Stress and allergic disease: Underlying mechanisms

Stress e *doença alérgica: Mecanismos subjacentes*

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ABSTRACT

While stress is recognised as being an important factor in exacerbation, worsening and lack of treatment response in several allergic diseases such as conjunctivitis, rhinitis, asthma and atopic dermatitis, its aetiopathogenic mechanisms are still poorly understood. In this article, the potential mechanisms responsible for the impact of stress on allergic disease are reviewed and the role of the neuroendocrine system and its interactions with the immune system, the interference with the oxidative pathway, the impact of corticoresistance and the importance of genetic factors addressed.

Keywords: Allergic disease, corticoresistance, genetics, immune system, neuroendocrine system, oxidative pathway, stress.

RESUMO

O stress *é reconhecido como um factor importante de exacerbação, agravamento e diminuição da resposta ao tratamento de várias doenças alérgicas, nomeadamente da conjuntivite, rinite, asma e dermatite atópica. Contudo, os seus mecanismos etiopatogénicos continuam mal esclarecidos. Neste artigo revêem-se os mecanismos potencialmente responsáveis pelo impacto do stress sobre a doença alérgica, abordando-se o papel do sistema neuroendócrino e das suas interacções com o sistema imune, a interferência com a via oxidativa, a influência da corticorresistência e a importância dos factores genéticos.*

Palavras-chave: *Corticorresistência, doença alérgica, genética, sistema imune, sistema neuroendócrino, stress, via oxidativa.*

INTRODUCTION

The term stress refers to an organism's adaptive response to a stimulus causing tension or overload, the threat of decompensation or loss of homeostasis. Stress may be physical, psychological, or both. Depending on how long it lasts it may be acute (hours/days) or chronic (months/years).

Hans Selye[1] in 1936 was the first to consider stress a common denominator in all adaptive reactions of an organism, and not directly harmful for health. The idea that stress led to physiopathological changes came after, with stress distress defined as a psychophysiological reaction to harmful physical or psychological stimuli[1,2].

Before the inflammatory basis of allergic disease was discovered in the second half of the twentieth century, these diseases were considered psychogenic, and asthma and atopic dermatitis classified among the seven classic psychosomatic diseases[3]. Later, George Salomón was the first to describe the impact of emotional states (psychological stress) on natural killer (NK) cells, increasing susceptibility to infections. The same author later described a correlation between the level of stress and the lymphoproliferative response[4].

Recognition of the reciprocal regulatory relationship between the nervous system and the immune system gave rise to a new field of study, called psychoneuroimmunology. Chronic stress is associated with multiple pathologies, such as cardiovascular (high blood pressure, arteriosclerosis, ischaemic myocardiopathy), psychiatric (depression), endocrine (diabetes mellitus, dyslipidaemia), gastrointestinal (irritable bowel syndrome), neurological (CVAs) and infectious[5]. The opposite is also true, with organic diseases impacting on mood and triggering stress; a two-way relationship[6].

Response to stress depends on several factors, particularly the time involved (acute *versus* chronic stress) and degree of exposure, the type of stress and also age, gender, personality type, any pre-existing pyschopathology, the body's defence mechanisms and genetic predisposition, amongst others.

Stress is known to be an important factor in the triggering, exacerbation and lack of treatment response in several allergic diseases, to wit, conjunctivitis, rhinitis, asthma and atopic dermatitis. Its aetiopathogenic mechanisms are still poorly understood, however. In this article, current understanding of the possible mechanisms responsible for the impact of stress on allergic disease is reviewed.

