

POINT OF VIEW

The causal relationship between stress and asthma

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Although the clinical assumption of an association between stress and asthma morbidity is longstanding, evidence of its existence is fairly recent. Improvements in our understanding of both stress system activity and asthma pathophysiology have pointed to this association as a complex neuroendocrine-immune system interaction¹.

The stress and immune systems play a crucial role in maintaining homeostasis. The stress response is coordinated and mediated by the centres of the stress system in the brain, along with their respective peripheral limbs. Activation of the central stress system leads to the secretion of corticotropin-releasing hormone (CRH), and hence to the stimulation of pituitary adrenocorticotrophic hormone (ACTH) and adrenocortical glucocorticoid secretion. In addition, stress system activation leads to the stimulation of the systemic sympathetic and adrenomedullary nervous systems, and thus to the peripheral secretion of norepinephrine (NE), epinephrine (E), and several neuropeptides².

The immune system is responsible for the defence against different injurious agents. Once the magnitude of the immune response exceeds a certain threshold, activation of the stress response occurs, and its effects antagonise or potentiate those of the

immune response. Whether stress activates or inhibits these immune responses is often dependent on the duration and quality of the stress stimulus³.

The principal peripheral stress hormones, glucocorticoids and catecholamines (NE, E), affect major immune functions. Recent evidence indicates that stress hormones influence the immune response in a multi-dimensional manner; both glucocorticoids and catecholamines systemically mediate the shift towards a T helper-2 (Th2) response by suppressing antigen presentation and Th1 production and by up-regulating Th2 cytokine production. On the other hand, in certain local responses and under certain conditions, stress hormones may actually facilitate inflammation via redeployment of immune cells, induction of TNF- α , IL-1, IL-6, IL-8, and C-reactive protein production or through activation of the CRH-substance P-histamine axis. Therefore, it is becoming increasingly clear that stress hormone-induced inhibition or upregulation of the systemic or local pro- and anti-inflammatory mediator production as well as Th1/Th2 balance may affect disease susceptibility and outcome^{2,4}.

Data from animal models clearly indicate that stress may produce a marked increase in allergen-induced airway inflammation⁵. It appears that different mechanisms in acute versus chronic stress influence the inflammatory responses of the airway. In acute stress, activation of the hypothalamic-pituitary-adrenal (HPA) axis and consequent cortisol release lead to reduction of airway inflammation. Conversely, after repeated exposure to stress (chronic stress) HPA axis activity is suppressed and its anti-inflammatory effect is reduced, allowing exacerbation of the chronic airway inflammatory responses⁶.

Clinical data indicate that exposure to stress in early development results in functional changes in im-

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mune reactivity of susceptible children, thus potentiating the inflammatory response. A recent meta-analysis of 34 prospective cohort studies by Chida et al.⁷ investigated the influence of psychosocial factors on atopic disorders; the major atopic disease assessed was asthma (90.7 %), followed by allergic rhinitis (4.7 %), atopic dermatitis (2.3 %), and food allergies (2.3 %). Overall the meta-analysis revealed a positive association between psychosocial factors and future atopic disorder. More notably, the subgroup analysis of healthy and atopic populations showed that psychosocial factors had both an etiological and a prognostic effect on atopic disorders. In their conclusions the authors suggested the use of psychological interventions in addition to the conventional physical and pharmacological interventions in order to successfully prevent and manage atopic disease. Therefore, allergy can be regarded as the *allostatic* or, more correctly, *cacostatic load*, i.e. the disease burden or cost the body has to pay in order to maintain stability outside the normal homeostatic range (*allostasis* or, more correctly, *cacostasis*)¹.

The findings that chronic stressors facilitate exacerbations of childhood asthma are supported by more recent observational studies on the role of the social environment in children and adolescents with asthma⁸; in addition, victimisation and missed school because of “feeling unsafe” are important but poorly understood risk factors for asthma morbidity that pertain to a large population of children and adolescents⁹.

In line with the above mentioned clinical observations, a series of recent findings have formed the basis for the “hypothesis of foetal programming” of asthma; this hypothesis proposes that stress experienced during pregnancy may lead to vulnerability of the immune system towards atopic diseases and asthma. In an experimental setting Pincus-Knackstedt et al.¹⁰ showed that stress during pregnancy aggravates asthma of the offspring in later life by greatly modifying the immune response to allergens and impairing lung organogenesis. A birth cohort study in Manitoba, Canada, using health care and prescription databases, assessed the association between maternal distress during the first year of life and onward, and asthma at the age of 7 years. An increased risk of childhood asthma among children exposed to continued maternal distress from birth until 7 years of age was demonstrated. Exposure to maternal depression and anxiety limited to the first year of life did not have a demonstrable association with subsequent asthma¹¹.

In the acute setting, viral infection of the respiratory tract constitutes not only the most common precipitant of asthma exacerbations but may also induce non-

specific airway hyperresponsiveness in allergic or even non-allergic children. Consequently, the attenuated host defense responses to viral infection under stress conditions may facilitate airway reactivity, therefore enhancing childhood asthma exacerbations¹².

