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Social stress and asthma: The role of corticosteroid insensitivity

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Abstract

Psychosocial stress alters susceptibility to infectious and systemic illnesses and may enhance airway inflammation in asthma by modulating immune cell function through neural and hormonal pathways. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis. Release of endogenous glucocorticoids, as a consequence, may play a prominent role in altering the airway immune homeostasis. Despite substantial corticosteroid and catecholamine plasma levels, chronic psychosocial stress evokes asthma exacerbations.

Animal studies suggest that social stress induces corticosteroid insensitivity that in part may be due to impaired glucocorticoid receptor (GR) expression and/or function. Such mechanisms likely promote and amplify airway inflammation in response to infections, allergen or irritant exposure. This review discusses evidence of an altered corticosteroid responsive state as a consequence of chronic psychosocial stress. Elucidation of the mechanisms of stress-induced impairment of glucocorticoid responsiveness and immune homeostasis may identify novel therapeutic targets that could improve asthma management.

Keywords

Airway inflammation; psychosocial stress; corticosteroids; innate immune system

“...the regulation of gene expression by social factors makes all bodily functions... susceptible to social influences...” Eric Kandel, Nobel Laureate¹

Introduction

Ethnic disparity in asthma prevalence, morbidity and mortality is highly correlated with low socioeconomic status and urban living, both of which are predisposing factors to psychosocial stress. Perception of stress in epidemiological studies associates with socioeconomic status and health². Social stress was identified next to air pollution and urban living as one of the most significant contributors to asthma exacerbations^{3, 4}. Predisposing factors to psychosocial stress such as low socioeconomic status also correlate with health care disparity in asthma prevalence, morbidity and mortality⁵. Both physical and social factors induce stress^{3, 4}.

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Clinical implications: Social stress prolongs allergen-induced airway inflammation, increases asthma exacerbations and contributes to asthma morbidity and mortality.

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Evidence suggests that stressful experiences evoke asthma exacerbations⁶⁻¹². Asthma patients respond with increased bronchial tone to distressful experiences¹³, listening to stressful interactions¹⁴ or exposure to asthma-related visual brain stimulation¹⁵. Further, school examinations induce asthma exacerbations in children¹⁶. The mechanisms of bronchoconstriction in response to such *acute* stress may include alterations in adrenergic (sympathetic) and cholinergic (parasympathetic) neural control. Asthma exacerbations were also noted in patients suffering from chronic depression and anxiety as well as in adults¹⁷ and children¹⁸ who had inadequate social support. For instance, greater caregiver-perceived stress was independently associated with subsequent risk of recurrent wheeze in early childhood and high levels of caregiver stress predicted increased wheezing in the index children¹⁹. Severely negative life events in another study increased the risk of asthma attacks in children, and this risk was magnified if the child's life situation was characterized by multiple chronic stressors²⁰. Chronic caregiver stress in early childhood was also associated with the development of atopy while increased stress in the home predicted higher levels of IgE expression, enhanced allergen-specific lymphocyte proliferation, and differential cytokine expression in children²¹. The increase in asthma symptoms during *chronic* stress may be due to the combined effects of hormones, neurotransmitters, and neuropeptides involved in the autonomic control and inflammation of the airways. While stress may alter the magnitude of the airway inflammatory response elicited by allergens, irritants and/or infections in persons with asthma²², the precise mechanisms are unknown. This review discusses evidence that highlights the role of altered corticosteroid function in modulating airway inflammation due to social stress.

What is stress?

Hans (János) Selye defined stress as a state of altered homeostasis resulting from either an internal or external stimulus. Stressors can be physical or psychological in nature. All organisms experience stress, which by itself, is necessary for biological and social adaptation to the environment and for health²³. The physiological response to stress involves the development of adaptive neuroendocrine mechanisms²⁴⁻²⁶. These mechanisms are designed to counteract stress and to restore homeostasis. Stress, however, also evokes physiological changes that may potentially promote disease. Selye called this kind of stress “distress”: The reaction to noxious physical or psychological stimuli involves a short-term activation of the neuroendocrine and autonomic nervous systems that promotes adaptation and survival during the period of challenge. Such mechanisms, termed *allostasis*, literally mean “re-establishing stability through change”²⁶. During allostasis, adaptive mechanisms operate at a higher or lower level than during “normal” homeostasis. For example, emotional distress elevates heart rate and blood pressure as well as elevating glucocorticoid levels and suppressing expression of inflammatory cytokines. Assuming allostatic responses cease when no longer needed, the organism adapts to and survives the immediate challenge without suffering long-term consequences. If, however, the same responses are repeatedly activated or persist over a longer period of time, receptor alterations and tissue damage occur that precipitate or exacerbate disease processes. This has been termed *allostatic load*²⁶.

Acute stress, the “flight-or-fight response” (positive stress) is a response to a perceived threat or challenge that requires a short period of time in which to successfully adapt. Such stress evokes an immediate activation of the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic corticotrophin-releasing hormone (CRH) stimulates adrenocorticotrophic hormone (ACTH) secretion from the pituitary that in turn promotes the release of corticosteroids from the adrenal cortex. The HPA axis is one of the central mechanisms by which stress, detected by the brain, promotes adaptive physiological responses. Acute stressors, through the stimulation of the sympathetic nervous system, prepare the body for an immediate

response and are beneficial. The HPA axis modulates immune/inflammatory responses to prevent such responses from becoming unchecked.