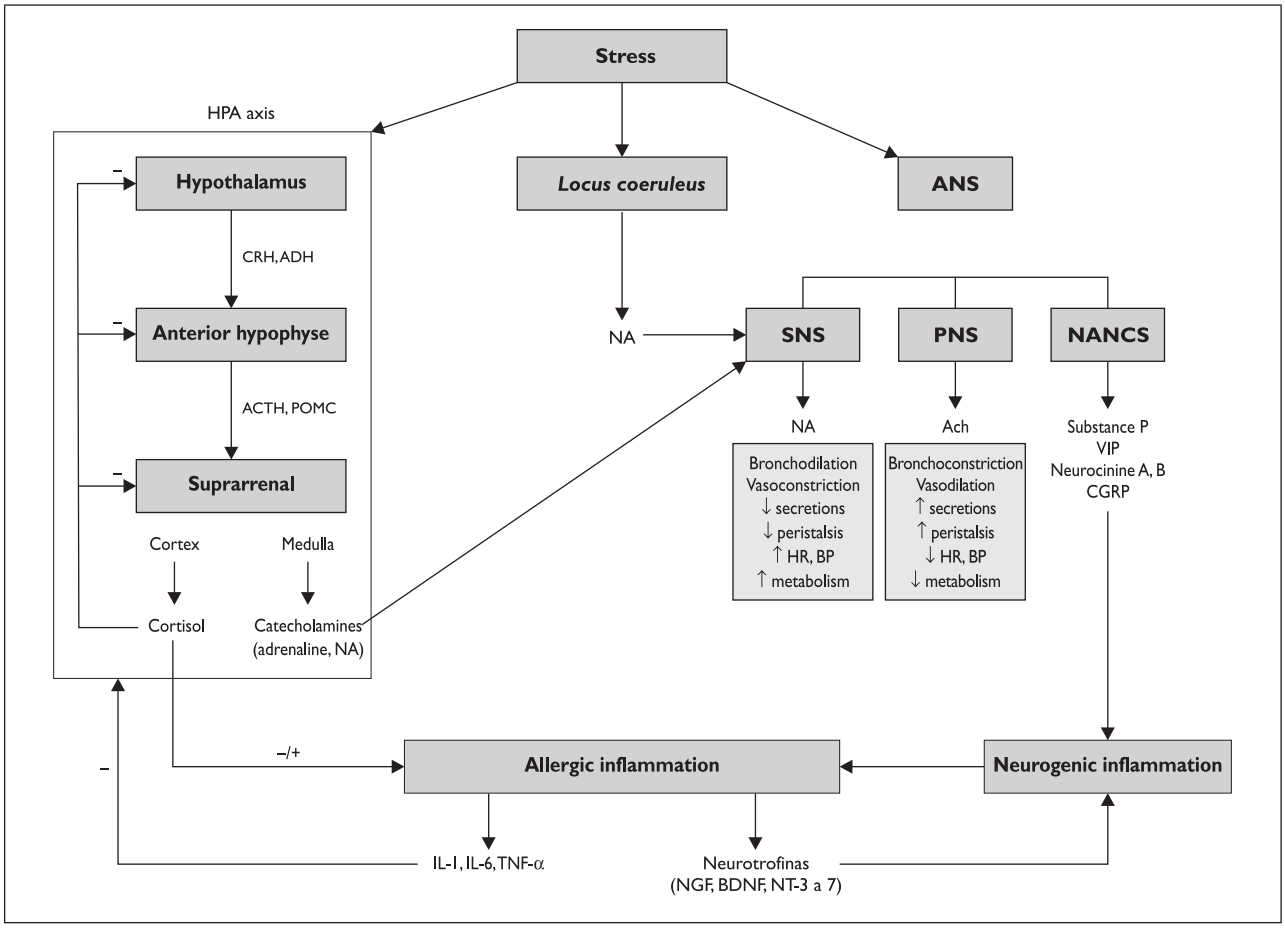
MECHANISMS

Stress induces a series of physiological, emotional and behavioural responses designed to protect the host and re-establish homeostasis. In cases of excessive or prolonged responses, as happens in chronic exposure to stress, they may become harmful to the organism[7,8]. The mechanisms may in isolation or together help explain the relationship between stress and allergic disease and have garnered a great deal of interest.

