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Stress and acquired glucocorticoid resistance: A relationship hanging in the balance

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Glucocorticoid resistance; psychological stress; toll-like receptors; social disparities

Remembering that there is a yin and yang to everything helps us resolve the ostensible paradox between production of stress-induced cortisol, which is typically thought of as an anti-inflammatory hormone, and worsening of asthma and other inflammatory processes. Endocrine-immune responses differ in relation to acute and chronic stress.[1] In response to chronic psychologic stress, key physiologic systems (eg, the hypothalamic-pituitary-adrenal axis, sympathetic-adrenal medullary system, and proinflammatory immune response) might operate at higher or lower levels than in normal homeostasis. It is the disturbed balance of these integrated systems that can translate into adverse health outcomes. Immune and neuroendocrine defensive biologic responses important for the short-term response to stress might, under chronic stress conditions, exact a toll if not checked and eventually terminated.[2] For example, it has been proposed that chronic psychologic stress, resulting in prolonged activation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary system axes, might result in a counterregulatory response in stimulated lymphocytes and consequent downregulation of the expression, function, or both of glucocorticoid receptors, leading to functional glucocorticoid resistance.[3] This hypothesis had not previously been explicitly examined among subjects with asthma.

A study reported in this issue of the *Journal* provides further insight into the underlying mechanisms that might link stress and asthma expression. Miller et al[4] examined the relationship between chronic social stress as indexed by low family support and relative resistance to glucocorticoids in asthmatic children (preteens and adolescents) and a healthy control group. In these cross-sectional analyses they demonstrate that PBMCs harvested from asthmatic subjects who perceived low parental support (ie, greater stress) were more resistant to hydrocortisone's effects on cytokine expression (IL-5 and IFN-γ) and activation of eosinophils relative to asthmatic subjects reporting higher parental support. These *in vitro* effects were not evident in healthy control subjects. These authors were also careful to

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examine the effects of both inhaled and oral steroid use, which did not seem to influence the findings.

Notably, the majority of patients with glucocorticoid-insensitive asthma have an acquired form of steroid resistance.[5] These data, the first in human subjects, add chronic social stress to a growing list of environmental factors that can induce functional glucocorticoid resistance in asthmatic subjects.[6] Stress-induced glucocorticoid resistance might have a number of important clinical implications. Although it has been long known that asthmatic subjects have a variable response to glucocorticoid therapy, a mainstay of asthma therapy,[7] there are a subset who are severely impaired given that their symptoms are relatively or totally refractory even to high dose steroids, although still vulnerable to the side effects of excessive glucocorticoid use.[6] Moreover, this might have implications for understanding the greater asthma morbidity seen in urban poor communities, in which residents are particularly burdened by the cumulative effects of multiple social stressors.[8,9] Another notable finding by Miller et al[4] is the inverse relationship between family income level and hydrocortisone resistance, although this was not robust across all outcomes (ie, evident only for IL-5). Studies in both primate[10,11] and murine[12,13] models link social status and chronic social stress to hypercortisolism and steroid resistance. Research focused on associations among race/ethnicity, socioeconomic status, and acquired glucocorticoid resistance in human subjects remains sparse and needs to be expanded. Specifically, the relationship between race/ethnicity and socioeconomic status and relative glucocorticoid resistance contributing to differential asthma morbidity in high-risk populations warrants further research. This might inform new interventions that provide support and reduce stress in these high-risk populations that could reverse the relative steroid insensitivity, in addition to consideration of alternative therapeutic management (ie, new anti-inflammatory medications). For the latter, we also need further research to understand the molecular mechanisms underlying glucocorticoid resistance in this context.

In addition to the extant research cited by Miller et al,[4] further insight into the cellular and molecular mechanisms underlying stress-induced steroid resistance is provided in a number of recent studies. Chronic psychologic stress is known to alter innate and adaptive immune responses to a variety of pathogenic challenges, with Toll-like receptors playing a key role. Evidence in murine models suggests that psychologic stress might operate in a Toll-like receptor 4–dependent manner, for example. Powell et al[12] have demonstrated that stress modulates Toll-like receptor cytokine secretion in response to CpG DNA and polyinosinic:polycytidylic acid (poly I:C) in splenic dendritic cells, rendering the dendritic cells resistant to glucocorticoids. Zhang et al[14] have also demonstrated an association between stress and Toll-like receptor 4–mediated phosphoinositide 3-kinase/Akt signaling in mice. Oxidative stress pathways have also been implicated in the link between psychosocial stress and asthma,[15] as well as steroid-resistant asthma.[16,17] This could particularly be relevant in persistent or difficult-to-control asthma, in which neutrophilic, rather than eosinophilic, inflammation predominates.[18] Indeed, it was recently shown that oxidative stress contributes to steroid resistance in the context of neutrophilic inflammation in a mouse model of acute asthma exacerbations.[19]

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Finally, genetic and epigenetic studies tell us that exposure to altered glucocorticoid receptor response through early development, even beginning *in utero*, programs major changes in the endogenous neuroendocrine and immune mechanisms that can, in turn, lead to increased vulnerability to asthma.[20] It will be important to begin to understand factors related to developmental programming of glucocorticoid sensitivity during critical periods of development, which could play a role in the etiology of inflammatory respiratory disorders, as well as subsequent morbidity.

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