

The Role of Stress in Asthma

Insight from Studies on the Effect of Acute and Chronic Stressors in Models of Airway Inflammation

RATTANJEET S. VIG,^a PAUL FORSYTHE,^b
AND HARISSIOS VLIAGOFTIS^a

^a*Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

^b*The Brain-Body Institute and McMaster University Department of Pathology, Hamilton, Ontario, Canada*

ABSTRACT: Asthma, a chronic inflammatory disease of the airways, is greatly influenced by psychosocial factors and stress. This review looks at clinical studies that have shown strong associations between psychological stress and asthma to identify potential mechanisms for these interactions. Furthermore, we review animal studies involving stress and airway inflammation or airway hyperresponsiveness, and discuss possible mechanisms of stress action in asthma. In conclusion, further research, both in humans and in animal models, into the mechanisms of stress-induced changes in asthma exacerbation are required to help better understand the complex makeup of asthma and assist in the development of therapies directed at the interplay between the nervous system and airway inflammation.

KEYWORDS: asthma; atopy; psychological stress; neuroimmunomodulation; acute stress; chronic stress; animal models; inflammation; disease; clinical studies

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways defined by persistent symptoms of wheezing, chest tightness, coughing, variable reversible airway obstruction, and airway hyperresponsiveness (AHR). Although asthma can be characterized as a syndrome because of its wide variety of pathogenesis and manifestations, the resulting symptoms are largely due to epithelial damage, infiltration of the bronchial mucosa with lymphocytes, eosinophils and

Address for correspondence: Harissios Vliagoftis, 550A HMRC Department of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2S2. Voice: 780-492-9295; fax: 780-492-5329.
e-mail: hari@ualberta.ca

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other inflammatory cells, increased mucus production, and edema that may lead to airway smooth muscle hyperplasia and airway remodeling.^{1,2} Until the inflammatory basis of the disease was described in the second half of the 20th century, asthma was considered as purely or primarily psychogenic, and was commonly referred to as “asthma nervosa.”

A number of observational studies indicate that psychological stress is closely related to asthma severity in both children and adults and may also be involved in the development of the disease. Between 20% and 35% of asthmatics experience exacerbations of their disorder during periods of stress.³ The mental health of asthmatic children is an important predictor of asthma morbidity,⁴ and has been linked to asthma mortality.^{5,6} Psychological distress in children is associated with asthma that is more difficult to manage,⁷ with more frequent and lengthier hospital admissions,⁸ and functional disability.⁹

What is missing from these studies is a clear indication of the mechanism of the interactions between stress and asthma. A workshop by the National Heart, Lung and Blood Institute¹⁰ suggested that the role of psychological stress in asthma should be an area of intense study. Since then, it has been increasingly recognized that psychosocial factors, as an environmental stressor, may have important roles in the severity of asthma symptoms and potentially in the induction of allergic diseases in general. However, to date there is little understanding of the mechanisms of the interaction between stress and the asthmatic response and further studies are needed to elucidate these important pathways.

STRESS

Stress, or the general adaptation syndrome, was first described by Hans Selye^{11,12} as “the state manifested by a specific syndrome, which consists of all the nonspecifically induced changes within a biological system.” Stress is considered the common denominator of all the adaptive reactions in the body, and, as such, stress cannot be directly detrimental for health. The concept that stress in certain cases may precipitate physiological changes leading to disease was first explored by Hans Selye,¹¹ who called that stress “distress.” This stress response may be defined as the psychophysiological reaction to noxious physical or psychological stimuli.

When the body is challenged physically or psychologically, short-term activation of the neuroendocrine and autonomic nervous systems promotes adaptation and survival during the period of challenge. This has been termed *allostasis* meaning literally “reestablishing stability through change.”¹³ During allostasis, physiological systems operate at a higher or lower level than during “normal” homeostasis; for example, emotional distress may lead to elevated heart rate and blood pressure as well as elevated glucocorticoid levels that in turn suppress the production of inflammatory cytokines. Providing allostatic responses are shut off when they are no longer needed, the body is

able to adapt to and survive the immediate challenge without suffering long-term consequences. However, if the same response systems are activated over a longer period of time or remain active when no longer needed, these adaptive changes lead to other consequences, including receptor desensitization and tissue damage that may precipitate or exacerbate disease processes. This has been termed *allostatic load*, and it refers to the price the tissue or organ pays for an overactive or inefficiently managed allostatic response.