Stress and the neuroendocrine system

Intercommunication between the central nervous system (CNS) and the immune system is via the hypothalamic-pituitary-adrenal axis (HPA axis) and the autonomous nervous system (ANS). This communication is mediated by the action of hormones (adrenaline and corticosteroids), neurotransmitters (acetylcholine, noradrenaline (NA), serotonin, histamine, glutamic acid, gamma-aminobutyric acid (GABA)), neuropetides (adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), prolactin, bradykinin, somatostatin, vasoactive intestinal peptide (VIP), substance P (SP), neuropeptide Y, enkephalin, endorphin), neurotrophins (nerve growth factor – NGF) and cytokines[9] (Figure 1).

Perception of stress induces activation of the paraventricular nucleus of hypothalmus, with secretion of the corticotropin-releasing hormone (CRH) and ADH, along with the activation of *locus coeruleous*, NA produc-



Legend: ACh – acetylcholine, ADH – antidiuretic hormone, ACTH – adrenocorticotrophic hormone, BDNF – brain-derived neurotrophic factor, CGRP – calcitonin gene related peptide, CRH – corticotropin-releasing hormone, HR – heart rate, HPA – hypothalamic-pituitary-adrenal, NA – noradrenaline, NGF – nerve growth factor, NT – neurotrophin, POMC – pro-opiomelanocortin, SNA – autonomous nervous system, NANCS – non-adrenergic, non-colinergic system, PSN – parasympathetic nervous system, SNS – sympathetic nervous system, BP – blood pressure, VIP – vasoactive intestinal peptide.

Figure 1. Stress and the neuroendocrine system

tion centre and which is also activated by CRH[5]. CRH and ADH activate the HPA axis, stimulating ACTH production by the anterior lobe of hypophysis with consequent activation of cortisol and catecholamines (adrenaline and NA) secretion by the adrenal cortex and medulla respectively[5]. The increased cortisol and catecholamines allow swift mobilisation of energy and oxygen to the necessary locations, i.e. the muscles and brain. Cortisol's anti-inflammatory action means it further plays a vital role in defence against the harmful effects of the pro-inflammatory response which is activated by stress[10].

In response to prolonged stress, CRH's expression of mRNA in the hypothalmus and of pro-opiomelanocortin (POMC) in the anterior lobe of hypophysis, precursor of ACTH, simultaneously increases hypersecretion of CRH and ACTH. However, continued exposure to CRH induces a decrease in expression of the CRH-R1 receptors in the hypophysis via negative feedback, with consequent drop in ACTH production in response to CRH

and drop in cortisol secretion[7,11]. While basal expression of ADH by the hypothalmus is low, its increase in response to chronic stress is substantial. Hence in the presence of CRH (but not in isolation) ADH acts in synergy to potentiate ACTH production through binding to an ADH receptor, without effecting POMC transcription, allowing ACTH response to new stress-inducing stimuli to be maintained, despite the decrease in CRH-R1 receptors secondary to prolonged activation of the HPA axis[11,12].

In acute exposure to stress, the rise in cortisol decreases worsening of allergic inflammation[7]. Several authors have described a lesser increase in cortisol levels in response to stress in allergic patients than in healthy controls[13], although there have been no prospective studies clarifying whether this difference is a cause or consequence of allergic disease. Other authors have shown that children and adults with a swifter resolution of allergic asthma exacerbations have a higher rise in cortisol levels during the exacerbation than those with a less swift resolution[14,15].

These studies highlight the importance of the HPA axis's integrity in the course of allergic disease and could explain the heavier negative impact stress has on patients in whom this axis is suppressed. Cortisol also plays a vital regulatory role in the HPA axis. It decreases CRH and ACTH synthesis and secretion via negative feedback on the hypothalamus and hypophysis respectively[16]; lowers CRH-R1 expression in the hypophysis with a simultaneous decrease in their response to CRH's stimulating effect[16]; in binding to the corticosteroid receptors (GR) in the hypocampus, it negatively regulates the paraventricular nucleus of hypothalmus and the HPA axis[17].