The aforementioned adaptive responses to acute stress stand in distinction from those of chronic stress, where the presence of prolonged stress induces maladaptive responses that promote disease. Traditionally, stress in clinical studies suggests chronic psychological (maladaptive) stimuli. Reduced social status, loss of a job, death of a loved one, long-term anxiety, repeated exposure to violence and depression^{4, 23, 27} are examples of such stressors. The clinical studies linking psychosocial factors with asthma severity are observational and cannot determine causality. Animal models may offer novel insight into the mechanisms relating psychosocial risk factors to physical health²⁷.

Animal models of stress and asthma

To date, few studies have investigated the effects of stress on allergen-induced airway inflammation. For example, in a rat model of unpredictable changes in daily living conditions, increased edema and cellular influx were observed in inflamed paws and airways²⁸. Repeated ultrasound-induced stress in ovalbumin-sensitized mice increased inflammatory cell number, IL-4, IL-5²⁹, TNF α ³⁰ and eotaxin³¹ in the airways. In pregnant BALB/c mice, maternal stress increased susceptibility of the offspring to allergic sensitization to ovalbumin³².

A model of social disruption stressor (SDR) has been used to study the effects on allergic airway inflammation in our laboratory. Since this platform mimics human psychological stress, such an approach may be more relevant than exposure to sound, ultrasound or physical stressors. In SDR, the social hierarchy of a cohort of young male mice is disrupted by an older, aggressive intruder, and a stress response is elicited by repeated experience of defeat and loss of social status³³⁻³⁸. Exposure to psychological defeat as a consequence of confrontation is a relatively common experience in industrialized societies. Accordingly, epidemiological and psychosocial studies show that younger age, lower educational level, subordinate socioeconomic status or rank all lead to repeated experience of defeat and contribute to stress³⁹⁻⁴¹. Social stressors may also modulate immune responses and predispose to asthma morbidity in humans^{4, 5, 27}. Using the SDR model, we showed that combined exposure to allergen and repeated stress prolonged and enhanced the allergic airway response and reduced the glucocorticoid sensitivity of Th2 cytokine release by immune cells *in vitro*^{42, 43}. Recently, stress-related glucocorticoid resistance of Th2 cytokine production by T cells was also reported in asthmatic children who reported inadequate social support¹⁸.

The molecular mechanisms by which SDR enhances allergic airway inflammation remain unclear. Earlier findings in rodent models of stress revealed acute atrophy of the immune organs that increased susceptibility to viral or bacterial infections^{24, 25}. Stress in the SDR model however was not immunosuppressive. We found *increased* spleen mass and enhanced p65 expression in the nuclear extract of the SDR mice, suggesting activation (not suppression) of the innate immune cells and Th2-type immune mediators. There are indications that both the duration (acute vs. chronic or repeated) and type of stressors can alter the effects of corticosteroids⁴⁴. Opposing effects of short- and long-term stress on the immune system were suggested in models of restraint⁴⁴ and the forced swim test⁴⁵. In restraint stress mice are placed in ventilated Plexiglas restrainers [11.5 cm \times 3 cm (diameter) with 8–0.5 cm diameter air holes for 2 hours. In the forced swim stress model, mice are individually placed in 10 cm deep water (23–24°C) in an uncovered, cylindrical Plexiglas container, where they are required to swim or float for 2 minutes. When applied chronically (daily for 25 days), both the restraint and forced swim stress models enhanced inflammatory responses⁴⁵. Chida and colleagues showed that repeated psychological stress exacerbated allergic airway responses, and pretreatment of mice with the glucocorticoid receptor antagonists RU486 before allergen challenge, abolished

the stress effects. On the other hand, in acute/short-term stress, airway inflammation⁴⁶ and bone marrow eosinophilia in allergen-sensitized animals were inhibited, and this inhibition was abrogated by RU486 or metirapon⁴⁷, suggesting that endogenous corticosteroids effectively suppress allergic inflammation. Accordingly, corticotropin-releasing hormone (CRH)-deficient mice experienced significantly enhanced cellular inflammation to allergic sensitization as compared with that of wild-type mice⁴⁸.

Direct comparison of the SDR stressor with a repeated restraint stress paradigm also suggests differential effects on the immune function^{49, 50}. While the HPA axis and the sympathetic nervous systems were similarly activated by both stressors, repeated restraint disrupted the circadian rhythm of the HPA axis, and a prolonged elevation of circulating corticosterone levels with splenic hypotrophy, suppressed mononuclear cell function and cytokine production,⁴⁹ and these responses were restored with RU486⁵¹. In comparison, repeated cycles of SDR elevated circulating corticosterone levels but did not disrupt the circadian rhythm of the HPA axis, induce splenic hypotrophy or suppress mononuclear cell activation⁵². Further, development of glucocorticoid insensitivity of cytokine production by splenocytes⁵³ was observed in SDR but not the restraint stress model⁵⁴. Taken together, exposure to sound²⁹⁻³² or psychological stressors⁵⁵ enhances an allergic immune response while restraint stress suppresses it. Further, while acute stress evokes immunosuppression, after prolonged or repeated stress glucocorticoid insensitivity may develop. Although paradoxical, increases in circulating corticosterone due to repeated psychological stress may promote a loss of the anti-inflammatory properties of corticosteroids and in fact perpetuate airway inflammation⁵⁵. Endogenous glucocorticoid levels can regulate the development, distribution and function of immune and structural cells⁵⁶⁻⁵⁸ but the effects of stress-induced glucocorticoid release on airway immune function require further study.

