Stress and Atopic Disorders: Asthma and the Seasonal Allergic Response

Rosalind J. Wright
Harvard Medical School

Sheldon Cohen
Carnegie Mellon University, scohen@cmu.edu

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Stress and Atopic Disorders: Asthma and the Seasonal Allergic Response

Rosalind J. Wright, M D MPH
Sheldon Cohen, PhD

Educational Objectives
Upon completion of this Cyberounds®, the participant should be able to:

• Define atopy and give examples of three associated clinical disorders
• Describe the effects of stress on neuroimmunoregulation and the consequent modulation of the hypersensitivity response
• Describe the pathophysiology of chronic stress and effects on the HPA axis
• Describe local pulmonary interactions between the immune system and autonomic nervous system in the response to stress
• Describe relationships between psychological stress and oxidative stress
• Describe the potential role of stress and glucocorticoid resistance in asthma
• Describe genetic modification of the risks of psychological stress and asthmatic expression
• Discuss treatment strategies for modifying the relationship between stress and the immune response

Atopy can be considered a genetically and environmentally determined predisposition to a number of clinically expressed disorders including allergic rhinitis (AR), atopic dermatitis (AD) or eczema, and allergic asthma (AA) regulated through immune phenomena in which many cells (i.e., mast cells, eosinophils, and T lymphocytes) and associated cytokines, chemokines and neuropeptides play a role. Overlapping mechanisms of inflammation central to the pathophysiology of these atopic disorders involve a cascade of events that include the release of immunologic mediators triggered by both immunoglobulin E (IgE)-dependent and -independent mechanisms. Biological hypersensitivity to environmental stimuli is a fundamental feature of atopy. Increasingly, atopy has been conceptualized as an epidemic of dysregulated immunity. The exploration of host and environmental factors that may alter immune expression and potentiate the expression of atopic disorders is an active area of research.

Mechanisms linking psychological stress, personality, and emotion to neuroimmunoregulation as well as increased risk of atopy have been increasingly elucidated. Hormones and neuropeptides released into the circulation when individuals experience stress are thought to be involved in regulating both immune-mediated and neurogenic inflammatory processes. Dysregulation of normal homeostatic neural, endocrine, and immunologic mechanisms can occur in the face of chronic stress leading to chronic hyperarousal and/or hyporesponsiveness that may impact atopic disease expression. This Cyberounds® will discuss our understanding of the role of psychological stress in atopy. Stress may have independent effects but also may play a role through the enhancement of neuroimmune and hypersensitivity responses to other environmental factors operating through similar pathways.

Q1. Biological hypersensitivity to environmental stimuli is a fundamental feature of atopy predisposing to a number of clinically expressed disorders including allergic rhinitis (AR), atopic dermatitis (AD) or eczema, and allergic asthma (AA).

☐ True
☐ False

Psychological Stress and the Endocrine System
Psychological stress has been associated with the activation of the sympathetic and adrenomedullary (SAM) system and the hypothalamic-pituitary-adrenocortical (HPA) axis (as discussed in previous Cyberounds, the nervous system is the interpreter of which events are "stressful" and determines the behavioral and physiological responses to the stressor). Negative emotional responses to environmental stressors disturb the regulation of the HPA axis and the SAM systems; that is, in the face of stress, physiological systems may operate at higher or lower levels than during normal homeostasis. It is the disturbed balance of these systems that is relevant to disease. Immune, metabolic, and neural defensive biological mechanisms important for the short-term response to stress, may produce long term damage if not checked and eventually terminated. The potential detrimental cost of such accommodation to stress has been conceptualized as allostatic load, (i.e. wear-and-tear from chronic under- or overactivity of the allostatic system). For example, shifts in the circadian rhythm of cortisol have been found among persons under chronic stress.

A number of altered neuroendocrine and immune changes in response to stress have been demonstrated in subjects with AD, i.e., altered responsiveness of the HPA axis and the SAM system, increased eosinophil counts and elevated IgE expression. More recently increased responsiveness of the HPA axis in response to a heel prick stressor in newborns with a family history of atopy or elevated levels of cord blood IgE has been demonstrated. Whether the altered HPA responsiveness will lead to increased risk of developing atopy in later life remains to be seen.