In humans, stress can manifest itself in various ways. Acute stress, often dubbed the flight-or-fight response or positive stress, is one where there is a perceived threat or challenge, which requires a small period of time for which to successfully adapt, like an immediate threat of an exam.¹⁴ This stress leads to the immediate activation of the hypothalamic-pituitary-adrenal (HPA) axis. Release of the hypothalamic corticotrophin-releasing hormone (CRH or CRF) stimulates release of adrenocorticotrophic hormone (ACTH) from the pituitary, which in turn promotes the release of corticosteroids from the adrenal cortex.¹⁵ The HPA axis is one of the central mechanisms by which stress, detected by the brain, alters physiological function throughout the body. Acute stressors, via the stimulation of the sympathetic immune system, prepare the body for an immediate response and can lead to beneficial effects.¹⁶ The overall effect of the HPA axis on immune/inflammatory responses is to prevent them from proceeding unchecked by suppressing the response as soon as they begin.

These effects are clinically opposite to chronic stressors, where the presence of a long-term stress maintains the output of stress molecules via the HPA axis and sympathetic stimulation, exhausting the body of its resources.¹⁴ The reference to stress in clinical studies usually refers to chronic psychological stress. These types of stress include reduced social status, death of a friend or family member, loss of a job, long-term anxiety, and depression.

STRESS ON THE IMMUNE SYSTEM

Stress activates a number of biological pathways and has a number of biological effects that may be involved in asthma pathophysiology (FIG. 1). Whether stress activates or inhibits these pathways is often dependent on the duration and quality of the stress stimulus. In this review we will discuss primarily the effects of stress on airway inflammation.

Stress has been shown to have a variety of immunomodulatory effects both positive and negative. There is a substantial volume of literature demonstrating that psychological stress may influence inflammatory and immune cell trafficking, cell proliferation, and cell function including cytokine and inflammatory mediator production. Stress can modulate these responses through nerve pathways that connect the autonomic nervous and the immune systems as well as through the release of hormones and neuropeptides, which have the potential to interact with immune cells.