The activation of the ANS is another fundamental pillar in stress response and in intercommunication between the CNS and the immune system, as it stimulates organs and systems which play a weighty role in the immune system, to wit the liver, spleen, thymus, bone marrow, lymphatic glands, skin and the digestive and respiratory systems. The ANS is made up of the sympathetic nervous or noradrenergic system (SNS), the parasympathetic or colinergic nervous system (PNS) and by the non-adrenergic, non-colinergic or peptidergic system (NANCS). NA and acetylcholine are the SNS and PNS neurotransmitors in turn, so the NA secreted by the *locus coeruleous* contributes to the activation of the SNS. The SNS and PNS have antagonistic actions and it is the balance between these two systems which leads to the normal functioning of the organs.

The SNS is in charge of mobilising the energy and oxygen necessary for a fight-or-flight response to a stressful situation by increasing the heart rate, blood pressure and metabolism, decreasing secretions and peristalsis and inducing vasoconstriction and bronchodilation. The PNS, however, has the opposite effects, inducing increased secretions, vasodilation and oedema, and is the main system responsible for bronchoconstriction[8]. The NANCS has several mediators, i.e. the VIP, the SP, neurokinins A and B and the calcitonin gene related peptide (CGRP), particularly involved in neurogenic inflammation (as discussed in a later section).

Stress and the immune system

The activation of the nervous and endocrine systems by stress strongly impacts on the behaviour of immune system cells. CRH, produced by the hypothalamus and peripherally by injured tissues, may bind to the CHR receptors on the surface of mast cells and induce degranulation, with release of cytokines and pro-inflammatory mediators[19]. The mast cells themselves synthesise and secrete CHR in response to the stimulation of their FcεRI receptor[20].

Some studies suggest the degranulation of the Th_1/Th_2 balance towards Th_2 to be an important mechanism in the immune changes induced by chronic stress[21]. Corticosteroids and catecholamines, in inhibiting IL-12 production by antigen presenter cells (the main inducer of Th_1 response via stimulation of IFN-γ secretion by the T and NK cells), stimulates the predominance of the Th_2 profile, with pro-

duction of IL-4, IL-10 and IL-13[22,23]. VIP, known as an anti–inflammatory neuropeptide, also stimulates the Th_2 profile. In addition to the abovementioned mechanism, VIP also induces expression of co-stimulatory molecules in activated macrophages and in immature dendritic cells, in addition to being able to exercise its action directly on T CD4+ lymphocytes, promoting Th_2 differentiation[24].

Neurotrophins also contribute to upsetting the Th_1/Th_2 balance towards Th_2, and can thus add to worsening of allergic inflammation in response to stress and the reactivation of latent viruses under greater psychological stress, as has been seen *in vitro*[25].

Neurotrophins and neuropeptides are the main mediators of neurogenic inflammation (Table I), an inflammatory response resulting from the modulatory action of these neuromediators on immune and/or structural cells[26]. Stimulation of the sensory nerve endings in response to stress and chemical stimuli (produced during inflammation and tissue lesion) results in the secretion of pro-inflammatory neuropeptides which mediate the excitatory function of NANCS by binding to three tachykinin receptors: NK-1 (specific to SP), NK-2 (specific to neurokinin A) and NK3 (specific to neurokinin B)[27]. VIP mediates NANCS's inhibitory function[24].

Neuropeptides are rapidly degraded by peptidases, namely neutral endopeptidase (present in the mucosa and submucosa of the airway) and angiotensin converting enzyme (present in vascular cells)[28]. The rapid degradation of the neuropeptides means their actions are limited in time and restricted to the place in which they're produced[29], and they are considered important in initiating neurogenic inflammation[30,31]. However, the decrease in peptidases activity contributes to the continuation of this inflammatory process. Interestingly, despite neurotrophins, which act as nerve growth factors[32], decreasing in several areas of the brain in rats[33] as a response to chronic stress, this is not seen in areas of allergic inflammation. Here expression increases[34]. In an animal model of asthma, Hahn *et al* showed that IL-1β, TNF-α and Th_2 cytokines strongly stimulate production of nerve growth factor (NGF) and the neurotrophic factor derived from brain–derived neurotrophic factor (BDNF) via the epithelial cells of several areas, which is not the case with IFN-γ, a Th_1 cytokyne[35].

