg (C) mice three days after the last ovalbumin inhalation. Data are expressed as mean $\pm$ S.D. * p < 0.05 and ** p < 0.01 compared to non-stressed mice. This figure is adapted from the Reference.²⁸

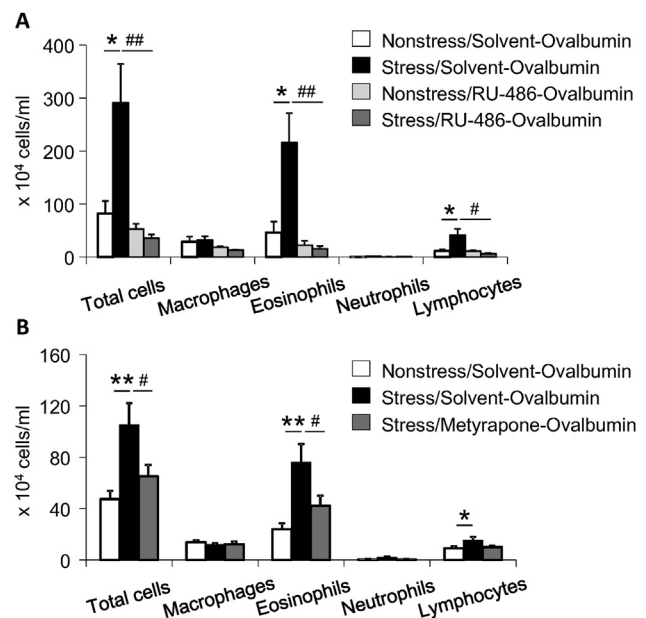


Fig. 4. Endogenous glucocorticoids play an important role in the stress-induced increase in inflammatory cells in the bronchoalveolar lavage (BAL) fluid of asthmatic mice. Mice were sensitized with two intraperitoneal injections of ovalbumin and aluminum hydroxide on days 0 and 5. On days 17 and 24, the mice were challenged with aerosolized ovalbumin for 1 h. Psychological stressors were applied from days 17–23. RU-486 (A), a glucocorticoid receptor antagonist, or metyrapone (B), a glucocorticoid synthesis inhibitor, was administered before each psychological stress exposure. The numbers of total cells, macrophages, eosinophils, neutrophils, and lymphocytes in BAL fluids were counted three days after the last ovalbumin inhalation. * p < 0.05 and * p < 0.01 compared with non-stressed mice with solvent; # p < 0.05 and ## p < 0.01 compared with stressed mice with solvent. This figure is adapted and modified from the Reference³⁴ with permission.

In helper T cell differentiation to Th1 or Th2 phenotypes, glucocorticoids inhibit the capacity for antigen-presenting cells to produce IL-12 and enhance the differentiation of thymocytes into IL-4-producing cells, which together enhance Th2 cytokine production in a cluster of differentiated (CD4⁺ T cells.^{35–37} Furthermore, Wiley *et al.* reported that the local administration of corticosteroids during concomitant mucosal allergic sensitization amplified Th2 cytokine production in lymphoid tissues after re-exposure to allergens.³⁸