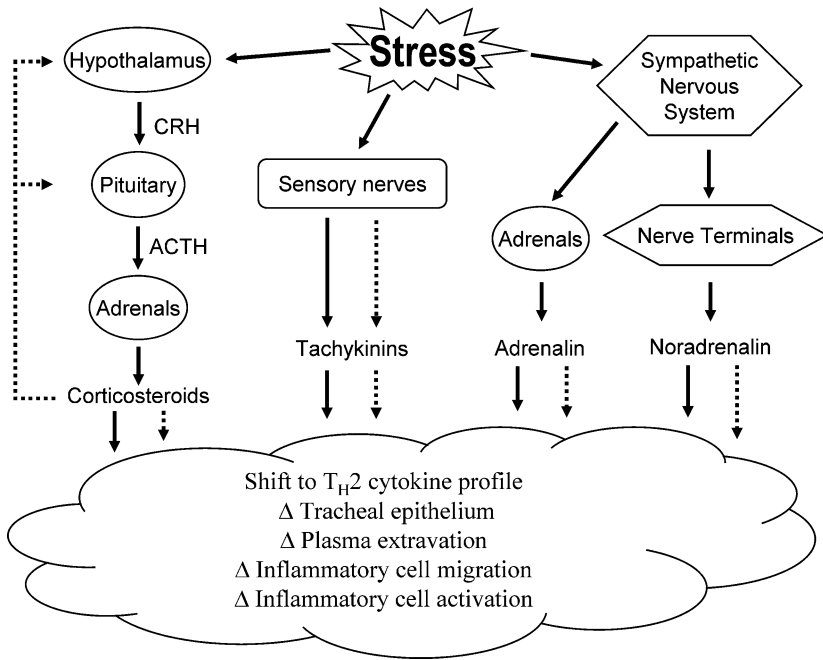


FIGURE 1. Mechanisms of action of the stress response (*solid arrows* indicate stimulation, *dashed arrows* indicate inhibition). The stress response via the brain activates the HPA axis, which produces corticosteroids as the final hormone, and also the sympathetic nervous system. Additionally, stress can induce or inhibit release of tachykinins from primary sensory nerves. The release of these molecules, depending on the duration and intensity of the stress, can exert numerous positive or negative effects on the body.

Acute stress induces an adrenal hormone-mediated redistribution of immune cells from the blood to other compartments of the immune system.¹⁷ There is evidence that immune cells in these cases redistribute to the skin, where they may enhance skin immune function,^{18,19} which is partly mediated by gamma interferon (IFN- γ).²⁰ In a similar fashion, exposure to laboratory stressor tasks for a few minutes has been shown to induce suppression of T cell mitogenesis and increase the number of circulating CD8⁺ and natural killer cells.^{21,22} These effects appear to be mediated by the autonomic nervous system²³ and are associated with alterations in the production of cytokines, such as interleukin (IL)-1- β , IL-2, and IFN- γ .^{24,25}

Although acute stress augments certain immune responses, it has also been shown to inhibit other aspects of the immune response. In humans for example, stress induced by examinations can cause downregulation of T cell function and altered cytokine levels and ratios in human patients.¹⁰ This is due to the shift of the immune response induced by stress from an antibacterial T_H1 response toward a humoral T_H2 response.²⁶

In contrast to the effect of acute stress, which augments immune responses, chronic stress seems to depress the migration of immune cells from the blood,²⁷ an effect that correlates with the attenuation of responsiveness to corticosteroids. Although many of the factors released by the HPA axis remain the same between acute and chronic stresses, the temporal nature of the stress response induces opposite effects in chronic stress as compared to acute stress. These differences may be due to the differing mechanisms that take place with regard to acute and chronic stress states, as well as exhaustion of the body attempting to cope with repeated or chronic stressors.

It has been observed that not all individuals show the same response to stress-induced alterations in immune function. There is some evidence that patients with conditions believed to be affected by stress, such as atopic dermatitis, are more sensitive to stress-induced immune system dysfunction than normal individuals.²⁸

In humans, chronic clinical stress has been shown to play an important role in disease, usually resulting in exacerbation of symptoms, primarily in inflammatory diseases. Mental stress, anxiety, and anger have been found to be positively correlated with cardiac ischemia,²⁹ periodontal disease,³⁰ inflammatory bowel disease,³¹ as well as ulcerative colitis^{32,33} and it is hypothesized to play major roles in autoimmune diseases, such as Graves' disease, multiple sclerosis, rheumatoid arthritis, and others.³⁴⁻³⁷ Chronic stress also promotes lymphocyte apoptosis via a mechanism independent of the HPA axis.³⁸

Working knowledge into the functions of the HPA axis, the primary mechanism whereby the effects of stress are carried throughout the body, has greatly increased only in the last few decades, and, combined with existing knowledge of the sympathetic nervous system, only recently has stress begun to be recognized as a fundamental physiological process that regularly influences well-being and disease states.

HUMAN STUDIES RELATING STRESS AND ASTHMA

Good clinical evidence regarding the effect of stress and asthma is relatively sparse apart from observational and some epidemiological studies. Many of the early studies examined the link between the nervous system and asthma using suggestion (hypnotic or conscious), and they described its effects on asthma symptoms. A review by Isenberg *et al.*³ shows that studies in this field reveal that 35% to 40% of asthmatics develop bronchoconstriction following relevant suggestion or following other stressful stimuli. This effect is greater and more consistent in asthmatics, although even nonasthmatic individuals develop bronchoconstriction as a result of suggestion. Pastorello *et al.* used suggestion to indicate that a saline solution was a bronchodilator or bronchoconstrictor, but found no significant changes in respiratory measures.³⁹ In contrast, a study

in elderly male patients, showed that the recollection of an asthma attack either consciously or through hypnotism, was sufficient to cause a significant rise in minute ventilation.⁴⁰ In some of these studies the effect of suggestion in normal controls was not studied. Despite this important criticism, a number of studies show an increase in airway resistance and reduction in forced expiratory volume following hypnotism and suggestion of anger, fear, and recollection of asthma in adults^{41,42} and children.⁴³