While chronic exposure to stress does not have a direct stimulatory effect on the neurotrophins, neurogenic inflammation (mediated by neuropeptides secreted in response to stress) may be responsible for inducing local production of neurotrophins. While under physiological conditions the nervous system cells are the source and main target of neuropeptides and neurotrophins, during allergic inflammation the structural cells (keratinocytes, epithelial, endothelial and smooth muscle cells, submucosal gland cells) and immune system cells (monocytes, macrophages, mast cells, T lymphocytes, eosinophils) can also produce them, also constituting their target in the expression of their receptors[36-40]. Neurotrophins act by binding to the following receptors of the cellular surface: $p75^{NTR}$ (pan-neurotrophin receptor to which bind, with low affinity and specificity, all the mature neurotrophins), TrkA (tropomyosine-related kinase A, known specifically as NGF), TrkB (activated by BDNF, neurotrophin 4 and 5) and TrkC (primarily known as neurotrophin 3)[41].

Intense and continuous local production of neurotrophins during allergic inflammation by structural and im-

Table I. Principal neurogenic inflammation mediators

Neurotrophins	Neuropeptides
Nerve growth factor (NGF) Brain-derived neurotrophic factor (BDNF) Neurotrophin-3/4/5/6 and 7	Tachykinins (substance P, neurokinin A and B) Vasoactive intestinal peptide (VIP) Calcitonin gene related peptide (CGRP) Neuropeptide Y

mune cells stimulates secretion of neuropeptides by sensory nerve endings[42], impacting on the intensity and length of local immune responses. In this way neurotrophins are important in boosting and maintaining neurogenic inflammation, a vicious cycle of neuroimmune interactions which potentiate allergic inflammation[26,35,42]. Neurogenic inflammation is the result of the important vasodilator effects of its mediators (SP is one of the strongest vasodilators known, 100 times stronger than histamine in identical molar concentrations[43]) and of the modulatory action of neuropeptides and neurotrophins on immune system cells. This has been widely described in the literature[40].

SP acts on monocytes and macrophages, increasing TNF-α and IL-12 production. Further, it also directly induces degranulations of mast cells[44]. NGF has a significant modulatory action on mast cells, recruiting them, influencing their development and promoting their survival as a co–factor of stem cell factor[45,46]. In an animal model of allergic respiratory disease, the blocking of NGF signalling by transnasal application of neutralising antibodies inhibited the initial allergic response induced by the allergen, which is mediated by the degranulation of mast cells[47]. Due to their anti–apoptotic action, neurotrophins promote survival of eosinophils during allergic inflammation[34,35,48], contributing to eosinophilia, an important source of inflammatory cytokines (e.g. IL-4, IL-13) and chemokines (e.g. RANTES, MCP-1), plus stimulating mucin production[35].

Several studies have shown chemotatic activity on NGF and BDNF eosinophils, neurotrophin–3 and neurotrophin-4[35,49]. In general, neurogenic inflammation contributes to manifestation of allergic disease in different organs (eyes, airway, skin), leading to vasodilation, increased vascular permeability and oedema, pruritis and recruitment and activation of immune cells. In the airway it increases secretion of mucous and also induces bronchoconstriction via increased cholinergic activity[18], which is stimulated by tachykinins[50]. Neurotrophins may also induce bronchial hyperreactivity (BHR), in the presence or absence of inflammation of the airway, as shown in an animal model treated with NGF in which HRB was induced with no prior inflammation of the airway[51].

NGF also seems to be involved in remodelling of the airway in inducing the production of collagen and migration of fibroblasts and their differentiation into myofibroblasts[52,53]. It also plays a weighty role in increasing vascularisation in inducing the proliferation of endothelial and vascular smooth muscle cells and in stimulating the release of pro–angiogenic factors[54]. An animal model of asthma suggests the direct role of neurotrophins in the induction of a Th_2 profile in that treatment with anti-NGF antibodies decreases the function of Th_2 cells and that the TrkC receptor was found in these cells but not in Th_1 cells[55]. BDNF also showed increased production of specific IgE and reduced type Th_1 cytokines, favouring the Th_2 response[56].

