Review Articles

Contribution of stress to asthma worsening through mast cell activation

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ABSTRACT

Objective: To review the available evidence linking stress to asthma and to investigate whether mast cells contribute to the effect of stress through activation by corticotropin-releasing hormone (CRH).

Data Source: The PubMed database was searched for articles (1998-2011) using the keywords *anxiety, asthma, exacerbation, inflammation, mast cells, socioeconomic status, stress, violence,* and *worsening.*

Study Selection: Articles were selected based on their relevance to the topic, with emphasis on clinical or epidemiologic data linking stress to asthma and studies that offered possible explanations for how stress may affect asthma.

Results: Many articles point to an association between stress (socioeconomic status, interpersonal conflicts, emotional distress, terrorism) and asthma exacerbations but without any distinct pathogenetic mechanism. A few articles have reported reduced circulating cortisol and/or sensitivity to corticosteroids. We propose that mast cells, known to be involved in the pathophysiology of asthma, can be activated by CRH, which is secreted under stress in the lungs, leading to selective release of proinflammatory mediators. This effect may be augmented by neuropeptides or cytokines. CRH also reduces T-regulatory cell production of interleukin 10, which in known to inhibit allergic mast cell activation.

Conclusion: More studies are required to investigate lung levels of CRH and selective mast cell mediators. Reducing stress and using CRH receptor antagonists and/or mast cell blockers may serve as possible new therapeutic approaches for asthma.

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Introduction

Numerous studies have documented an alarming increase in asthma during the last 20 years[1] but without identifying any distinctive pathogenetic triggers.[2] Worse yet, asthma exacerbations continue to elude any definitive explanation and constitute the main reason for asthma-related severity and morbidity.[2,3] A recent review focused on asthma exacerbations but only included brief mention of "psychological factors/stress."[4]

Considerable evidence indicates that stress worsens allergic diseases in general[5–7] and asthma in particular.[8,9] A recent meta-analysis of 43 studies, 90% of which were on asthma, reported a positive association between psychological factors and atopic disorders.[10] Consequently, it is important to attempt to understand how stress influences asthma exacerbations.
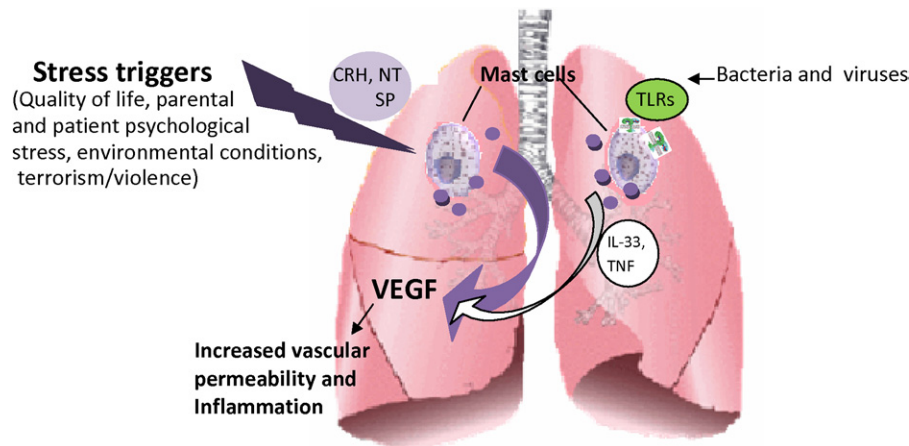
It has been proposed that asthma worsening with stress may be due to a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis,[11] less cortisol production in response to stress in asthmatic patients compared with nonasthmatic controls,[12,13] or cortisol insensitivity due to chronic psychological stress through impaired glucocorticoid receptor expression or function.[14] Moreover, one study showed that children with asthma who experienced acute and chronic stress had a 5.5-fold reduction in expression of glucocorticoid receptor messenger RNA (mRNA) and 9.5-fold reduction in β_2-andrenoreceptor mRNA expression in the peripheral leukocytes,[15] implying that they would be resistant to treatment with the respective drugs. It would be important to extend these findings to other tissues relevant to asthma.