Other prolonged clinical studies in asthmatic patients tend to show similar stress-induced effects. In one set of studies,^{44,45} Sandberg *et al.* followed a large cohort of chronic asthmatic children over an 18-month time course, using a diary system to record positive and negative events, and showed a significant correlation between stressors and the induction of asthma exacerbations. The first study concluded that severe events without the presence of a chronic stress increased the risk of an asthma attack significantly between 2–6 weeks after the event. However, in children with chronic stress, a severe event could precipitate an increased risk of asthma attack within the first 2 weeks. Another study conducted by Smyth *et al.*⁴⁶ also found an association between variable mood states or the presence of stressors with lower peak expiratory volumes in asthmatic patients. Other studies have associated psychological distress in children with asthma that is more difficult to manage,⁷ with more frequent and lengthier admissions to the hospital,⁸ and functional disability.⁹ One of these studies was also able to correlate the length and number of hospitalizations with anxiety, stigma of being asthmatic, neuroticism, and hostility.⁸ Similar findings linking psychological morbidity to asthma mortality in children have been conducted in Australia,⁶ the United States,⁵ and in adults in England.⁴⁷ All of these studies show that stress plays a very strong role in the development of chronic asthma and on the probability, number, and severity of asthma exacerbations. In addition, asthma induces stress and negative emotional responses, which some studies above could correlate with a further deterioration of asthma.⁴⁸

So, is the correlation between stress and asthma a result of asthma inducing negative stress or does stress in fact worsen asthma symptoms? A third form of human studies in this area involves inducing a short-term stress on an individual in an attempt to answer that very question. Asthmatics that are stressed with a method of forced oscillation have significantly higher airway impedance as compared to controls.⁴⁹ Other methods of inducing stress, via an examination or computer puzzle test, have also been used. Adolescent asthmatics undertaking a stressful computer puzzle test have increased breathlessness.¹⁶ Asthmatic students respond to allergen challenge with increased airway inflammation during stressful examination periods compared to low-stress periods.⁵⁰ Other studies are not as conclusive. One paper found no significant relationship between daily life stress and serum IgE levels or bronchial hyperresponsiveness.⁵¹ Studies have shown that stress-induced changes in physiological parameters of breathing may be similar in asthmatic and nonasthmatic children

but these changes may have higher clinical significance in asthmatics due to their higher baseline airway resistance.⁵² Such changes may be the result of differences in coping behavior, as passive stressful tasks like watching bloody surgeries or other stress-inducing videos cause increased airway resistance in asthmatics in comparison to active stressful tasks like arithmetic.⁴¹ Similarly, relieving stress by writing about stressful experiences, a task that helps to improve coping, improves a number of physiological parameters of asthma for long periods.⁵³

Explanations for the purported enhancement of asthmatic symptoms by stress which do not involve directly alteration of airway physiology or inflammation have also been suggested. Stress can change an asthmatic's perception of breathlessness and lead him or her to believe that his condition is deteriorating despite an absence of changes in physiologic parameters of breathing.¹⁶ Additionally, stress might affect self-management strategies and adherence to treatment plans and therefore can lead to deterioration of asthma control during periods of stress. It is also commonly believed that asthma can induce stress in patients, although one study demonstrated that in most patients, asthma exacerbations do not provoke a physiological stressor response.⁵⁴ This is a possible explanation for the observation of Rimington *et al.*⁵⁵ that increases in Hospital Anxiety and Depression scale scores lead to symptom scores above what is expected by lung function and other objective measurements. Finally, psychological stress correlates with an increased risk of acute respiratory infections,^{56,57} which are an important trigger of asthma exacerbation. Although the foregoing explanations are possible, we believe that there is an abundance of epidemiological data to suggest that the regulatory mechanisms affected by stress are more complicated than previously supposed, and directly affect the pathophysiology of the asthmatic response.