Recent *in vitro* studies have suggested SP may induce the Th_{17} phenotype in individuals with heightened anxiety[57]. The mechanism responsible remains to be elucidated but the authors of the study in question speculate that an insufficient regulation by regulatory T cells (Treg) may be involved, as IL-10 and IL-2 (cytokine essential in *in vivo* Treg homeostasis[58] and in its *in vitro* immunosupressor status[59]) levels were decreased. Th_{17} cells play a weighty role in defence against extracellular bacteria and fungi[60], promoting an intense chemotaxis of neutrophils to the sites of inflammation via secretion of IL–8 by fagocytes and local cells (activated by IL-17, IL-21, IL-1β, IL-6, TNF-α cytokines), which makes the inflammatory process corticosteroid-resistant.

There is a two-way interaction between the nervous system and the immune system in that the immune system also modulates the function of the nervous system. One of the mechanisms is the result of the cytokines secreted, namely in response to viral infections. Viral infections may agravate the allergic response via different mechanisms: this is the most frequent trigger of asthma exacerbation[61], and it may cause nonspecific BHR[62], inducing secretion of cytokines with action on the HPA axis[63,64]. The presence of virus in infected cells is recognised by the detection of

synthesised double-strand RNA molecules during viral replication.

This signal leads to transcription and secretion of type I interferons (IFNs) (IFN-α and IFN-β), TNF-α, IL-1 and IL-6 by activated immune cells, namely macrophages (and microglia in the CSN), endothelial cells, fibroblasts and neurons. This pro-inflammatory and antiviral environment protects the as-yet-uninfected neighbouring cells, making them resistant to viral replication. The type I IFNs also activate NK cells (lytic function; when stimulated by IL-12 they secrete IFN-γ (type II IFN), crucial in the control of infection prior to the activation of T cells) and increase expression of MHC class I, facilitating presentation of CD8+ T cells. In the presence of IL-12 (secreted by macrophages and dendritic cells) and IFN-γ, CD4+ T cells differentiate themselves towards Th_1, promoting cellular immunity through the activation of macrophages (IFN-γ secretion) and CD8+ T cells (IL-2 secretion).

These cytokines bind to the receptors present at several levels of the HPA axis, stimulating production of cortisol via action on the hypothalamus (principal mechanism) or via direct action on the hypophysis or suprarrenal[63]. Further, there are cytokines which are produced locally by the brain, anterior hypophysis and suprarrenal, whose paracrine action seems to increase and maintain the activity of the HPA axis during chronic inflammation[63]. The additional secretion of cytokines by immune system cells is under normal circumstances inhibited by negative cortisol feedback, protecting the organism from an exaggerated antiviral response (tissue damage, auto-immune response or septic shock)[63].

Stress and the oxidative pathway

Imbalance between reactive oxygen species (ROS) and antioxidants is called oxidative stress. The name ROS stems from its great capacity to oxidate proteins, lipids and DNA, leading to significant structural damage. ROS abound in the intra- and extracellular media and are produced by endogenous (e.g. cellular metabolism products) and exogenous (e.g. environmental pollution, tobacco smoke) sources[65]. Psychological stress has been described as an additional environmental factor with pro-oxidative action[66], although how this happens remains to be elucidated.

Endogenous antioxidants are the first line of defence against ROS, including antioxidant enzymes (e.g. superoxide dismutase families, catalase, glutathione peroxidase, glutathione s-transferase and thioredoxin) and nonenzymatic mechanisms (low molecular weight: glutathione, ascorbate, urate, bilirubin, lipoic acid; high molecular weight: albumin, proteins bound to free metals such as transferrin)[65].