In addition, stress-induced glucocorticoid release in asthma aggravates the Th2-type immune response by reducing regulatory T (Treg) cell quantity and activity. Freier *et al.* demonstrated that acute psychological stress decreased the expression of Treg cell-related effector molecules, as well as the proportion of CD4⁺ Foxp3⁺ Treg cells in individuals experiencing mental stress.³⁹ Treatment with glucocorticoids during the delivery of antigens eliminated the development of IL-10-secreting dendritic cells (DCs) and suppressed naïve T-cell differentiation into Treg cells, which impaired allergen-specific respiratory tolerance and Treg cell development.^{37,40} Indeed, the population of Treg cells among CD4⁺ cells was significantly reduced in patients with post-traumatic stress disorder (PTSD) compared with those in non-PTSD controls.⁴¹ Furthermore, Treg cell phenotype according to the expression of CD127 and human leukocyte antigen-DR markers were altered in patients with PTSD, suggesting that psychological stress is involved in the disruption of immune homeostasis through the modulation of Treg cell differentiation and function.⁴² We also reported a reduction in CD4⁺ CD25⁺ cell populations in bronchial lymph node (BLN) cells on the third day after allergen inhalation in stressed asthmatic mice compared to those in non-stressed asthmatic mice. Moreover, the significant difference in the Treg cell population in BLN cells between stressed and non-stressed mice was completely abrogated in MORKO mice (Fig. 5).²⁸ Thus, a reduced number of Treg cells, and a defect in the function of Treg cells in response to psychological stress, suggests the abrogation of immune tolerance due to the stress exposure, leading to stress-induced activation of the asthmatic immune response with a Th2/Treg imbalance. Furthermore, a MOR-dependent receptiveness to psychological stress might be involved in this mechanism. Thus, while inhaled glucocorticoids have been widely used in the treatment of ongoing inflammation in asthma, psychological stress-induced endogenous glucocorticoid secretion risks increasing the magnitude of inflammation triggered by subsequent allergen exposure.

Perspectives

Psychological stress is deeply involved in asthma development and exacerbation. The receptivity to psychological stress by the brain plays a pivotal role in initiating signal transduction processes, followed by the efflux of neuropeptides such as opioids and histamine. The signal is transduced from the brain to the lungs mainly through the activation of the HPA axis, which leads to the release of stress hormones such as glucocorticoids. The activity of the neuroendocrine system amplifies Th2-type immune responses in the lungs via the induction of Th1/Th2 or Treg/Th2 imbalance. We, and other investigators, have accumulated evidence indicating that stress-mediated endogenous glucocorticoid secretion contributes to the exacerbation of asthma. However, exogenous glucocorticoids have been widely used in the short-term relief or long-term control of asthma based on the worldwide guidelines for asthma

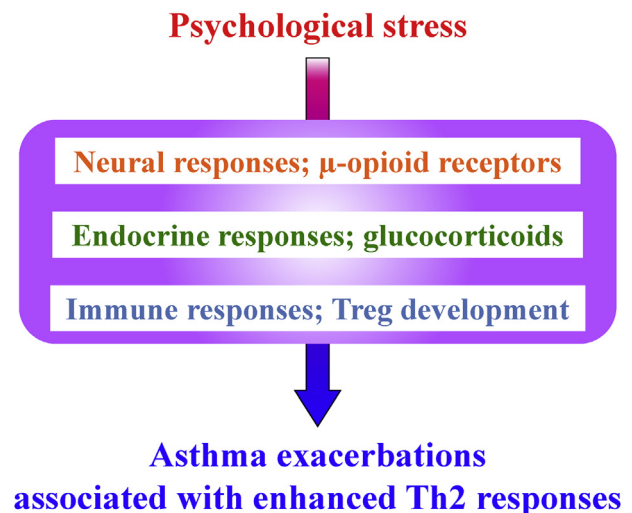


Fig. 6. Schematic diagram of the stress signal transduction pathway from the brain to the lungs in allergic asthma. Psychological stress stimuli induce the efflux of neuropeptides such as opioids from the central nervous system, which transduce the signal from the brain to the lungs through the activation of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, leading to endocrine responses such as the release of glucocorticoids. Glucocorticoids directly enhance Th2-type inflammation or suppress regulatory T (Treg) cells or Th1-type inflammation in the lungs, and this is strongly associated with psychological stress-induced asthma exacerbation.

