The Brain and Asthma: What Are the Linkages?

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Abstract
Stress has been associated as an important contributor to asthma in some patients. The mechanisms, however, which underlie this relationship remain unclear. In this review, the role of stress will be examined in relationship to the development of airway inflammation. As will be discussed, stress may not cause inflammation but enhances its expression when it develops to a second signal. In addition, recent studies using function magnetic resonance imaging (fMRI) have shown that specific circuits in the brain, i.e., anterior cingulate cortex and insula, are activated in relationship and intensity to the development of a late-phase response (LPR) to inhaled antigen, and that these brain signals are predictive and associated with the development of airway inflammation as measured by sputum eosinophils. Finally, in studies with mice, chronic stress enhances airway inflammation to an inhaled antigen, and these effects are associated with the development of corticosteroid unresponsiveness. Collectively, these data suggest that chronic stress enhances asthma severity through a number of novel mechanisms and the resulting increase in severity of asthma may not be responsiveness to standardly used treatments.

Asthma is characterized by reversible airflow obstruction, bronchial hyperresponsiveness, and airway inflammation [1]. Of these characteristics, airway inflammation is central to the pathogenesis and pathophysiology of asthma, as well as being a principal target for treatment. In addition, it is well demonstrated that environmental factors interact with the at-risk host to initiate immune responses that lead to airway inflammation [2–4]. These factors include allergens, respiratory infections, microbes, dietary factors, and stress [5]. Understanding how these factors may affect asthma and its underlying features has provided insight into the pathophysiology of airway dysfunction seen in this disease. Following on this concept, considerable insight has been gained into the pathophysiology of asthma through the study of the influence of respiratory infections and allergic sensitization [6]. In contrast, the role and contribution of stress to asthma has turned out to be a more complex, and at times, confusing
story [7–10] with limited information on how stress affects or interacts with airway inflammation and thus influence asthma.

For many years, the focus on stress in asthma was largely limited to acute events and exploring the interaction of these stimuli on the autonomic nervous system regulation of airway smooth muscle responses, i.e. bronchospasm. These observations were helpful in providing insight into acute dysregulation of airway smooth muscle tone and an ‘attack’ of asthma, but did not fully advance our thinking or provide information on how stress could relate to the persistence and severity of asthma, and, in particular, how airway inflammation would fit into this process. In the past decade, there has been a shift in our thinking and the study of stress, or psychological factors, on asthma from acute responses towards how stress-related events influence airway inflammation and serve to influence the persistence and severity of disease.

This shift in focus has occurred, from my perspective, for a number of reasons. First, a recognition and realization that airway inflammation is a central and critical feature of asthma both at a pathogenetic and pathophysiologic level [2–4]. Second, there has been clarification of differential and distinct effects to acute versus chronic stress on the immune response, and the greater importance of chronic stress to asthma and underlying inflammation. Third, it has become apparent that stress, like other inciters or triggers of asthma, may be primarily a cofactor in the expression of asthma or its severity, and stress by itself may have limited effects on asthma. Fourth, technologic advances now provide tools to identify and measure the myriad of mediators and cells involved in the inflammatory processes; in addition, these products can now be detected and quantitated in relationship to airway dysfunction. Fifth, tools are available to identify the regulatory genetic signals involved in these reactions. Finally, imaging techniques were previously not available to detect central nervous system activation or the pathways activated in association with peripheral responses, in the case of asthma, the airflow obstruction and inflammation, and to link these neurocircuits to the resulting immune function, inflammation, and clinical characteristics. Given these advances, there has emerged significantly greater insight and appreciation of the involvement and integration of emotions, stress, and the nervous system in the pathophysiology of asthma. These advances will be the focus of the following discussion.

**Differences in Acute versus Chronic Stress and Their Potential Role in Asthma** (fig. 1)

Acute stress, or the ‘fight-or-flight’ response, is provoked by the appearance of a sudden, single event and the immediate response of the host to this event; a response which is largely designed for host preservation. Immediately following an acute stressful event, there is the activation of the adrenal gland with a rapid outpouring of catecholamines and corticosteroids. Both of these adrenal mediators are important to host protection and can have profound effects on features of asthma, which include
a relaxation of airway smooth muscle tone by catecholamines and anti-inflammatory actions on phylogenetic cell function by corticosteroids.

Using allergic-sensitized mice, Forsythe et al. [11] compared the effects of acute vs. chronic stress on the airway inflammatory response to an inhaled allergen. In naïve, allergen-sensitized, nonstressed mice, inhalation of ovalbumin caused the mouse to have a significant increase in bronchial alveolar leukocytes in their lavage fluid. In the presence of an acute stress, however, this allergen-provoked increase in leukocytes was significantly suppressed. Using adrenal-cortical blocking agents, the investigators were able to show that cortisol secretion in response to an acute stress prior to the allergen challenge was responsible for suppression of resulting allergic inflammation.

In contrast, when mice were subjected to chronic stress and then challenged with ovalbumin, the increase in airway leukocytes to inhaled allergen was enhanced. Furthermore, with the use of pharmacological probes, the investigators were able to show that cortisol generation did not play a role in regulating this enhanced response to an allergen challenge or was ineffective. They proposed that during chronic stress, the inflammatory response was ‘corticosteroid resistant’. Using chronic stress, Forsythe et al. [11] were able to show that the normal suppression of inflammation found with acute stress was lost because the regulatory effects of corticosteroids were altered from chronic stress.