Mechanisms of stress-induced glucocorticoid insensitivity: Role of the GR

Our studies⁴² showed that social stress prolonged the airway inflammation to allergen in mice including hyperresponsiveness to methacholine challenge, increased BAL eosinophil and lymphocyte numbers, and elevated levels of cytokines, chemokines and immunoglobulins, reflecting activation of both the innate and adaptive immune system. Importantly, heightened inflammation occurred in the presence of elevated serum corticosterone in mice exposed to social stress and allergen suggesting a diminished inhibitory action of endogenous corticosteroids⁴². Conceivably, repeated exposure to social stress skews the immune status towards a Th2 phenotype in the airways inducing a persistent and amplified inflammation after allergen challenge. Such changes, in part, may be due to endogenous corticosteroid insensitivity, mediated by decreased function and expression of the GR. In fact, *in vitro* splenocyte studies suggest that stress and allergen are synergistic in reversing the immunosuppressive action of corticosteroids on pro-inflammatory cytokine production by immune cells⁴³. The combination of stress and allergen exposure also profoundly altered the *in vitro* corticosteroid responsiveness of LPS-stimulated splenocytes⁴². Investigators previously showed that stress-induced disruption of the glucocorticoid action was associated with a failure of the GR to translocate to the nucleus^{53, 59}, and GR binding to glucocorticoid response elements in the nuclear fractions of splenocytes was attenuated⁴². Stress alone significantly inhibited GR binding to glucocorticoid response elements^{53, 59} but additional *Af* exposure of the stressed mice did not increase this effect⁴². Thus, the mechanism by which the synergistic reversal of corticosteroid action occurs in LPS-stimulated cells from the allergen- and stress-exposed mice remains unclear.

Since constitutive GR expression is essential for an adequate glucocorticoid action, we also investigated GR expression both in the spleen and the lung of mice exposed to stress, allergen or the combination of the two. GR mRNA and protein expression was significantly inhibited

in the allergen- and stress-exposed group in comparison with the allergen-sensitized control mice⁴². We speculate that an impaired nuclear translocation and DNA binding together with reduced GR mRNA and protein expression may in part explain the observed alterations in corticosteroid responsiveness. Although evidence suggests that stress modulates AHR and airway inflammation in mice^{29, 30, 32, 44, 46-48, 55, 60}, our recent study is the first demonstration that social stress enhanced the allergic airway response in association with innate immune cell corticosteroid insensitivity and impaired GR translocation and expression. GR expression is regulated by complex transcriptional and post translational mechanisms that can be significantly modified by inflammatory processes during airway inflammation⁶¹. Indeed reduced GR expression was reported in asthmatic and COPD patients with insensitivity to corticosteroid treatment^{62, 63}. While these findings may point to potential mechanisms of asthma exacerbation and diminished effectiveness of corticosteroid therapies a number of questions remain unanswered. For instance, what is the mechanism of reduced GR expression in the lung? While GR expression is likely to be reduced by homologous ligand down-regulation (by GR agonists) during the combination of stress and allergic inflammation, other pathways may be also operational. Specifically, the human GR α isoform can be transrepressed by NF- κ B, a mechanism that could mediate steroid insensitivity in the inflamed tissue^{62, 64}. Interestingly, ligand-induced GR down regulation is a significant mechanism in various tissues and cell types but not in T lymphocytes⁶⁴. Thus, innate immune cells may be important. The exact cell types that are ultimately responsible for mediating the effects of corticosteroid insensitivity in the lung however still need to be identified. It is also unclear whether low levels of GR mRNA are due to suppression of promoter activation, decreased mRNA stability, or both⁶⁴. Further, the expression and function of the human GR are distinct from that of the mouse. For example, it is unclear whether transrepression of the GR α by NF- κ B plays a role in corticosteroid resistance in mice. Existence of the dominant negative GR β isoform (a genetic variant of the GR in humans that was also implied in glucocorticoid resistance^{61, 64, 65}) could not be demonstrated in mice either.

GR signaling and glucocorticoid resistance in airway inflammation

In the canonical signaling pathway, glucocorticoid binding to the intracellular receptor (GR) induces molecular rearrangement of the GR-HSP90 heterocomplex and promotes GR nuclear localization, homodimerization, and DNA-binding. The activated GR homodimer exerts its genomic effect by interacting with specific DNA elements, termed glucocorticoid response elements (GRE), located within regulatory regions of glucocorticoid-responsive genes (Figure 1). After recruitment of co-activators or co-repressors, the GR modulates the rate of gene transcription in the nucleus by transactivation or transrepression. Transactivation is an increased rate of gene expression triggered by GRE which acts in “trans”, i.e. intermolecularly (this may be considered the opposite of “cis”-acting i.e., intramolecular). On the other hand, transrepression is a process whereby one protein represses (i.e., inhibits) the activity of a second protein through a protein-protein interaction⁶⁶. The protein that is repressed is usually a transcription factor whose function is to up-regulate the rate of gene transcription. Hence the net result of transrepression is down regulation of gene transcription⁶⁷. The phenomenon of transrepression was first observed in the ability of the glucocorticoid receptor to inhibit the transcriptional promoting activity of the AP-1 and NF- κ B transcription factors. Both transactivation and transrepression are important in mediating the anti-inflammatory effects of glucocorticoids.