Overall, the consensus has emerged that stressful situations and events are affecting the severity of asthma. What is not clear is whether this increased severity of asthma is the direct result of increased inflammation during high stress states or results from other effects of the nervous or endocrine systems directly on pulmonary physiology. The study of Liu *et al.*⁵⁰ shows that stressed individuals have the potential to develop higher degrees of inflammation but did not show any baseline differences between high and low stress states. Several other important questions also remain. Many of the studies above seem to identify only a subpopulation that is more greatly affected by stressors than others. Is this a result of the cumulative effect of stress, or do genetic aspects of the individual make certain individuals more prone to the effects of stress? Does stress only exacerbate existing symptoms, or is it also responsible for the development of atopy in the individual initially? Our ability to answer these questions and determine the mechanisms of stress in human patients is limited beyond the studies that have already been described. In order to see the effect of stress on asthma and be able to discern the mechanisms behind such outcomes, it becomes vital to use animal models.

THE USE OF ANIMAL MODELS TO STUDY THE RELATIONSHIP BETWEEN STRESS AND ASTHMA

Human studies have established the association between stress and immune function. More recent cohort studies are further looking into these effects by collecting more data on these associations. Since human studies are not often suitable to identify the mechanism of these interactions, much of the evidence regarding the pathways of the effects of stress on asthma comes from animal models. Using animal models, the level and type of stress can be controlled and quantified and other interventions can be used to define the desired pathways. Just as in some of the human studies, the animal models of stress can use short-term stressors and chronic or repeated stressors that may have different effects on allergic inflammation.

Short-Term Stress

The literature has provided much insight into the effects of acute stress on allergic inflammation models. Our group, using a Balb/c mouse model of allergic airway inflammation and restraint stress for 1 h per day for three consecutive days, showed a significant reduction in accumulation of inflammatory cells in the BAL, but increased levels of BAL IL-6, IL-9, IL-13, and no change in IL-10 and IFN- γ levels.⁵⁸ The use of a specific corticosteroid inhibitor, RU486, reversed these BAL changes.⁵⁸ It is thus apparent that in this short-term stress model, the elevated levels of corticosteroids in stressed animals (unpublished data) may result in a reduction of inflammatory cell infiltration in the airways and may alter BAL cytokine levels. This observation is supported by the fact that CRH-deficient mice develop increased airway inflammation and elevated IL-4, 5, 13, RANTES, IFN- γ , and Eotaxin BAL levels after OVA sensitization and challenge compared to normal controls.⁵⁹ This effect is believed to be the result of near-absent corticosteroid and catecholamine production from the adrenal gland because of the absence of the stimulus for their release.

Similar to our study, an elevation in corticosteroids is also seen in a rat model of water-avoidance stress, which also results in increased tracheal epithelial short-circuit activity and elevated response to CRH.⁶⁰ This confirms that stress may induce not only inflammatory changes that may affect asthma, but also physiological changes in the airways, which may contribute to it. Another physiological change can be seen in guinea pigs, where injection of CRH, which not only is a stress hormone itself but also an indirect stimulator of corticosteroid release, reduces OVA-induced plasma extravation in guinea pig airways via the inhibition of tachykinin release from primary sensory nerves.⁶¹ These studies, despite using different animal models, together show that short-term stress results in the activation of CRH and corticosteroid release, which reduces inflammation and plasma extravation, and that this mechanism may involve the inhibition of tachykinin release and physiological changes in the tracheal

epithelium. This correlates with the current asthma research into the important role that neuronal and nonneuronal tachykinins play in airway inflammation, mast cell activation, cytokine secretion, bronchial hyperresponsiveness, and mucoid secretion.⁶²⁻⁶⁴

