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 interaction.

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 adrenocorticotropic 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 neuropeptides.

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 stimulus.

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.

Data from animal models clearly indicate that stress may produce a marked increase in allergen-induced airway inflammation. 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 responses.

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 potenti-
ating 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 as-
essed was asthma (90.7 %), followed by allergic
rhinitis (4.7 %), atopic dermatitis (2.3 %), and food al-
lergies (2.3 %). Overall the meta-analysis revealed a
positive association between psychosocial factors and
future atopic disorder. More notably, the sub-
group analysis of healthy and atopic populations
showed that psychosocial factors had both an eti-
ological and a prognostic effect on atopic disorders. In
their conclusions the authors suggested the use of
psychological interventions in addition to the conven-
tional physical and pharmacological interventions in
order to successfully prevent and manage atopic dis-
ease. Therefore, allergy can be regarded as the allo-
static or, more correctly, cacostatic load, i.e. the dis-
ease burden or cost the body has to pay in order to
maintain stability outside the normal homeostatic range (allostasis or, more correctly, cacostasis)6.

The findings that chronic stressors facilitate exac-
terations of childhood asthma are supported by
more recent observational studies on the role of the
social environment in children and adolescents with
asthma6; 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 adoles-
cents6.

In line with the above mentioned clinical observa-
tions, a series of recent findings have formed the ba-
sis for the “hypothesis of foetal programming” of
asthma; this hypothesis proposes that stress experi-
enced during pregnancy may lead to vulnerability of
the immune system towards atopic diseases and
asthma. In an experimental setting Pincus-Knackst-
edt et al.10 showed that stress during pregnancy ag-
gravates asthma of the offspring in later life by great-
ly modifying the immune response to allergens and
imparing lung organogenesis. A birth cohort study
in Manitoba, Canada, using health care and prescrip-
tion databases, assessed the association between
maternal distress during the first year of life and on-
ward, 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 de-
pression and anxiety limited to the first year of life did
not have a demonstrable association with subse-
quent asthma11.

In the acute setting, viral infection of the respira-
tory tract constitutes not only the most common precipi-
tant 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 experi-
ments which have suggested that early psychologi-
cal and physical stress aggravates asthma later in
life by inducing hyporresponsiveness of the HPA
axis, human studies have also shown that various
stressors during the early part of a child’s life may af-
fect the HPA axis and result in dysregulation of the
immune system, leading to the development of asth-
ma1. 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 asth-
atics who were on long-term treatment with in-
haled corticosteroids (ICS); however, a growing num-
ber of studies have subsequently recognised that
allergic/asthmatic patients, who were not treated
with ICS, were also likely to have an attenuated ac-
tivity and/or responsiveness of their HPA axis13.

Buske-Kirschbaum et al. found that children with
allergic asthma showed significantly attenuated cor-
tisol responses to psychosocial stress when com-
pared with matched healthy controls, pointing to a
dysfunction of the HPA axis in patients with this dis-
order14. Our group reported the results of a prospec-
tive 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 start-
ing 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 al-
lergic disease, regardless of the organ affected, may
be associated with reduced activity and/or respon-
siveness of the HPA axis. Production of certain aller-
gic inflammation-related cytokines may blunt the re-
sponse of the HPA axis to both inflammation and
acute stress, thus contributing to the aggravation of
allergic inflammation because of insufficient anti-in-
fiammatory restraint1. The heterogeneity of glucocor-
ticoid 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 asth-
matic children on ICS appears to exist, and may be
detected even when small to moderate doses of in-
haled corticosteroids are employed13. We do not

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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 genes. 

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 exist. Substantial in vitro experimental evidence indicates that DNA methylation of genes critical to T helper cell differentiation may induce polarization towards or away from an allergic phenotype. Thus, asthma risk may be modified by epigenetic regulation.

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.

REFERENCES

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