Alternatively, we propose that the effect of stress in asthma may be mediated through activation of mast cells[5,16] (Fig 1) by cortico-

Fig 1. The proposed interrelationships among stress-related neuropeptides, lung mast cells, and proinflammatory molecules in the pathogenesis of asthma.

tropin-releasing hormone (CRH) secreted under stress in the lungs. CRH secreted under stress in the lungs is known to contribute to the pathophysiology of asthma.[17–20]

Data supporting a role of stress in asthma exacerbations

Individual stressors

Increasing evidence suggests that different psychological stressors can worsen or precipitate asthma (Table 1). However, the timing and chronicity of stress, as well as the quality of stress, could yield different outcomes in patients with asthma.[21] It may, therefore, be important to identify asthma subphenotypes that may be more susceptible to stress.[22]

Quality of life. There was an inverse relationship between the socioeconomic status (as characterized by poverty) and pulmonary function and lung inflammation in children with asthma measured after a laboratory stressor.[23] Living in an emergency shelter also increased the incidence of asthma.[24] High caregiver anxiety associated with immigrant status and low income was also linked to increased risk of developing asthma among wheezing infants, as measured by frequency of emergency department visits and hospitalizations.[25]

Psychological status of patients. The strongest evidence comes from an association between worsening emotional status of the patient and an increase in the risk of frequency and severity of asthma attacks. One of the first studies to document such a relationship followed up a group of children with diagnosed asthma for 18 months. They showed that severe psychological events, such as loss of a caregiver or loss of security due to a divorce, significantly increased the risk of an asthma attack within 24 hours if there was also chronic stress.[26] In another prospective study, 32 adults with asthma were followed up for 140 days with daily records, pulmonary function tests, and psychological status tests. A significant positive correlation was found in 50% of patients, implying the possible existence of a susceptible subgroup among relationship stress, anxiety, and worsening pulmonary function.[27]

A comprehensive study was performed with a postal survey on risk factors for asthma and atopic diseases among Finnish first-year university students aged 18 to 25 years. It demonstrated that concomitant personal conflicts increased the risk of asthma, even when adjusted by parental health, education, and passive smoking at an early age.[28] Another study reported that breaking off a life partnership in middle-aged adults led to increased risk of asthma more than twice as much as the general population.[29] A similar relationship was also apparent between patients experiencing panic attacks and asthma.[30] Finally, a study conducted in Russia from 1975 to 2005 showed that there was also a significant association between suicide attempts, as an indicator of stress, and asthma mortality.[31]

Table 1
Examples of sources of stress and the effect on asthma manifestations

Stress type	Pulmonary end point	n	Reference	Year
Quality of life				
Immigrant status	ED visits, hospitalizations due to asthma attacks	177	25	2003
Living in shelters	Parent-reported asthma attacks, ED visits and hospitalization	104	24	2009
Patient psychological status				
Panic attacks	Self-reported asthma attacks and physician-diagnosed asthma	591	30	2005
Loss of family member, divorce	Daily diaries, peak-flow values	90	26	2000
Broken off a life partnership	Self-reported wheezing episodes	4,010	29	2009
Perceived low support from parents	IL-5, IL-6, IFN-γ	143	32	2009
Psychological distress or suicide	Asthma mortality	Not applicable	31	2010
Parent psychological status				
Maternal stress	Risk of asthma	10,667	43	2002
Presence of psychiatric disorder in mother	Prevalence of asthma	1,087	42	2009
Urban lifestyle and environmental noise	Physician-diagnosed asthma	652	34	2008
Stressed caregivers	Higher risk of smoke exposure (high salivary cotinine)	198	40	2011
Violence or terrorism				
After September 11th attacks	Self-reported increase in asthma severity	71,437	35	2002
After September 11th attacks	2005 survey worse asthma	3,664	36	2005
War-related experience	Physician-diagnosed asthma	2,066	38	2010
After September 11th attacks	Lower respiratory symptoms 2 and 4 years after September 11th attacks	Not applicable	37	2003, 2005

Abbreviations: ED, emergency department; IFN-γ, interferon γ; IL, interleukin.

In an attempt to investigate specific mechanisms, a study measured peripheral blood mononuclear cell production of proinflammatory cytokines.[32] There was a strong correlation between children with asthma perceiving low support from their parents, thereby facing greater stress and anxiety, and increased serum levels of interleukin (IL) 5, IL-6, and interferon γ released from peripheral blood mononuclear cells. In another study, airway antigen challenge of college students with mild asthma during both a low-stress phase (midsemester or 2 weeks after final examination) and a stress phase (final examination week) resulted in a significant increase in sputum and airway eosinophils, as well as increased eosinophil-derived neurotoxin and IL-5 levels only during the stress period.[33]

Environmental stressors

Noise. One multicenter, German study investigated the effect of long-term noise exposure on asthmatic and nonasthmatic 12-year-old boys and girls and found a significant association between noise annoyance (particularly at night) with increased physician-diagnosed asthma prevalence in girls but not boys.[34] The authors did not suggest any explanation fro these sex-specific differences.