Transactivation GRE up-regulates anti-inflammatory genes such as the NF- κ B inhibitor I κ B α , the AP-1 inhibitor glucocorticoid-inducible leucine zipper (GILZ) or IL-10 (Figure 1A). Transrepression GRE mediates transcriptional down-regulation (Figure 1B). In its monomeric form, the activated GR can also modulate transcription independent of the canonical GRE pathway⁶⁸. For example, GR physically interacts with other transcription factors (a mechanism

called “tethering”), such as nuclear factor κ B (NF- κ B), activator protein-1 (AP-1), signal transducers and activators of transcription (STAT) or CAAT Enhancer Binding Protein (C/EBP), and modulates activation of target genes^{69, 70}. Figure 1C illustrates that the activated monomeric GR with the help of HDAC (histone deacetylase), can interfere with the p65 and p50 NF- κ B heterodimer activation of the κ B responsive element (κ B-RE). Although the main function of HDACs in the context of regulating gene transcription is to modify histones and chromatin structure, different HDAC isoforms were identified to have various cytoplasmic and nuclear regulatory functions. HDAC1 for example is considered to be a transcriptional co-activator⁷¹ and impaired HDAC2 function has been implicated in corticosteroid resistance of asthmatic and COPD patients⁷². Phosphorylation-dephosphorylation is an important mechanism in the function of the transcription regulator enzyme, RNA polymerase II. Figure 1D shows that the GR may interfere with transcription activation through dephosphorylating RNA polymerase II⁷⁰.

GR expression and function are regulated by transcriptional and post translational mechanisms⁶⁴ such as kinase-dependent phosphorylation as well as by homologous ligand down-regulation (by GR agonists) that can be significantly modified by stress and increased NF- κ B expression⁶¹. Our studies⁴² showed that SDR enhanced expression of NF- κ B in the nuclear fraction of immune cells parallel with an impairment of GR nuclear translocation, DNA binding and a decrease in the expression of GR. A mutual transrepression between the GR and NF- κ B maybe responsible for mediating steroid insensitivity in the inflamed airways in asthma⁶²⁻⁶⁴. Mechanisms by which NF- κ B can affect glucocorticoid responsiveness are illustrated in Figure 2. Glucocorticoid binding to the GR induces molecular rearrangement of the GR-HSP90 heterocomplex and promotes GR nuclear translocation, homodimerization, and DNA-binding. These processes can be modulated by GR/NF- κ B interactions. NF- κ B for example can directly interfere with GRE-mediated transactivation as well as transrepression (Figure 2A)⁵³. Indirect inhibition of the GR function maybe achieved by transcription factor “tethering” (Figure 2B). Thus, GR/NF- κ B interactions regulate GR expression, modulate nuclear translocation of the GR and affect GRE-mediated function as well as transcription factor “tethering” in the inflamed airways. It is important to note that while the GR is ubiquitously expressed, regulation of the GR gene leads to differences in the expression of GR transcript and protein in individual cell types^{73, 74}. Cell type-specific increase in NF- κ B for example in dendritic cells, may significantly inhibit GR expression and modulate allergic airway inflammation during stress.

Role of the innate and adaptive immune system in stress and the asthmatic response

Altered innate immune cell-T cell interactions may play a role in stress-induced enhancement of immune responses. After interaction with the antigen-presenting cells and recognition of the antigen, naive CD4 T cells rapidly undergo a differentiation process that promotes development of four functionally distinct cell subsets characterized by a mutually exclusive pattern of transcription factor and cytokine secretion. Th1 cells express Tbet and secrete IFN γ while Th2 cells are GATA3 positive, produce IL-4, IL-5, IL-9, and IL-13⁷⁵⁻⁷⁷. The proinflammatory Th17 cells express Ror γ t and produce IL-17 while the Foxp3 positive regulatory (Treg) T cells release IL-10 and TGF β and exert profound immunosuppressive activities. A critical role of CD4 T cells in the immune response to allergens has been supported by evidence including previous studies on asthmatic patients and animal models⁷⁶⁻⁷⁹. We have shown that T cell activation in asthmatic patients^{80, 81} and in a Brown-Norway rat model of allergic airway inflammation^{82, 83} was associated with production of IL-4 and IL-5, but not IFN γ ⁸²⁻⁸⁴ and that an asthmatic phenotype was transferable from sensitized to naïve animals by CD4 T cells⁸⁵. Our studies also demonstrated that deficiency of either IL-4 or IL-5 abolished

allergic airway inflammation⁸⁶ while overexpression of IL-5⁸⁷ or IL-9^{88, 89} was responsible for exaggerated eosinophilia, mucus production and airway hyperresponsiveness.