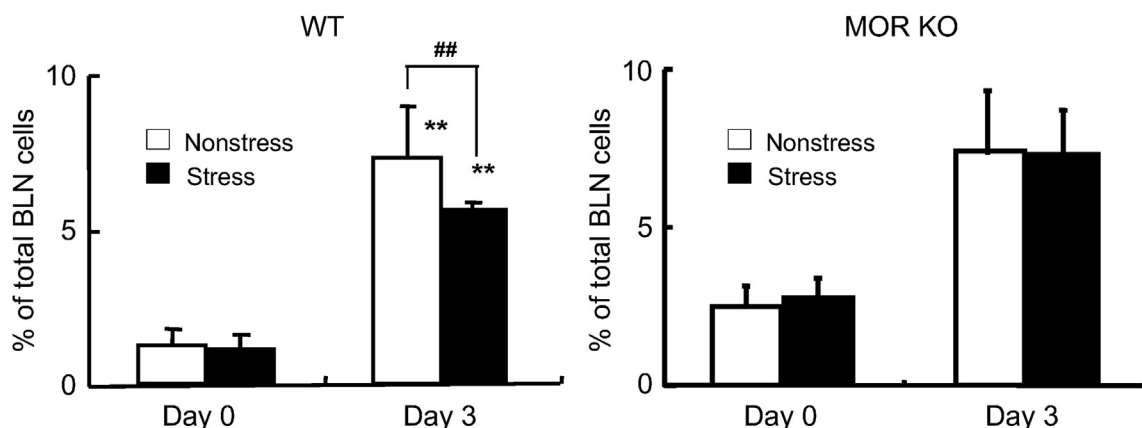


Fig. 5. μ -opioid receptors are involved in the stress-induced reduction of regulatory T cells in the bronchial lymph node (BLN) of asthmatic mice. BLN cells from non-stressed (open bars) and stressed (closed bars) wild-type asthmatic mice and μ -opioid receptor (MOR) knock-out (KO) asthmatic mice were analyzed for the percentages of regulatory T (Treg) cells defined as CD4⁺ CD25⁺ before (day 0) and three days after culture with ovalbumin. The numbers of Treg cells are shown as percentages of the total number of BLN cells. Data are expressed as mean $\pm$ S.D. ** p < 0.01 compared with day 0; ## p < 0.01 compared with non-stressed mice. This figure is adapted and modified from the Reference.²⁸

management. How we should interpret this apparent discrepancy between the roles of foe and friend played by glucocorticoids in allergic inflammation has not yet been resolved.⁴³ In this review, we suggest, as one possibility, that glucocorticoids may play a distinctive role in the regulation of Th2 immune responses depending on the time points, frequency, and compartment of the appearance of this hormone, the attenuation of asthmatic airway inflammation in the case of inhaled glucocorticoids during on-going inflammation, and the enhancement in the case of chronic and systemic glucocorticoids such as chronic exposure to psychosocial stress.

Because asthma is a heterogeneous disorder, several groups of researchers have proposed asthma phenotypes based on pathological and clinical features in order to identify more effective asthma therapies specific to each phenotype.⁴⁴ A novel strategy is needed for the reduction of morbidity and mortality of psychological stress-related asthma. Recently, it is becoming clear that the differences in sensitivity to psychological stress based on the translational control of gene expression may affect asthma exacerbation. Therefore, studies on signal transduction pathways through the modulation of epigenetic and transcriptional activity in asthma-relevant cells may be needed to assess the psychological stress-related phenotypes of asthma and immune responses.⁴⁵ In this review, we propose a consecutive pathology from the brain to the lungs in asthma, which is exacerbated by psychological stress (Fig. 6); this pathology is attracting attention as a conceptually advanced and novel phenotype in asthma pathogenesis in the psychologically stressful living conditions of the 21st century.

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Conflict of interest

The author has no conflict of interest to declare.