Allergen-mediated inflammation with T lymphocyte activation is central to the allergic asthmatic response. In one working paradigm T-helper (Th) cells have been phenotypically divided into two profiles of differentiated cell function having different profiles of cytokine release upon activation (e.g., Th1 and Th2). Th1 cells tend to express interleukin-2 (IL-2) and interferon gamma (IFN-γ) and Th2 cells tend to express IL-4, IL-5, and IL-13. Allergy and asthma expression may also be influenced by cytokines produced through pathways or inflammatory processes not necessarily directly related to the Th1:Th2 dichotomy. For example, some proteins are secreted both by Th1 and Th2 cells [e.g., tumor necrosis factor alpha (TNF-α)]. Studies suggest that TNF-α, produced by both lymphocytes and macrophages, is involved in the atopic response. Activation of Th2 lymphocytes underlying allergen sensitization is associated with increased IgE production through release of Th2 cytokines. Seroepidemiological studies have shown an association between increased total IgE levels in early childhood and allergic asthma which increases in magnitude and significance over the first four to six years of life.

Recent animal data suggest that increased maternal stress prenatally is associated with an elevated cortisol response to stress in the newborn affecting Th1 /Th2 cell differentiation. While the ability to activate an increase in cortisol in response to some stimuli in early life may be adaptive, prolonged exposure to stress may change the cortisol response if examined at a later developmental stage. Chronic stress may induce a state of hyporesponsiveness of the HPA axis whereby cortisol secretion is attenuated, leading to increased secretion of inflammatory cytokines typically counterregulated by cortisol. A state of stress induced HPA hypo responsiveness has been demonstrated in some research subjects with chronic inflammatory disorders including atopic disorders. An attenuated cortisol response has been found among adolescents with positive skin test reactivity and a clinical history of allergic rhinitis, atopic dermatitis, or asthma compared with those with skin test positivity alone or nonatopic individuals. Further studies are needed to examine relationships between individual patterns of cortisol response to stress across different developmental periods and the subsequent expression of atopy.

Other regulatory pituitary (i.e., corticotrophin) and hypothalamic hormones [i.e., corticotrophin releasing hormone, (CRH) and arginine vasopressin (AVP)] of the HPA axis have systemic immunopotentiating and proinflammatory effects. For example, acute psychological stress (for example, immobilization in rats) results in skin mast cell degranulation, an effect inhibited by anti-CRH serum administered prior to stress. Mast-cell mediators, in turn, are responsible for many of the immediate symptoms of nasal allergy and manifestations of atopic dermatitis. Mechanisms linking stress and mast cell function have
been extensively reviewed recently\textsuperscript{25}. Although hormones of the sympathetic and adrenal medullary and HPA systems are those most often discussed as the biological substances involved in stress responses, alterations in a range of other hormones, neurotransmitters, and neuropeptides found in response to stress may also play a part in the health effects of stress and need to be further studied. For example, stressor-associated increases in growth hormone and prolactin secreted by the pituitary gland and in the natural opiate beta-endorphins and enkephalins released in the brain are also thought to play a role in immune regulation\textsuperscript{26}.

Q2. Shifts in the circadian rhythm of the HPA axis may influence the expression of atopic disorders.
- True
- False

Q3. Chronic stress may induce a state of imbalance of the HPA axis whereby cortisol secretion is attenuated or increased, leading to increased secretion of inflammatory cytokines typically counterregulated by an optimal level of cortisol in the body.
- True
- False

**Stress and Autonomic Control of Airways**

The balance between functional parasympathetic and functional sympathetic activity in relation to stress, emotional stimuli, and immune function may also be important for the expression of asthma and allergic rhinitis. Local interactions between the immune system and the autonomic nervous system are only partially understood\textsuperscript{27}. Increased activity of the parasympathetic nervous system was once thought to be the dominant mechanism responsible for the exaggerated reflex bronchoconstriction (airway narrowing) that occurs in asthmatic subjects, although more recent work challenges this idea\textsuperscript{28}. In the initial phases, narrowing of the airways in asthma is thought to result primarily from inflammation. Evidence suggesting a number of cholinergic anti-inflammatory pathways triggered through vagus nerve activation including inhibition of macrophages and secretion of TNF-alpha\textsuperscript{29} complicate our understanding and need to be explored in the context of atopy.

More recent evidence demonstrating nerve-mast cell communication in response to stress and the potential import of these interactions in the respiratory system suggests this may be a fruitful area of research relative to stress and allergic asthma\textsuperscript{30}. Tachykinins derived from e-NANC nerves influence airway smooth muscle contraction, mucus secretion, vascular leakage, and neutrophil attachment. In experimental studies, tachykinins, especially substance P, have been linked to neurogenic inflammation\textsuperscript{31} and regulation of stress hormonal pathways\textsuperscript{32} as well as being implicated in asthma\textsuperscript{33,34} and neurogenic skin disorders\textsuperscript{35}. Recent data from a mouse model suggested that stress-induced airway hyperreactivity and enhanced allergic inflammation (OVA sensitization) was mediated by tachykinins\textsuperscript{36}.