The dynamic balance between the production of ROS and the antioxidant response is fundamental, at the risk of cellular damage occurring. Li N *et al* suggest a hierarchical model to explain response to oxidative stress (Figure 2)[67,68]. Thus, low levels of oxidative stress (Level 1) lead to transactivation of the nuclear factor erythroid-derived 2 (Nrf-2) transcription factor, responsible for activation of transcription of over 200 genes with antioxidant, anti-inflammatory and cytoprotector functions.

When this pathway's capacity for defence is overtaken by a greater production of ROS, there is activation of other potentially harmful cascades of intracellular signal-

Level of oxidative stress		**Level 1**	**Level 2**	**Level 3**
Cellular response	Normal	Anti-oxidant defence	Inflammation	Toxicity
Signalling pathway	–	Nrf-2	MAPK	Mitochondrial disorder

Glutathione depletion →

Legend: MAPK – mitogen-activated protein kinase, Nrf-2 – nuclear factor erythroid-derived 2

Figure 2. Hierarchical model of response to oxidative stress (adapted from reference 68)

ling, as is the case of activation of mitogen–activated protein kinase (MAPK) and NF-kB (Level 2). These induce expression of pro–inflammatory agents, to wit cytokines (IL-4, IL-5, IL-8, IL-10, IL-13, TNF-α), chemokines (MIP-1α, MCP–3, RANTES) and adhesion molecules (ICAM-1, VCAM-1).

Increasing the activation and recruitment of effector cells through the products released, this 'defence' response works towards perpetuating allergic inflammation. A still–higher level of oxidative stress may in the final case trigger a cytotoxic response with its origins in mitochondria, culminating in cellular apoptosis or necrosis (Level 3). The role of this last response in the pathogenesis of allergic disease remains to be elucidated.

In addition to its pro-inflammatory action, oxidative stress also seems to play an auxiliary role in sensitisation to aeroallergens[69,70]. This role may be explained, at least in part, by oxidative stress's impact on the antigen presenter cells, namely the dendritic cells (DCs). In a study into animal DCs, oxidative stress resulting from exposure to chemical substances eliminated by an exhaust pipe inhibited DC's maturation induced by binding lipopolysaccharides (LPS) to the toll-like receptors (TLR), and IL-12 secretion[71]. This effect may interfere in the production of IFN-γ by T cells, suppressing Th_1 differentiation and favouring a bias to Th_2. A second animal model study showed that decrease in glutathione levels in DCs in response to oxidative stress decreased Th_1 response but that treating these DCs with N-acetylcysteine, a thiol precursor, restored Th_1 immunity[72,73].

Stress and corticosteroid resistance

Corticosteroids' potent anti-inflammatory action make them the most-used pharmacological group in the treatment of allergic diseases, inducing or inhibiting the expression of target genes. However, it is known that a subgroup of patients does not respond to corticotherapy even in high doses, something resulting from the interaction of several factors, namely genetic, environmental and immunological[74].

It is known that chronic exposure to stress, in causing prolonged activation of the HPA axis, may lead to a counter-regulatory response with subregulation of glucocorticoid receptor (GR) expression and/or function, leading to an acquired functional resistance[11,74,75]. In an *in vitro* study, Miller *et al* found that the circulating mononuclear cells in adolescent and preadolescent asthmatics from dysfunctional families were more resistant to the effects of hydrocortisone in terms of expression of cytokines (IL-5 and IFN-γ) and activation of eosinophils than were those of their counterparts with greater parental support[76].

The subregulation of the gene which codifies the GR may, at least in part, explain this phenomenon of corticoresistance[74–76]. Another possible mechanism is the GR's incapacity to undergo translocation to the nucleus or to bind to the DNA, where it interferes with genetic expression[77]. The decrease in the GR's mRNA and its protein expression have also been described[78]. It is not yet clear if the drop in mRNA is the result of suppression of promoter activation, of its decreased stability, or both[79]. Expression of GR is subregulated by binding of cortisol in situations of co-existing stress and allergic inflammation, but other causes may be involved, to wit the inhibition of expression of the isoform GRα gene by the nuclear-kB (NF-kB) factor in the inflamed tissues[79,80].