Violence. Increasing reports indicate an association among anger, violence, and asthma worsening. One study involving a telephone survey conducted among Manhattan residents 5 to 9 weeks after the September 11th attacks found that, among the adult respondents with asthma, 27% reported experiencing more severe asthma symptoms after the September 11th attacks, a significant increase compared with normal seasonal patterns.[35] In another study investigating violence-associated stress, 45% of enrollees in Medicaid managed care residing in New York City, who responded to a survey conducted in 2005, reported worsened asthma after the September 11th attacks.[36] These results were confirmed by another survey of residents in a 1-mile area around World Trade Center 2 and 4 years after the September 11th attacks.[37] However, it should be considered that these individuals, especially in the latter study, were exposed to environmental pollution or debris that could have exacerbated their asthma. Another study of a large sample of patients in Kuwait, who experienced fear for their lives during the Iraqi invasion, reported diagnosis of asthma more than twice as often as civilians 13 years later.[38]

Family or caregiver stressors

There has been some evidence that parental stress could exacerbate other environmental stressors, such as pollution. One study of 2,500 children aged 5 to 9 years with new-onset asthma and no prior history of asthma or wheezing[39] were followed up for 3 years, and a significant correlation was found between high parental psychosocial stress and the effect of traffic-related pollution for asthma incidence. Another study reported that more than half of inner-city children studied were exposed to second-hand smoke and that such children were at significant risk of smoke exposure when their caregivers were depressed or stressed.[40]

In a study of twins in Puerto Rico, both paternal and maternal stress increased asthma morbidity in their children.[41] Presence of minor psychiatric disorders in mothers documented using the 20-item Self-Report Questionnaire (depression, anxiety, somatic disorders, developed by the World Health Organization) was significantly associated with the presence of asthma in their children, 34.4% of whom had atopic and 62.4% nonatopic asthma.[42] In an attempt to identify potential mechanisms, one study also found that maternal stress may be responsible for the immune response involved in childhood asthma.[43]

Mechanistic explanations for the connection between stress and asthma

Large knowledge or data gap

In addition to some evidence of a dysfunctional HPA axis, less cortisol production, and decreased sensitivity to corticosteroids mentioned earlier, a recent article reported that allergic asthma was reduced in CRH$^{-/-}$ mice and concluded that it was due to less cortisol production.[44] Interestingly, another recent article reported that CRH reduces the production of IL-10 from T-regulatory cells[45] in atopic dermatitis and may worsen this condition by reducing the inflammatory effect of IL-10. IL-10 is also inhibitory for mast cells, and its reduction will increase IgE-receptor expression and signaling.[46]

Effect of mast cells on the link between stress and asthma

Mast cells are involved in the pathophysiology of asthma.[17–20] Mast cells derive from a distinct hemopoietic precursor and mature under local tissue microenvironmental conditions.[47] They are necessary for the development of allergic reactions through crosslinking of their surface receptors for IgE (FcεRI),[48] leading to degranulation and the release of vasoactive, proinflammatory, and nociceptive mediators; these mediators include arachidonic acid metabolites, histamine, proteolytic enzymes, and cytokines, such as IL-5, IL-6, IL-13, and tumor necrosis factor (TNF).[47,49]

Cytokines and chemokines elevated in stress. Many mast cell–derived mediators participate in asthma.[50] Moreover, some of these, such as histamine[51] and IL-6,[52] are increased in response to stress. Mast cells also produce IL-33 and worsen allergic inflammation.[53,54] For instance, IL-33 is considered to participate in the pathogenesis of asthma.[55] IL-33[56] can also activate mast cells to release proinflammatory cytokines,[57] increase their production of IL-13,[58] and promote mast cell survival.[58] We showed that IL-33 augments human mast cell release of vascular endothelial growth factor (VEGF) in response to substance P,[59] and mast cells have been considered sensors of cell injury through IL-33.[60] In fact, IL-33 was considered to link dendritic, epithelial, and mast cells in a mouse model of asthma.[61]

Mast cell mediators could also stimulate or augment the stress response. Mast cells can release large amounts of CRH,[62] whereas histamine released after mast cell activation has been shown to increase CRH mRNA expression in the hypothalamus.[63] In fact, hypothalamic mast cell activation stimulated the HPA axis.[64,65]