**Stress and Immune Function**

Atopic inflammation is thought to be orchestrated by activated T-lymphocytes and the cytokines they produce. The T helper cell Th-2 cytokine phenotype promotes IgE production, with subsequent recruitment of inflammatory cells that may initiate and/or potentiate allergic inflammation\textsuperscript{6}. For most children who become allergic or asthmatic, the polarization of their immune system into an atopic phenotype probably occurs during early childhood\textsuperscript{37}. These findings have sparked vigorous investigation into the potential influence of early life environmental risk factors for asthma and allergy on the maturation of the immune system, in
the hopes of understanding which factors will potentiate (or protect from) this polarization. There is evidence that parental reports of life stress are associated with subsequent onset of wheezing in children between birth and one year\(^{38}\). This relationship led to speculation that stress may trigger hormones in the early months of life which may in turn influence Th-2 cell predominance, perhaps through a direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of differentiation. Further examination of the relationships between caregiver stress on markers of early childhood immune response including IgE expression, mitogen- and allergen-specific lymphocyte proliferative response, and subsequent cytokine expression (INF-\(\gamma\), TNF-\(\alpha\), IL-10, and IL-13) was carried out in the same prospective birth-cohort mentioned above when the children were 2-3 years of age\(^{39}\). In adjusted analyses, higher caregiver stress in the first 6 months after birth was associated with increases in the children’s allergen-specific proliferative response (a marker of the allergic immune response), higher total IgE levels, and increased production of TNF-\(\alpha\) and reduced INF-\(\gamma\).

This sort of pattern deviates from the working Th1/Th2 paradigm. These data suggested to us that although the Th1-Th2 paradigm remains an important functional dichotomy to consider when interpreting quantitative differences in cytokine expression in response to environmental stimuli like stress, examination of other mechanisms (e.g., oxidative stress pathways, innate immune factors, neural-immune interactions) or a broader range of cytokines produced by cells both within and outside the immune system may better delineate the true complexity of the underlying mechanisms linking stress to allergic sensitization and asthma. Overlapping evidence points to some other mechanisms as discussed in the remainder of these Cyberounds\(^{\text{®}}\).

**Stress and Glucocorticoid Resistance**

An alternative hypothesis linking stress, neuroendocrine and immune function and inflammatory disease expression considers a glucocorticoid resistance model\(^{40}\). As we have come to understand the central role of airway inflammation and immune activation in asthma pathogenesis, asthma treatment guidelines have focused on the use of anti-inflammatory therapy, particularly oral and inhaled glucocorticoids or steroids. Asthmatics, however, have a variable response to glucocorticoid therapy\(^{41}\). Although the majority of patients readily respond, a subset of patients have difficult to control asthma even when treated with high doses of oral steroids. Our current understanding of the cellular and molecular mechanisms underlying steroid resistance in asthma and other inflammatory diseases have been recently reviewed\(^{42}\). Notably, the majority of subjects with glucocorticoid resistant or glucocorticoid insensitive asthma have an acquired form of steroid resistance thought to be induced by chronic inflammation or immune activation. Thus it is important to investigate those factors that may potentiate the development of functional steroid resistance so that we might intervene to prevent or reverse it. For example, studies have shown that allergen exposure effects glucocorticoid receptor binding affinity in T lymphocytes from atopic asthmatics\(^{43}\). It has been proposed that chronic psychological stress, resulting in prolonged activation of the HPA and SAM axes, may result in a counterregulatory response in stimulated lymphocytes and consequent downregulation of the expression and/or function of glucocorticoid receptors leading to functional steroid resistance\(^{40}\).

**Psychological Stress and Oxidative Stress**

Another possible mechanism linking stress to atopy and asthma is through oxidative stress pathways. A central feature of inflammation is that it is frequently mediated by reactive oxygen species (ROS), either acquired exogenously or as byproducts of normal metabolism. Individuals differ in their ability to deal with oxidant burdens, either due to genetic factors or other environmental factors that induce or augment oxidative stress. It has been proposed that differences in host detoxification provide the basis for either resolution or progression of inflammation in atopic individuals once exposed to an environmental trigger. It has been speculated that the inability to detoxify ROS species among atopic subjects leads to the release of chemotactic factors, the activation and recruitment of immune effector cells, prolonged inflammation, and the stimulation of bronchoconstricting mechanisms\(^{44}\). Suggested
factors which predispose susceptible subjects to allergic inflammation and asthma include chronic exposure to oxidative toxins (tobacco smoke, air pollution). An extension of the oxidative stress hypothesis is that psychological stress may be an additional environmental factor that augments oxidative toxicity and increases airway inflammation.