Bailey MT *et al* demonstrated that increased expression of NF-kB in the nucleus of immune system cells occurs together with GR's incapacity to undergo translocation to the nucleus, to bind to the DNA and with the decreased expression of GR[78]. Although expression of GR is ubiquitous, the regulation of the GR gene induces differences in the expression of its mRNA and its protein in different cellular subtypes[81]. Some studies have shown that the impact of chronic stress on the production of cytokines dependent on the TLR, that is, the TLR-4, may also contribute to this corticosteroid-resistance[82,83]. Further, the pathways of oxidative stress have been implicated in corticosteroid-resistant asthma by the predominance of neutrophilic inflammation (and not eosinophilic), as was seen in an animal model of asthma exacerbation[84].

From another perspective, genetic and epigenetic studies have shown that exposure to an altered GR response during the initial development stage (including *in utero*) induces major changes in the neuroendocrine and immune mechanisms and may potentiate the risk of asthma[85].

Stress and genetics

Several studies have shown the impact of genetic factors on basal cortisol levels and on their variations in accordance in adults and children, which could impact on the activity of the HPA axis[86]. Polymorphisms of the GR gene modify the sensitivity to cortisol produced in response to stress, also affecting the HPA axis[21,87]. In a study into asthmatic children, Miller GE *et al* saw that chronic exposure to stress decreased expression of the genes codifying GR and the $\beta_2$adrenergic receptor[88]. This is not seen in isolated acute exposure, although superimposition with chronic exposure has accentuated the impact of its genetic expression. These children under simultaneous acute and chronic stress show a 5.5 times reduction in GR mRNA and 9.5 times reduction in $\beta_2$adrenergic receptor mRNA compared to asthmatic children without this exposure. Further, the gene polymorphisms which codify factors involved in the feedback mechanisms in the response of glucocorticoids to stress, such as the CRH receptor (CRHR1 and CRHR2 genes), TNF-α and other cytokine *loci*, seem to be involved[86,87]. The variant CRHR1, the predominant receptor in the hypophysis and lungs, has been associated with a better response to inhaled corticotherapy[89].

Genetic polymorphisms of antioxidant enzymes may contribute to the inefficiency of this defence mechanism (e.g. glutathione-s-transferase polymorphism (GST) M1 and GSTP1). In a study into asthmatic children, more significant respiratory symptoms were seen in children with null genotypes or GSTP1 Val/Val. When there were two genotypes, respiratory symptoms were even more severe[90]. Interestingly, the abovementioned polymorphisms were seen in approximately 50% and 40% of the population respectively, which reveals their impact on public health[91].

Stress and allergic disease

Stress is recognised as a factor with negative impact on allergic disease, to wit, in conjuntivitis[37,92], rhinitis[93,94], asthma[7,14,15,30,31,88,95,96] and atopic dermatitis[24,97,98]. Although each mechanism has been approached independently, the interaction between stress and allergic disease is extremely complex, with an important interconnection and regulatory relationship seen between the different mechanisms. The importance of the neuroimmune-endocrine system has been well mapped and addressed in this article. The neuroimmune-cutaneous system has been described more recently, and it is particularly important in neurogenic inflammation at cutaneous level and its role in the pathogenesis of these allergic cutaneous and inflammatory diseases is becoming increasingly important. This theme has been the subject of other authors' work, and does not lie within the scope of our work here[24,98].

CONCLUSION

There is no doubt that the relationship between the nervous and immune systems is a real, complex and two-way one. The difficulty in measuring the clinical impact of chronic exposure to stress in allergic disease has led to it being undervalued in the majority of cases. The mechanisms which, working in an independent or interconnected way, help to explain this relationship have solicited immense interest, but much remains to be discovered. Current understanding suggests that in genetically predisposed individuals, chronic exposure to stress may favour the expression of allergic disease and complicate management of it.

Better elucidation of the mechanisms responsible for the interaction between stress and allergic disease may help in the identification of new therapeutic targets, improving the approach to allergic disease.

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