Long-Term Stress

In contrast to short-term stress, chronic or repeated stress induces the reverse phenotype with regard to inflammation in animal models of asthma. Extending the 1-h daily restraint stress to a week in the mouse model we described above, we have shown a significant increase in BAL accumulation of all inflammatory cell types, but with no significant change in the cytokines tested.⁵⁸ A similar result was seen using unavoidable repeated sound stress for 24 h with increased BAL leukocytes (especially eosinophils) and increased airway hyperresponsiveness of tracheal smooth muscle.⁶⁵ However, in contrast to our studies, Joachim *et al.* identified increased AHR in addition to airway inflammation in stressed versus nonstressed controls. The two studies have a number of differences that may explain this discrepancy. Joachim *et al.* evaluated AHR using a different technique, an event that may or may not be involved in the described differences. More importantly, the latter paper used a different background of mice (CBA/J instead of Balb/c). This would indicate that genetic differences may be important for the manifestation of stress-induced or exacerbated asthma and may explain the fact that only a subgroup of patients with asthma experiences increased severity during episodes of stress.³ Also, the stressor in the latter study was of much longer duration compared to the stress in our study. This could indicate that different mediators of stress or different adaptation mechanisms employed, depending on the stressor, may have diverse effects on asthma symptoms.

The effects of long-term stress on airway inflammation have also been replicated in a rat⁶⁶ and a guinea pig model.⁶⁷ The rat model also showed an increase in allergen-induced plasma extravasation in the paw of stressed animals⁶⁶; however, another study of plasma extravasation in the synovium showed that repeated stress induces the opposite response.⁶⁸ This discrepancy may indicate tissue-specific responses to stress or possibly the result of different stress protocols.

These studies have confirmed the predictions from the observational human studies on the effects of stress on asthma. However, the main focus of future studies should be the identification of the pathways mediating these effects. The different response of airway inflammation in long-term stress as opposed to short-term stress models indicates that different mechanisms are at play. Our group has shown that corticosteroids are not involved in the effects of long-term stress on airway inflammation the way they are involved in the effects of short-term stress.⁵⁸ Joachim *et al.* have shown that the long-term stress mechanism likely involves the role of the neurokinin-1 (NK-1) receptor, which is present in the human lung and submucosal glands, in addition to on

mast cells, lymphocytes, and macrophages in rodents.⁶⁷ Substance P is the primary tachykinin that acts on the NK-1 receptor, whose inhibition in a sound stress guinea pig model with a highly specific inhibitor results in ablation of long-term stress-induced effects in the lung.⁶⁷

CONCLUSIONS

Stress is more than a mental construct; it is a physiologically relevant effector that has the capacity to significantly alter the human immune system and possibly airway physiology, and therefore has the potential to affect the development and manifestations of asthma. Studies in humans show the significant role that stress plays in stimulating asthma exacerbations, including negative correlations with important physiological markers of airway function. Discovering that stress does play a significant role in the quality of life of asthmatics is important, as will be discovering the mechanisms behind the negative impact of stress.

It is likely that a wide variety of factors may play a role, including psychological changes in perception of breathlessness¹⁶ and changes in coping behavior in combination with physiological changes, which may include alterations in airway structure or function, immune deregulation, and even possibly changes in smooth muscle reactivity. With many unanswered questions, more research is required to ascertain the exact effect of stress and the mechanisms in play. For example, much of the current research on the topic deals with the importance of stress on those currently diagnosed with asthma. However, stress affects those of all ages, including neonates, children, and even fetuses *in utero*. Stress may have a more profound and permanent impact on lung function and asthma phenotype in these cases. Additionally, while stress influences those with asthma, it is still to be seen whether it plays an important role in the sensitization to allergens or the development of asthma.

Regardless, to discover how stress affects immunity will undoubtedly provide further insights into the crosstalk between the nervous, immune, and endocrine systems and give us a better understanding of the root causes of asthma, and even possibly superior tools with which we can deal with, and hopefully prevent, this costly ailment.

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