Selective mast cell mediator release. Asthma is not always of allergic origin,[66] prompting the search for other triggers. A unique aspect of mast cell physiology that had been largely ignored in asthma is that they can secrete specific mediators without degranulation in response to a number of nonimmune triggers.[67] As a result, histologic studies are not likely to show evidence of mast cell activation. For instance, IL-1 can induce selective release of IL-6,[68] and CRH can stimulate selective release of VEGF, which is also proinflammatory and vasodilatory.[69] In fact, mast cells were recently shown to induce vascular leakage in an FcεRI-independent manner.[70] Moreover, viral polynucleotides can stimulate Toll-like receptor 3 to induce selective release of IL-13,[71] whereas bacterial lipopolysaccharide can induce selective release of TNF[72] and IL-1.[73] In fact, Toll-like receptors are increasingly invoked in the development of airway inflammation[74] through regulation of mast cell function.[75] Hence, the responsiveness of lung mast cell to such trigger may be affected by stress.

In addition to any direct effect of mast cell mediators, there could be additional mast cell–dependent actions. Activated mast cells were reported to stimulate T cells through TNF,[47,76] which may respond inappropriately to bacterial or viral infections known to exacerbate asthma.[77] Mast cells could also deliver TNF to the lymph

nodes, further triggering an immune response.[78] Mast cells also augment adaptive immunity by recruiting dendritic cells[79] and by regulating vascular and lymphatic vessels.[80]

How mast cells mediate the effect of stress. Stress typically results in secretion of CRH from the hypothalamus and activates the HPA axis.[81] However, CRH is also released outside the brain, where it has proinflammatory effects[81] through mast cell activation[82] (Figure 1). Some processes active in the lungs may be similar to those that have been described in the skin. For instance, CRH and CRH receptors (CRHRs) are expressed in human skin,[83] which may have its own equivalent of the HPA axis.[84] Stress induces local release of CRH in the skin[85] and stimulates skin mast cells,[86] leading to increased skin vascular permeability.[86] The peptide neurotensin augments the effect of CRH, leading to increased vascular permeability and inflammation in rodent skin.[87] CRH also increases vascular permeability in human skin, an effect dependent on CRHR-1 and mast cells.[88] Moreover, human mast cells express mRNA and protein for CRHR-1,[69] activation of which induces selective release of VEGF.[69]

Even though the effect of stress is obviously not limited only to lungs, there could be reasons why it may manifest primarily in the lungs. First, CRH, neurotensin, and substance P may be released preferentially in the lungs. Second, lung mast cells may express a higher number of CRHRs, making them more likely to respond to CRH than other tissues. For instance, skin biopsy samples from patients with stress-induced alopecia[89] and urticaria pigmentosa[90] were associated with increased expression of CRHR-1. Third, there may be higher expression in the lungs of the structural CRH analogues, the urocortins, which also stimulate mast cells.[91]

Conclusion

Additional studies should measure CRH levels in bronchoalveolar lavage fluid and serum, especially because we recently reported that CRH is increased in the serum of patients with atopic dermatitis,[92] which is often comorbid with atopic asthma.[93,94] Lung CRHR expression should also be evaluated.

Subgroups of asthmatic patients who may respond differently to stressors need to be distinguished. For instance, evidence has indicated an association between genetic polymorphisms with the *CRHR1* gene and lung responses to treatment. In particular, patients with chronic obstructive pulmonary disease with the heterozygous genotype in the minor allele rs242941 in the CRHR-1 sequence responded worse to inhaled corticosteroids than controls,[95] and asthma patients had lower bronchodilator response to albuterol.[96] However, this polymorphism does not provide information on the function of CRH; moreover, poor lung function does not necessarily indicate risk of asthma exacerbations.

Unfortunately, health care professionals rarely consider psychological support as part of guidelines for asthma treatment. For instance, a study in Germany found that 80% of general practitioners believe that stress plays an important role in the etiology of asthma, but only 11% refer their patients for psychological help.[97] Increasing evidence suggests that stress contributes significantly to frequency of exacerbation and/or severity of asthma. We propose that the mast cell is a unique immune cell that could be activated by stress-related triggers and could explain the effect of stress on asthma exacerbations. The multitude of mast cell mediators has given rise to new speculations about the possible role of these cells in inflammatory processes.[5,98–100]

Recognizing and reducing stress, possibly through the use of select CRH antagonists, and blocking stress-induced mast cell activation could be important. Future research should focus on the development of effective CRHRs and mast cell inhibitors.

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