Cell-cell interactions provided by dendritic cells (through MHC-II and CD86) and paracrine secretion of proinflammatory cytokines⁹⁰ are the main factors influencing CD4 T cell differentiation that determine the kinetics and magnitude of airway inflammation. Dendritic cells within the bronchial and alveolar wall cannot present antigen or stimulate T cells in their resting state. In response to allergen exposure however, proinflammatory, maturing dendritic cell precursors migrate from the bone marrow to the airway epithelium and evoke Th2-cell activation. These CD11b/MHC-II/CD86 positive myeloid dendritic cells have central importance in promoting airway inflammation and can be distinguished from the more tolerogenic plasmacytoid dendritic cells by membrane markers and intracellular mediators.

Although stress may impair asthma control^{6-12, 15, 91}, few studies address whether stress directly modulates immune function in disease. Our studies showed that levels of the immunoglobulin IgG1 and TARC (CCL17), a chemokine produced by dendritic cells and macrophages and responsible for attracting Th2 lymphocytes and activated dendritic cells⁹², were enhanced in mice exposed to stress alone. Both IgG1⁹³ and TARC⁹² are regulated by IL-4/IL-13 and are part of the Th2 immune response. Since these cytokine/chemokine and immunoglobulin changes occurred without the presence of antigenic stimulation, we hypothesized that alterations in innate immune cell function played an important role in mediating stress effects on airway inflammation. TNF α and IL-6 promote allergen-induced inflammation but also LPS-stimulated innate immune response. Therefore levels of TNF α and IL-6 are biomarkers of the activation state of innate immune cells both in the lung (*in vivo*) and in the spleen (*in vitro*). Activation of dendritic cells and macrophages⁹⁴ also contributes to elevating TNF α and IL-6 in mice that received Af+SDR.

Because TARC and IgG1 can also characterize Th2-type immune responses, we also raised the question whether animals exposed to repeated social stress would experience an increased susceptibility to developing allergic airway inflammation⁹⁵⁻⁹⁸. Combined exposure to allergen and stress significantly enhanced the numbers of eosinophils and lymphocytes in the airways. These cells will interact during the allergen-induced airway inflammation through the T lymphocyte-derived IL-4, IL-5 and GM-CSF, which are essential for promoting allergen-induced tissue eosinophilia. The genes for these cytokines are located in a cluster of chromosome 5q and are sensitive to corticosteroid regulation. The enhanced airway eosinophilia 48 h after allergen challenge was paralleled by increased release of the eosinopoietic IL-5 and GM-CSF, as well as IgG1 and TARC in the airways of mice exposed to both stress and allergen challenge.

Previous studies suggest that in response to LPS-stimulation, the dendritic cells derived from mice exposed to social stress, released increased levels of TNF α and IL-6 as compared with control animals. Interestingly, CD11c+/CD11b+ dendritic cells^{42, 99} were also less sensitive to the inhibitory effects of glucocorticoids than cells from control mice^{33, 35, 52-54, 100} and expressed increased levels of NF- κ B. Thus, myeloid dendritic cells may become primed during stress by activating NF- κ B and by nuclear translocation of p65. Although the exact mechanism remains unclear, it is plausible that increased corticosterone induces GR downregulation in these cells^{73, 101, 102}. Because activated GR constitutively inhibits NF- κ B function via several different mechanisms (see above), a decrease in GR expression may promote NF- κ B upregulation and activation. Dendritic cells “primed” by stress then become less responsive to corticosteroids. Our studies show that dendritic cell priming is amplified in the presence of allergic inflammation. Since enhancement of allergic airway inflammation in part requires interaction among dendritic cells and T cells of the submucosal airway tissue, dendritic cells and/or T cells may also be necessary for the glucocorticoid insensitivity seen after exposure to

stress. It is also possible that stress and asthma-induced immune cell glucocorticoid insensitivity are due to aberrant glucocorticoid receptor-NF- κ B interaction.

Role of the epithelial product SP-D in asthmatic inflammation

Stress and asthma may also affect glucocorticoid responsiveness of structural cells of the airways, such as epithelial and smooth muscle cells. These cells play an important orchestrating role and participate both in the initiation and resolution of the asthmatic airway response. An interesting potential link between the innate immune system and stress-induced modifications in corticosteroid responsive epithelial cell functions could be the hydrophilic epithelial product, surfactant protein D (SP-D)¹⁰³⁻¹⁰⁵.

SP-D is a member of the collectin family, composed of an N-terminal collagen and a C-terminal lectin domain. This protein is a constitutive mediator of antigen clearance and is capable of interacting with cellular components of both the innate and adaptive immune systems on mucosal surfaces¹⁰⁵. SP-D is synthesized and secreted primarily by type II alveolar epithelial cells, Clara cells and cells of submucosal glands in the lung. We have recently shown that patients suffering from chronic obstructive pulmonary disease expressed significantly lower levels of SP-D in their BAL than healthy controls¹⁰⁶. These studies also indicated that corticosteroid treatment significantly increased SP-D levels. It is possible that the beneficial effects of glucocorticoid therapy are partially mediated by enhanced SP-D expression in the lung. Indeed a cohort of evidence now supports the potent immunosuppressive activities of this lung collectin¹⁰⁷. *In vivo* studies on SP-D deficient mice demonstrated enhanced susceptibility to inflammation in infectious and inflammatory models, including allergic airway sensitization¹⁰⁵ and showed that one of the most prominent pathological characteristics in the SP-D deficient lung is the abnormal activation of alveolar macrophages and dendritic cells^{105, 108}. That SP-D plays a protective role on immune cells was confirmed using treatment with recombinant protein that suppressed activation of lymphocytes⁹⁸ and dendritic cells¹⁰⁸ and inhibited airway inflammation *in vivo*.