In addition to the evidence from animal experiments which have suggested that early psychological and physical stress aggravates asthma later in life by inducing hyporesponsiveness of the HPA axis, human studies have also shown that various stressors during the early part of a child's life may affect the HPA axis and result in dysregulation of the immune system, leading to the development of asthma¹. Low HPA axis activity in allergic patients has been reported in a large number of clinical studies. Initially, research focused on the HPA axis of asthmatics who were on long-term treatment with inhaled corticosteroids (ICS); however, a growing number of studies have subsequently recognised that allergic/asthmatic patients, who were not treated with ICS, were also likely to have an attenuated activity and/or responsiveness of their HPA axis¹³.

Buske-Kirschbaum et al. found that children with allergic asthma showed significantly attenuated cortisol responses to psychosocial stress when compared with matched healthy controls, pointing to a dysfunction of the HPA axis in patients with this disorder¹⁴. Our group reported the results of a prospective 12 month study of a cohort of 41 pre-adolescent asthmatic children who were placed on long-term treatment with inhaled budesonide and followed by serial low-dose synacthen tests. Approximately 10 % of our cohort had a low adrenal reserve before starting any ICS treatment. These patients and more than half of the remaining cohort, showed improved adrenal responses while receiving long-term ICS¹⁵. These findings support the concept that chronic allergic disease, regardless of the organ affected, may be associated with reduced activity and/or responsiveness of the HPA axis. Production of certain allergic inflammation-related cytokines may blunt the response of the HPA axis to both inflammation and acute stress, thus contributing to the aggravation of allergic inflammation because of insufficient anti-inflammatory restraint¹. The heterogeneity of glucocorticoid responsiveness, regardless of other possible causes (i.e. genetically determined receptor affinity), may reflect the variety of mechanisms involved in HPA axis regulation and the involvement of multiple cytokines with stimulatory or inhibitory actions in the regulation of the HPA axis.

A dose-dependent adrenal suppression in asthmatic children on ICS appears to exist, and may be detected even when small to moderate doses of inhaled corticosteroids are employed¹³. We do not

know whether these children would develop symptomatic adrenal insufficiency if they were treated with larger doses, but it is certainly possible. Sometimes the results of various studies appear contradictory. This could be the result of the variability in the sensitivity of the various testing methods to detect HPA axis impairment; for instance, morning serum cortisol or urinary free cortisol concentrations are generally poor discriminators of adrenal hypo-activity.

Recent research has disclosed interesting data regarding the role of genetics in modifying the risk of impaired stress response in asthma. A number of pathways through which stress may impact asthma expression could potentially be associated with genetic factors. The most important of these pathways are those that influence immune development and airway inflammation, including HPA axis, adrenergic system and cytokine pathway genes¹⁶.

Early-life experiences interact with the child's genotype to influence the developing immune and stress systems in a fashion that may predispose to or protect from asthma and other allergic diseases. Indeed, recent data suggest that a mechanism linking the social environment early in life and long-term epigenetic programming of behavioural and physical responsiveness to stress and health status later in life does exist¹⁷. Substantial *in vitro* experimental evidence indicates that DNA methylation of genes critical to T helper cell differentiation may induce polarisation towards or away from an allergic phenotype. Thus, asthma risk may be modified by epigenetic regulation¹⁸.

TAKE HOME MESSAGE

The stress system coordinates adaptive responses of the organism to stressors of any kind; inappropriate responsiveness may account for a variety of disorders. Asthma and allergy is characterized by a dysregulation of the pro-inflammatory versus anti-inflammatory and Th1 versus Th2 cytokine balance. The development of these conditions primarily depends on the genetic and epigenetic vulnerability of the individual, and the duration and timing of the stressful events to be deleted.

A number of factors, including psychosocial stress, viral infection, other environment, and allergy may influence the stress response and result in immune response dysregulation leading to asthma. There is also good evidence that genes involved in the stress and inflammatory response may affect asthma expression.

Pro- and anti-inflammatory cytokines involved in the pathophysiology of allergic disease, regardless of

the target organ affected, appear to be inversely associated with cortisol production. In line with this concept, the anti-inflammatory properties of ICS may have favourable effects on the HPA axis of asthmatics with a subnormal adrenal response at baseline which improves with successful long-term treatment. On the other hand, some patients may experience further deterioration of adrenal function, a phenomenon which may comprise a genetically determined response to ICS. As a rule, when ICS are administered at higher than conventional doses, they may be associated with secondary adrenal insufficiency.

Current evidence indicates that the stress-asthma relationship is causal. An increased risk of childhood asthma among children exposed to chronic distress has been demonstrated. On the other hand, production of certain allergic inflammation-related cytokines may blunt the response of the HPA axis to both inflammation and stress, contributing to the aggravation of allergic inflammation.

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