There is evidence that psychological stress has pro-oxidant properties that augments oxidative processes\(^{45,46,47}\). Irie and colleagues\(^{48}\) used classical conditioning to illustrate the role of chronic stress and oxidative damage. In these experiments, rats treated with ferric nitrilotriacetate, an oxidant, and conditioned to associated treatment with taste aversion therapy, had increased 8-OhdG with further taste therapy than unconditioned animals.

Evidence also supports the notion that psychological stress modifies the host response to other inflammatory oxidative toxins\(^{49,50,51,52}\). Recent animal data support a role for oxidative/antioxidative imbalance influencing a shift toward a Th2 phenotype in a model of autoimmunity in the rat\(^{53}\).

Environmental exposures that may interact with stress through these pathways include air pollution and tobacco smoke. While epidemiologic evidence suggests that asthma symptoms can be worsened by air pollution, air pollution has not been clearly associated with increased risk of sensitization and induction of disease\(^{54}\). Several investigators have suggested that the ability of air pollution to generate reactive oxidative species may explain its role in asthma and other respiratory diseases\(^{55,56,57}\). Ultrafine particles (<0.1 micron in diameter) have been demonstrated to increase oxidatively mediated inflammation in the lungs of rats\(^{58,59}\). In vitro studies demonstrate that PM10 is responsible for the production and release of inflammatory cytokines by the respiratory tract epithelium as well as the activation of the transcription factor NF kappa B and that these properties are mediated by the production of reactive oxygen species\(^{59}\). Air pollution contains other oxidative toxins, such as reactive quinones and polycyclic aromatic hydrocarbons\(^{57}\). Tobacco smoke also contains a number of compounds with oxidative potential, at least 50 of which are pro-carcinogens\(^{60}\). These include polycyclic aromatic hydrocarbons (PAH)\(^{56,61,62}\). Elevated levels of biomarkers linked to oxidative stress have been found among smokers relative to nonsmokers\(^{63,64}\). Young children are exposed to environmental tobacco smoke have increased levels of 8-OhdG, a biomarker of oxidative toxicity in infants\(^{65}\). Factors which produce oxidative stress (including psychological stress) are likely to be synergistic in their effects on adverse health outcomes\(^{49}\). Given that both tobacco smoke and air pollution contain toxins metabolized by enzymatic biotransformation to generate ROS, stress may interact with these exposures to augment oxidative toxicity leading to increased expression of asthma and allergic rhinitis\(^{6}\).

Q4. The effects of environmental toxins (air pollution, tobacco smoke) on atopy and asthma may be mediated by the common pathway of oxidative stress, a process that may be potentiated by chronic psychological stress.

- True
- False

**Genetics**

Most advances in our knowledge of the genetic and molecular events underlying the neurobiology of the stress response have occurred in animal models\(^{66}\). These animal data together with the preliminary discussions started above suggest that studies to determine the role of genetics in modifying the risk of the social/physical environment experienced through psychological stress may further inform pathways through which stress may impact asthma expression. Genetic factors of potential import include those that influence immune development and airway inflammation in early life, corticosteroid regulatory genes, adrenergic system regulatory genes, biotransformation genes, and cytokine pathway genes.
A recent review summarized studies that address the question to what extent genetic factors contribute to interindividual differences in HPA axis activity. A number of studies demonstrate the influence of genetic factors on variation in the cortisol awakening response and baseline cortisol levels in both adults and children. Other studies strongly suggest that genetic factors contribute to variability in cortisol response to stress. Variants of the glucocorticoid receptor (GR) gene may contribute to interindividual variability in HPA axis activity and glucocorticoid sensitivity in response to stress. In a recent study examining the impact of the three GR gene polymorphisms, BclI, N363S, and ER22/23EK on cortisol response to psychosocial stress, Wust et al. found that compared to subjects with the wild-type GR genotype (i.e., BclI CC and N363S AA, n = 36), 363S allele carriers showed significantly increased salivary cortisol responses to stress, whereas the BclI genotype GG was associated with a diminished cortisol response. Additional presumably good candidates include polymorphisms in the genes coding for factors involved in the feedback mechanisms in the glucocorticoid response to stress such as corticotrophin-releasing hormone (CRHRI and CRHR2), tumor necrosis factor alpha (TNF-alpha), and other cytokine loci. Studies suggest that TNF-alpha is involved in the atopic response. In addition, genetic polymorphisms of the TNF-alpha promoter region have been linked to differential risk for asthma. Pro-inflammatory cytokines (including TNF-alpha) are considered the principal messengers between the central nervous system (CNS) and immune system in the biological stress response. Elevated TNF-alpha can activate the HPA axis and has been associated with increased cortisol. In chronic stress, more persistently elevated TNF-alpha may result in dysregulation of the HPA axis, which may in turn play a role in the development of childhood asthma. Moreover, many effects of TNF-alpha are mediated by the induction of a cellular state consistent with oxidative stress. A recent study examined polymorphisms of the TNF-alpha promoter region (TNF-alpha308G/A) and linked specific variants to increased C-reactive protein (CRP), a proinflammatory marker. By considering genetic factors that may be relevant to both the stress response and asthma, we may better elucidate the mechanisms underlying the link between stress, the HPA axis, and HPA-related clinical states (e.g., asthma/atopy).