In response to acute inflammatory stimuli there is a protective surge in SP-D release in the airways^{95, 109}. Although the exact transcriptional activation pathways responsible for enhanced SP-D synthesis are not known, proinflammatory cytokines, second messengers as well as corticosteroids have been implicated^{106, 110}. In a recent study from our laboratory mice receiving allergic sensitization as well as repeated social stress produced significantly less SP-D in response to allergen inhalation than control (non-stressed) animals¹¹¹. We propose that stress-induced altered corticosteroid responsiveness of epithelial cells of the airways may inhibit SP-D production (Figure 3A). Stress also abrogates corticosteroid responsiveness of proinflammatory dendritic cells by increasing NF- κ B expression and function (Figure 3B). Diminished SP-D levels will then result in a failure of protection against dendritic cell and Th2-cell activation and the consequent allergic airway response (Figure 3C). The clinical relevance of these studies may foster the development of novel immune modulatory agents that will effectively treat airways inflammation in a glucocorticoid-insensitive state.

Therapeutic relevance

When inhaled corticosteroids appear ineffective in the treatment of asthma, health care providers often impugn that the patients are nonadherent¹¹². Other explanations, however, may be operative. Potentially, the patients are adherent to therapy, yet given environmental stress, there may exist a transient glucocorticoid-insensitive state that renders such therapy ineffective¹¹³. Although asthma exacerbation has long been thought to be affected by emotional states, evidence has only recently emerged to identify cellular and molecular mechanisms responsible for stress-induced glucocorticoid insensitivity.

For example it is conceivable that impaired SP-D production by epithelial cells in the lung contributes to the enhancement of allergic airway inflammation during stress and that therapeutic replacement or induction of SP-D will be a potentially effective adjunct or alternative approach. It is unlikely however that a reduced SP-D synthesis is solely responsible for the stress-induced changes in the pulmonary innate immune system and the significance of altered corticosteroid responsiveness of airway epithelial cells during social stress needs further clarification.

As discussed, NF- κ B activation, a pivotal signaling mechanism, mediates airway inflammation. Accordingly, IKK2 inhibitors or potentially p38 MAP kinase inhibitors could serve as nonsteroidal anti-inflammatory agents that could be effective in stress-enhanced airway inflammation. In parallel studies, we have shown that after exposure to IFN γ and TNF α , human airway smooth muscle cells and human precision cut lung slices become glucocorticoid-insensitive¹¹⁴, yet IKK2 inhibitors and p38 MAP kinase inhibitors remain effective in decreasing cytokine-induced chemokine/cytokine secretion¹¹⁴⁻¹¹⁶. Undoubtedly, more work is necessary in this area; however, the identification of novel therapeutic targets to overcome stress-mediated glucocorticoid insensitivity may offer substantial value in the management of asthma.

Conclusions

Stress profoundly affects the course of airway inflammation. In asthma, evidence now suggests that social stress prolongs allergen-induced inflammatory changes, increases asthma exacerbations and contributes to asthma morbidity and mortality. Recent studies highlighted the role of altered corticosteroid responsiveness of T cells, dendritic cells and airway epithelial cells in stress-induced enhancement of inflammation. Central to this process is the shift in the balance of the mutual transrepression of the GR and NF- κ B that results in steroid insensitivity and an increase in immune cell activation. Further studies are necessary to identify the therapeutic targets that can ameliorate stress effects on the immune system so that the “allostatic function” maybe restored.

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Abbreviations

ACTH	Adrenocorticotropic hormone
<i>Af</i>	<i>Aspergillus fumigatus</i>
AHR	Airway hyperreactivity
AP-1	Activator protein 1
BAL	Bronchoalveolar lavage
CD4	Cluster of differentiation 4
C/EBP	CCAAT enhancer binding protein
CRH	Corticotrophin-releasing hormone
Foxp3	forkhead box P3
GILZ	Glucocorticoid-inducible leucine zipper
GM-CSF	Granulocyte macrophage colony stimulating factor
GR	Glucocorticoid receptor
GRE	Glucocorticoid response elements
HPA	Hypothalamic-pituitary-adrenal axis
HSP90	Heat shock protein 90
IFN	Interferon
I κ B α	NF- κ B inhibitor α
IL	Interleukin
LPS	Lipopolysaccharide
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
Ror γ t	Retinoid-related orphan receptor γ t
RU486	Mifepristone (11 β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one)
SDR	Social disruption stressor

SP	Surfactant protein
STAT	Signal transducers and activators of transcription
TARC	Thymus and activation regulated chemokine
Tbet	T box expressed in T cells
TGF	Transforming growth factor
Th	T helper
TNF	Tumor necrosis factor