References

- Sandberg S, Järvenpää S, Penttinen A, Paton JY, McCann DC. Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 2004;**59**:1046–51.
- Clarke TC, Ward BW, Freeman G, Schiller JS. *Early Release of Selected Estimates Based on Data From the January–September 2015 National Health Interview Survey*. Division of Health Interview Statistics, National Center for Health Statistics; 2016. <https://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201509.pdf> [accessed 27.04.17].
- Wood PR, Smith LA, Romero D, Bradshaw P, Wise PH, Chavkin W. Relationships between welfare status, health insurance status, and health and medical care among children with asthma. *Am J Public Health* 2002;**92**:1446–52.
- Castro M, Schechtman KB, Halstead J, Bloomberg G. Risk factors for asthma morbidity and mortality in a large metropolitan city. *J Asthma* 2001;**38**:625–35.
- Maxmen A. Stress: the privilege of health. *Nature* 2016;**531**:558–9.
- Chen E, Chim LS, Strunk RC, Miller GE. The role of the social environment in children and adolescents with asthma. *Am J Respir Crit Care Med* 2007;**176**:644–9.
- Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med* 2002;**165**:1062–7.
- Yacoub MR, Lavoie K, Lacoste G, Daigle S, L'archevêque J, Ghezzo H, et al. Assessment of impairment/disability due to occupational asthma through a multidimensional approach. *Eur Respir J* 2007;**29**:889–96.
- Koyanagi K, Koya T, Sasagawa M, Hasegawa T, Suzuki E, Arakawa M, et al. Niigata Asthma Treatment Study Group. An analysis of factors that exacerbate asthma, based on a Japanese questionnaire. *Allergol Int* 2009;**58**:519–27.
- Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;**356**:982–7.
- Trump S, Bieg M, Gu Z, Thürmann L, Bauer T, Bauer M, et al. Prenatal maternal stress and wheeze in children: novel insights into epigenetic regulation. *Sci Rep* 2016;**6**:28616.
- Lim R, Fedulov AV, Kobzik L. Maternal stress during pregnancy increases neonatal allergy susceptibility: role of glucocorticoids. *Am J Physiol Lung Cell Mol Physiol* 2014;**307**:L141–8.
- Ohta K, Ichinose M, Nagase H, Yamaguchi M, Sugiura H, Tohda Y, et al. Japanese guideline for adult asthma 2014. *Allergol Int* 2014;**63**:293–333.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;**181**:315–23.
- Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SA, et al. Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Am J Respir Crit Care Med* 2012;**185**:356–62.
- Di Marco F, Santus P, Centanni S. Anxiety and depression in asthma. *Curr Opin Pulm Med* 2011;**17**:39–44.
- Chen E, Hanson MD, Paterson LQ, Griffin MJ, Walker HA, Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. *J Allergy Clin Immunol* 2006;**117**:1014–20.
- Subramanian SV, Ackerson LK, Subramanyam MA, Wright RJ. Domestic violence is associated with adult and childhood asthma prevalence in India. *Int J Epidemiol* 2007;**36**:569–79.
- Höglund CO, Axén J, Kemi C, Jernelöv S, Grunewald J, Müller-Suur C, et al. Changes in immune regulation in response to examination stress in atopic and healthy individuals. *Clin Exp Allergy* 2006;**36**:982–92.
- Wolf JM, Miller GE, Chen E. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. *Brain Behav Immun* 2008;**22**:433–41.
- Chida Y, Sudo N, Sonoda J, Hiramoto T, Kubo C. Early-life psychological stress exacerbates adult mouse asthma via the hypothalamus-pituitary-adrenal axis. *Am J Respir Crit Care Med* 2007;**175**:316–22.
- Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci U S A* 2005;**102**:13319–24.
- Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. *PLoS One* 2012;**7**:e40921.
- Rosenkranz MA, Esnault S, Christian BT, Crisafi G, Gresham LK, Higgins AT, et al. Mind-body interactions in the regulation of airway inflammation in asthma: a PET study of acute and chronic stress. *Brain Behav Immun* 2016;**58**:18–30.