Genes expressed in the lung involved in determining the effects of oxidative stress, specifically the glutathione S transferases, have been found to be functionally and clinically significant in recent studies related to atopic risk. Specific GSTP1 variants have been associated with increased histamine and IgE responses to air pollution oxidants and allergen in vivo. Maternal genetics related to oxidative stress genes may influence the child’s atopic risk beginning in utero. The fetal immune response is influenced prenatally. Seasonal sensitization of cord blood mononuclear cells to pollens has been demonstrated.

**Stress and Dysbiosis**

Recently there has been growing interest in the integrity of the indigenous microflora of the gastrointestinal tract in early life and the relationship to atopic disorders. Epidemiological and clinical studies suggest that non-pathogenic microbes including Lactobacillus in the gut play a role in the maturation of the immune system toward a nonatopic phenotype. Intestinal dysbiosis, or alterations in the integrity of indigenous microflora in the GI tract is now believed to be a contributing factor to atopic diseases among others. Factors including antibiotics, psychological and physical stress, and dietary components have been found to contribute to intestinal dysbiosis. A number of prospective intervention studies modifying the gut flora from birth have yielded results supporting the notion that this may be a promising approach to primary prevention of atopy in the future. Studies have shown that psychological and physical stress may disrupt the normal balance of intestinal microflora that may contribute to later disease. A recent experiment showed that separation of infant monkeys from their mothers, a psychological stressor, was associated with a significant decrease in protective fecal flora, particularly Lactobacilli. This same group demonstrated that this influence may begin even before birth documenting alteration in the intestinal microflora in newborn and infant monkeys when their mothers were exposed to an acoustical startle stress paradigm during pregnancy.

Evidence suggests that shifts in the population dynamics of enteric bacteria can be modulated by psychological stress. Stress results in increased bacterial adherence and decreased luminal
lactobacilli in the gut. These data suggest another pathway through which stress may be operating to influence risk for atopy.

Insights from Psychological Intervention Studies

Clinical studies demonstrating the efficacy of alternative modalities that reduce stress and alter mood states in treating atopic disorders add further support to the hypothesized link with stress and suggest alternative treatment approaches. These have been reviewed elsewhere. The mind-body paradigm linking psychological stress and affective states to asthma morbidity provides a useful framework to explore plausible mechanisms through which psychological interventions may be operating.

Evidence from overlapping research buttresses the notion that psychological interventions aimed to reduce stress and modify mood states influence asthma expression. Studies have demonstrated that the relaxation response is related to decrease in negative affective states, sympathetic nervous system activity, immune function, and circulating cortisol levels in healthy adult subjects. A meta-analysis of clinical outcome studies of autogenic training and asthma demonstrated effects on mood states, cognitive performance, and physiological variables. A recent meta-analysis provides the most thorough review of the evidence linking a range of psychological interventions to modulation of the human immune response. These authors found the most consistent evidence for hypnotic suggestion and conditioning interventions being linked to immune modulation.

Summary

Although the Th1-Th2 paradigm remains an important functional dichotomy to consider when interpreting quantitative differences in cytokine expression in response to environmental stimuli like stress, examination of other mechanisms (e.g., oxidative stress pathways, neural-immune interactions, intestinal dysbiosis) or a broader range of cytokines and neuropeptides produced by cells both within and outside the immune system may better delineate the true complexity of the underlying mechanisms linking stress to allergic sensitization and asthma. Psychological stress should be conceptualized as a social pollutant which can be ‘breathed’ into the body and disrupt a number of physiological pathways similar to how air pollutants and other physical toxicants may lead to increased risk for atopy. Stress may have independent effects but also may play a role through the enhancement of neuroimmune responses to other environmental factors operating through similar pathways.


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