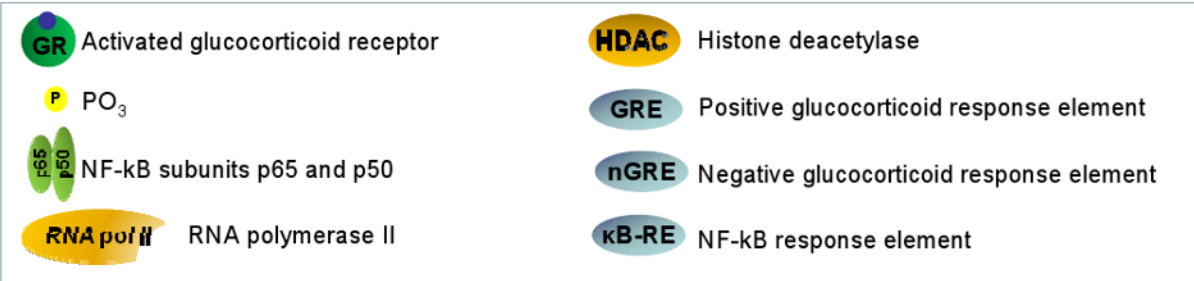
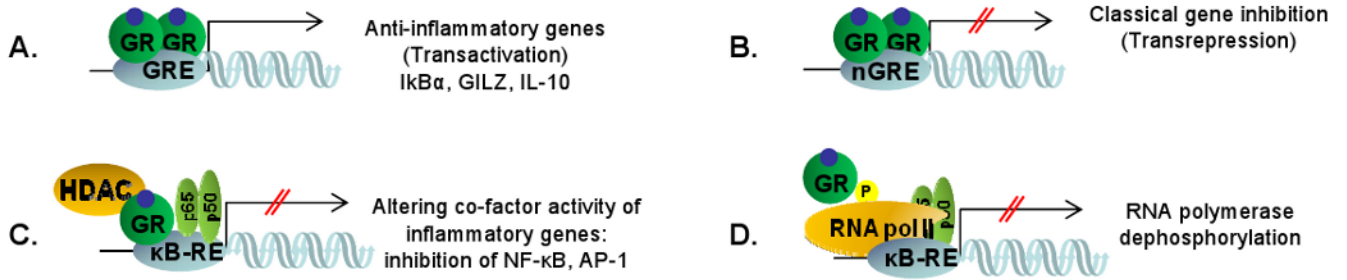


Figure 1. Mechanisms of glucocorticoid action. The activated glucocorticoid receptor (GR) homodimer binds to glucocorticoid response elements (GRE), located within regulatory regions of glucocorticoid-responsive genes in the nucleus. (A): Positive GRE mediates transcriptional up-regulation of anti-inflammatory genes such as $\text{IkB}\alpha$, the glucocorticoid-inducible leucine zipper (GILZ) or IL-10. B: Negative GRE mediates transcriptional down-regulation. C-D: In monomeric form the activated GR may interact with other transcription factors such as nuclear factor κB (NF κB). (C): This interaction can occur indirectly through transcriptional co-factor (HDAC) binding or (D): by RNA polymerase dephosphorylation.

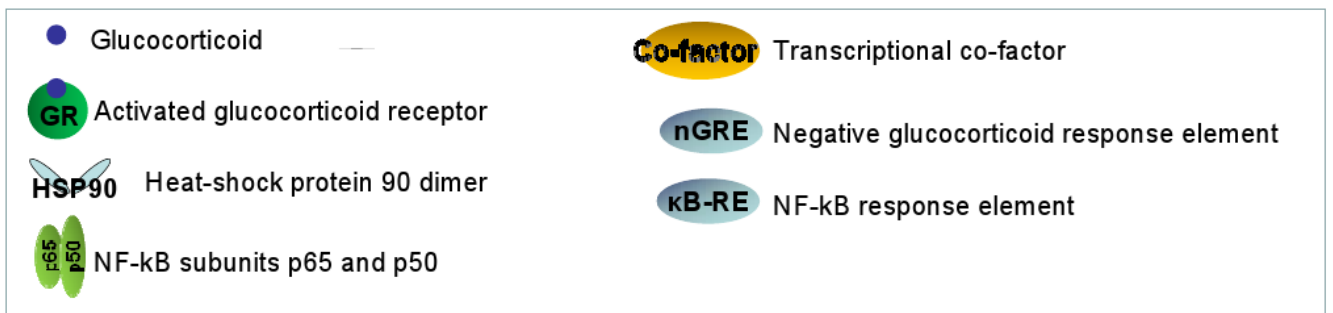
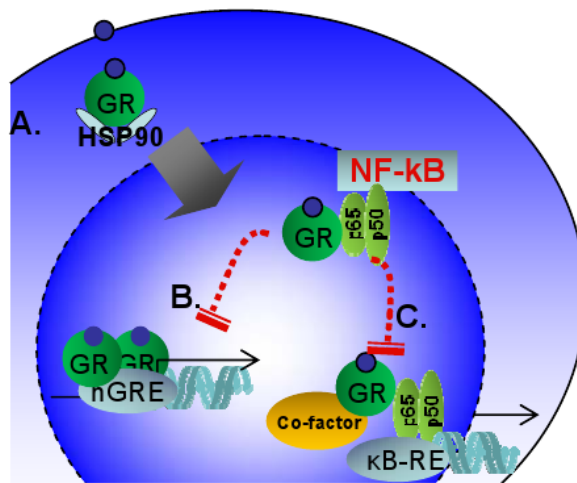