These animal studies help set the stage for our subsequent discussion and point out how stress, and what kinds of stress, may interact with inflammation in asthma. First, these studies indicate that the type of stress that influences allergic inflammation is important and evidence points to chronic rather than acute events as being most important. Second, chronic stress enhances, but possibly does not cause, inflammation, and its action on inflammation may be more of an ‘adjuvant’ or ‘primer’ than an initiator. Third, the effects of stress can be reflected in respiratory response of the
airway to an allergen challenge with the bronchial recruitment and presence of leukocytes serving as a marker for inflammatory activity. As will be discussed below, this approach can serve as a model for study. Finally, the effects of chronic stress that lead to enhanced allergic inflammation may relate to a loss of a normal corticosteroid-regulating action on leukocytes such that, under chronic stress, these cells become resistant to the anti-inflammatory actions of corticosteroids.

**Fig. 2.** Biology of the airway response to antigen. In some patients with asthma, there is a response to inhaled allergen. The immediate reaction with an acute fall in the FEV₁ is secondary to mast cell activation and its mediators leading to a bronchospastic response. Following this immediate reaction, there is the development of an inflammatory response, reflected by the recruitment of eosinophils, which produces a late-phase reaction with pulmonary obstruction.
bronchospasm and airway inflammation. This model also allows the investigators to examine the effect of a co-factor, i.e. stress, on aspects of the allergic airway response: acute bronchospasm, cellular inflammation, and late phase airflow obstruction. Collectively, this model allows the investigator to parse the effects of a reaction to inhaled allergens on these individual aspects of an allergic response, bronchospasm and inflammation, and determine how co-factors, in our case, stress, affects various aspects of this response.

Using the airway response to an inhaled antigen, we evaluated the effects of chronic stress on allergic inflammation [14]. In initial efforts, we used models of acute stress in relationship to an allergen provocation and did not note enhancement of the underlying inflammatory response (data not shown) or the reaction to the antigen challenge. As a consequence, we shifted our attention to the use of chronic stress and under these conditions to begin to determine and define the effects of stress on airway inflammation in asthma. For study, we used the final examination period of college as a chronic stress stimulus [14]. Final examination time at the University of Wisconsin occurs at the end of each semester and lasts for at least a week. For most undergraduate classes, the final examination is a, if not the, major determinant of a student’s final grade in a class, making this exercise highly important to the semester grade and potentially a source of considerable stress. Furthermore, most students have 4–5 final examinations during this week interval adding to the overall stress load of the individual during this time. As these examinations take place over at least a week, we considered them to be representative of chronic stress.

In this study [14], 20 University of Wisconsin undergraduate students volunteered to participate in our research project where we hypothesized that chronic stress associated with a final examination period would enhance allergic inflammation, and this enhancement could be demonstrated by using an allergen bronchoprovocation challenge as a model to elicit airway inflammation. All participants had asthma, did not take any asthma medications on a regular basis other than an as-needed short-acting bronchodilator, had an allergy to one of three test antigens used for an inhalation challenge (ragweed, cat or house dust mite), had an immediate response to an allergen inhalation challenge (fall in FEV₁ of at least 20%), and were able to produce sputum following saline induction and, in the sputum, demonstrate an increase in eosinophils following allergen challenge. The students underwent two allergen challenges: one during mid-semester (which we referred to as low stress) and one immediately following their last final examination (our stress phase). The order of these challenges was randomized such that one-half of the students had their initial study in the final examination stress phase and the other one-half with an initial study in the low-stress phase at mid-semester.

To determine if there were psychological effects of the final examination, stress-phase, students were asked to evaluate their levels of anxiety and depression. Scores for both anxiety (STAI) and depression (BDI score) showed small, but significant, increases during the stress phase of final examinations. Antigen challenge during
the stress-phase was associated with a significantly greater recruitment of leukocyte recruitment to the airway as measured in the induced sputum sample (fig. 3). The increase in leukocytes recruited to the airway during the stress phase was reflective of a greater proportion of these cells being eosinophils. Prior to the antigen challenge, the number of leukocytes and eosinophils were the same as the pre-stress-phase values suggesting that the effects of chronic stress on underlying airway inflammation in these students were largely on recruitment of cells at the time of the allergen challenge and stress, by itself, had not changed baseline levels of inflammation.

Blood samples had also been obtained in relationship to levels of stress. Interestingly, we found an increase in circulating eosinophils during the stress-phase and prior to challenge. Although not proven, these observations suggest that stress, by itself, had led to an increase in circulating eosinophils. Whether this was a result of stress stimulating the bone marrow to selectively release more eosinophils was not established but compatible with current information [15]. When a provocation of the airway in allergic subjects occurred with an antigen challenge, there were more eosinophils available in circulation to be recruited to the airway, and this was reflected by an increase in sputum eosinophils. It was almost like stress ‘primed the pump,’ in this case an increase in circulating eosinophils, for a greater response to a subsequent stimulus of asthma. Coinciding with this observation and, as a speculation to the cause of the increase in circulating eosinophils, was the finding that the ratio of interferon (IFN)-γ to interleukin (IL)-5 had shifted more towards a Th2 pattern. Collectively, these data suggest that chronic stress may affect asthma, and allergic inflammation, by causing a shift towards a greater Th2-like status, thus allowing for a greater inflammatory response with activation of asthma. The signals associated with stress that increased

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**Fig. 3.** The effect of stress from final examinations on sputum markers of inflammation. Sputum was obtained at baseline prior to antigen challenge and then again at 6 and 24 h postprovocation and 7 days later (n = 20). Reprinted with permission from Liu et al. [14]. □ = Low stress phase; ■= high stress phase; ** = p < 0.01, vs. baseline; † = p < 0.05; ‡ = p < 0.01, stress vs. low-stress.