- Papathanassoglou ED, Giannakopoulou M, Mpouzika M, Bozas E, Karabinis A. Potential effects of stress in critical illness through the role of stress neuropeptides. *Nurs Crit Care* 2010;**15**:204–16.
- Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol* 2009;**5**:374–81.
- Miyasaka T, Okuyama-Dobashi K, Masuda C, Iwami S, Sato M, Mizoguchi H, et al. The involvement of central nervous system histamine receptors in psychological stress-induced exacerbation of allergic airway inflammation in mice. *Allergol Int* 2016;**65**:S38–44.
- Okuyama K, Ide S, Sakurada S, Sasaki K, Sora I, Tamura G, et al. μ -opioid receptor-mediated alterations of allergen-induced immune responses of bronchial lymph node cells in a murine model of stress asthma. *Allergol Int* 2012;**61**:245–58.
- Okuyama K, Wada K, Sakurada S, Mizoguchi H, Komatsu H, Sora I, et al. The involvement of micro-opioid receptors in the central nervous system in the worsening of allergic airway inflammation by psychological stress in mice. *Int Arch Allergy Immunol* 2010;**152**:342–52.
- Kistemaker LE, Gosens R. Acetylcholine beyond bronchoconstriction: roles in inflammation and remodeling. *Trends Pharmacol Sci* 2015;**36**:164–71.
- Kim BJ, Jones HP. Epinephrine-primed murine bone marrow-derived dendritic cells facilitate production of IL-17A and IL-4 but not IFN- γ by CD4⁺ T cells. *Brain Behav Immun* 2010;**24**:1126–36.
- Van Loon GR, Appel NM, Ho D. Beta-endorphin-induced increases in plasma epinephrine, norepinephrine and dopamine in rats: inhibition of adrenomedullary response by intracerebral somatostatin. *Brain Res* 1981;**12**:207–14.
- Frank MG, Watkins LR, Maier SF. Stress-induced glucocorticoids as a neuroendocrine alarm signal of danger. *Brain Behav Immun* 2013;**33**:1–6.
- Okuyama K, Dobashi K, Miyasaka T, Yamazaki N, Kikuchi T, Sora I, et al. The involvement of glucocorticoids in psychological stress-induced exacerbations of experimental allergic asthma. *Int Arch Allergy Immunol* 2014;**163**:297–306.
- Blotta MH, DeKruyff RH, Umetsu DT. Corticosteroids inhibit IL-12 production in human monocytes and enhance their capacity to induce IL-4 synthesis in CD4⁺ lymphocytes. *J Immunol* 1997;**158**:5589–95.
- DeKruyff RH, Fang Y, Umetsu DT. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4⁺ lymphocytes by inhibiting IL-12 production. *J Immunol* 1998;**160**:2231–7.
- Miyaura H, Iwata M. Direct and indirect inhibition of Th1 development by progesterone and glucocorticoids. *J Immunol* 2002;**168**:1087–94.
- Wiley RE, Cwiartka M, Alvarez D, Mackenzie DC, Johnson JR, Goncharova S, et al. Transient corticosteroid treatment permanently amplifies the Th2 response in a murine model of asthma. *J Immunol* 2004;**172**:4995–5005.
- Freier E, Weber CS, Nowottn U, Horn C, Bartels K, Meyer S, et al. Decrease of CD4⁺FOXP3⁺ T regulatory cells in the peripheral blood of human subjects undergoing a mental stressor. *Psychoneuroendocrinology* 2010;**35**:663–73.

40. Stock P, Akbari O, DeKruyff RH, Umetsu DT. Respiratory tolerance is inhibited by the administration of corticosteroids. *J Immunol* 2005;**175**:7380–7.
41. Sommershof A, Aichinger H, Engler H, Adenauer H, Catani C, Boneberg EM, et al. Substantial reduction of naïve and regulatory T cells following traumatic stress. *Brain Behav Immun* 2009;**23**:1117–24.
42. Jergović M, Bendelja K, Vidović A, Savić A, Vojvoda V, Aberle NA, et al. Patients with posttraumatic stress disorder exhibit an altered phenotype of regulatory T cells. *Allergy Asthma Clin Immunol* 2014;**10**:43.
43. Vliagoftis H. Psychological stress and asthma: a new enemy within. *Int Arch Allergy Immunol* 2014;**164**:109–11.
44. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–24.
45. Rosenberg SL, Miller GE, Brehm JM, Celedón JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol* 2014;**134**:1009–15.