Figure 2. Hypothesized mechanisms by which glucocorticoid resistance could occur. (A): Glucocorticoid binding to the GR induces molecular rearrangement of the GR-HSP90 heterocomplex and promotes GR nuclear translocation, homodimerization, and DNA-binding. (B): This process can be modulated by GR/NF-κB interactions, directly by affecting transactivation (GRE-mediated) as well as transrepression of GR functions. Indirect inhibition of the GR function may be achieved by transcription factor “tethering”.

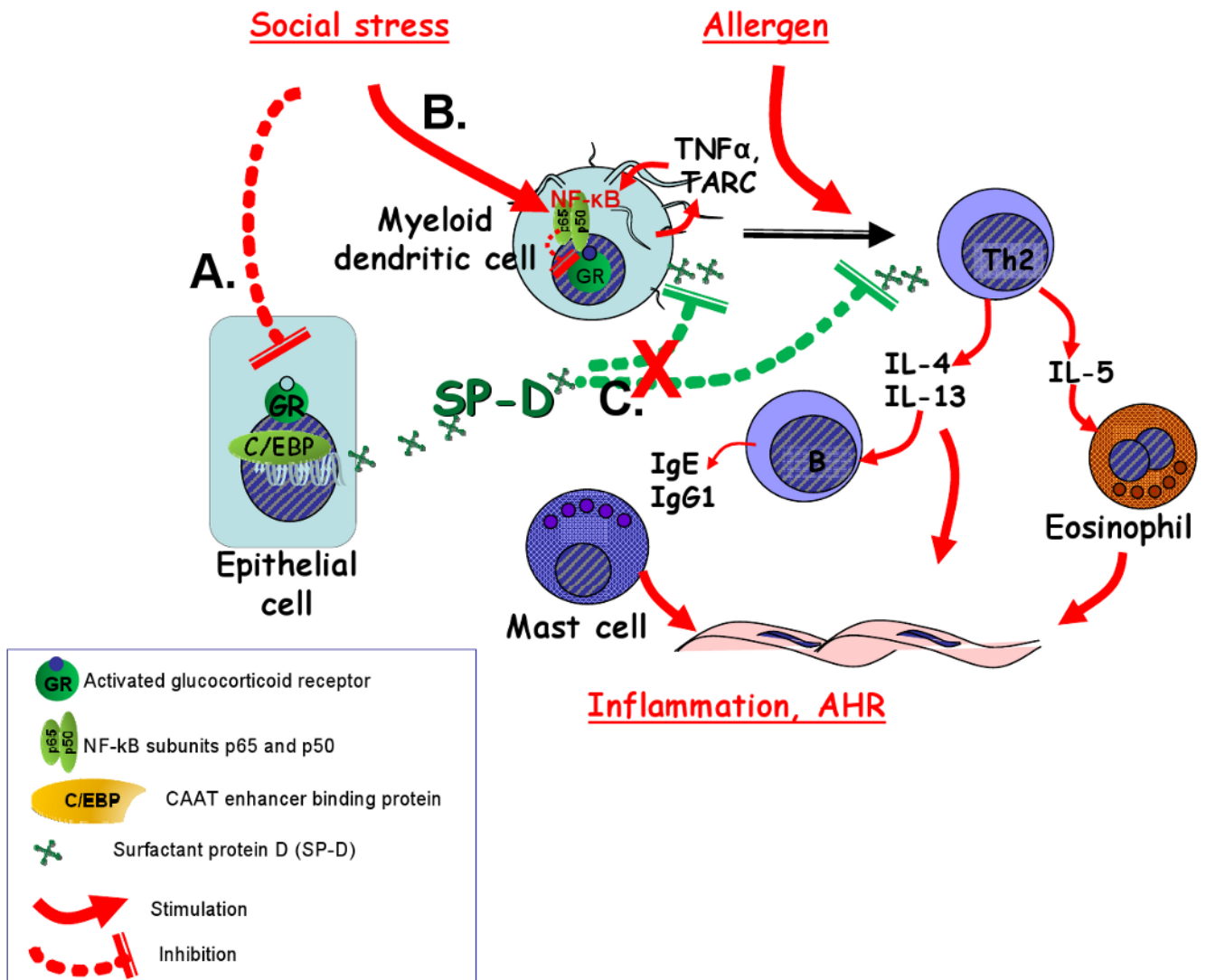


Figure 3. Proposed mechanism of how stress-induced glucocorticoid insensitivity could affect the innate immune system during the allergic airway response. (A): Altered corticosteroid responsiveness of airway epithelial cells may inhibit SP-D production. (B): Stress abrogates corticosteroid responsiveness of proinflammatory dendritic cells. (C): Diminished SP-D levels will result in a failure to protect against dendritic cell and Th2-cell activation and the consequent allergic airway response.