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Unlocking the stress-allergy puzzle: need for a more comprehensive stress model

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Type I hypersensitivity is the core mechanism responsible for acute reactions to allergens and the primary mechanism for many allergic disorders, including allergy to foods or venoms. In other disorders in which allergen exposure is more chronic, such as allergic rhinitis or asthma, cellular mechanisms also come into play. Moreover, the efficacy of anti-IgE treatment for asthma demonstrates that although IgE-driven hypersensitivity reactions may be only one component driving symptoms, they are clearly important. Skin prick tests (SPTs), believed to be entirely a type I hypersensitivity-mediated process, are widely used to determine sensitivity in allergic disease, yet there is limited information on factors that affect them.

In this issue, Heffner et al¹ report on the impact of stress and anxiety on SPT results, which provides an elegant reductionist model to examine how psychological factors contribute to IgE-mediated allergic reactions. The investigators previously used a standardized stress test (Trier Social Stress Test) in a cohort of young adults with allergic rhinitis to show a stress-by-anxiety interaction on SPT size.² In the present article, they focused on a subset of these subjects who had positive SPT results after the task that were negative at baseline; 60% of their original study cohort was in this category. They observed that subjects with anxiety levels higher than the median had significantly more negative-to-positive SPT conversions after stress than subjects with anxiety levels lower than the median. No differences were observed between low- and high-anxiety subjects after the nonstress control task. The investigators concluded that these were predominantly conversions of false-negative test results because 75% of these were to allergens to which the participants reported being reactive, although there were no serum IgE tests performed to verify those conclusions.

These findings highlight the need to incorporate more comprehensive assessments of the stress process in allergy and asthma research.³ That is, many studies report effects of life stressors or psychological functioning on allergic or respiratory outcomes. However, we know that psychological dysfunction can moderate effects of acute and chronic stress effects and vice-versa.^{4,5} Assessment of such interactions in future research may more fully elucidate the role of psychological stress in the expression and management of allergic diseases.

Data from animal models and in vitro systems clearly show that mediators associated with stress and anxiety can directly modify mast cell activity and overlap with neuronal pathways that contribute to acute allergen-triggered reactions in vivo. It has been known for many years that there is a bidirectional communication between mast cells and nerves,⁶⁻⁸ but the clinical consequences of that interaction have not been well explored. Mast cells and nerves are in close proximity in peripheral tissue and mast cells produce and have receptors for neurotrophic factors.⁹ Afferent nerve fibers express receptors for a range of mediators that are produced by mast cells, including histamine, adenosine, serotonin, cysteinyl leukotrienes, tryptase, and trypsin.¹⁰ Activation of nociceptive receptors on C-fibers leads to physiologic changes consistent with a response to a “danger signal.” Depending on the tissue, this can be diarrhea and vomiting, sneezing and coughing, itch, or wheal-and-flare reactions. The description of Fc receptors for IgE and IgG on superior cervical ganglion neurons (and calcium signaling in response to IgE-allergen crosslinking) suggests that nerves have the potential to be directly activated by allergen in sensitized individuals.⁵ In addition, mast cells can respond to several neurotransmitters, the best studied being the response to the sensory neuropeptide substance P through actions on the neurokinin-1 receptor.¹¹ One provocative example of nerve-mediated mast cell activation comes from a study in which rats were repeatedly challenged with allergen associated with an auditory tone. Afterward, the auditory tone alone was able to induce mast cell degranulation, showing Pavlovian conditioning of mast cell activation.¹² The role of nerves in generation of symptoms after allergen challenge has been shown in different animal models, including models of asthma and food allergy. There is evidence for a contribution of cholinergic and capsaicin-sensitive sensory nerves in the development of acute responses to allergen in animal models.¹³⁻¹⁶

Stress and anxiety also are associated with variable activation of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis. Almost all leukocytes, including cells of the innate and adaptive immune systems, have receptors for hormones or neuronal mediators released during stress, including glucocorticoids, substance P, neuropeptide Y, corticotropin-releasing hormone (CRH), prolactin, epinephrine, norepinephrine, and serotonin.¹⁷ Mast cells are activated by acute psychological stress in rodents and humans,^{18,19} and activation of mast cells in the gastrointestinal tract by acute stress results in perturbed epithelial barrier function and motility. The major pathway of mast cell activation involves peripheral CRH acting directly on mast cells.^{19,20} There is also interaction between CRH and neuropeptides in the modulation of mast cell activation. Low doses of substance P can trigger calcium signaling in mast cells in the absence of degranulation,²¹ perhaps lowering the threshold for stimulation through another pathway, such as CRH or the high-affinity IgE receptor. Substance P also increases the expression of CRH receptor on mast cells.²²

Although the SPT is a surrogate marker of allergy, it would be of interest to extend these findings to a physiologic outcome such as the response to a nasal allergen challenge, particularly because stress has significant effects on epithelial barrier function that could modify antigen uptake²³ and contribute to clinical reactivity through nonimmune mechanisms. Also, the potential role of stress in food allergy is a growing area of research.²⁴ In the context of food allergy, allergen-specific IgE levels are useful in diagnosis and curves

have been generated for some foods to provide levels that are 95% predictive of clinical reactivity.²⁵ However, IgE levels are not in themselves diagnostic and many individuals with sensitization do not exhibit any clinical reactivity to foods. IgE levels also provide no predictions about severity of reactions. These observations have led to the hypothesis that there may be other contributing factors to the development of allergic symptoms beyond IgE and mast cells. Given the findings of Heffner et al,¹ it would be interesting to examine whether higher anxiety and stress could in part explain the clinically observed variability in responses to food exposure within and between subjects over time, irrespective of food-specific IgE levels. As the investigators state, the cohort also had anxiety levels (measured by the State-Trait Anxiety Scale) that were below the levels that would be expected in a patient cohort. There is a need to evaluate the contribution of stress and anxiety in patient cohorts and to evaluate how these parameters influence symptoms that are associated with the disease.

These data also suggest that interventions focused on lowering stress and anxiety might have a significant effect on decreasing the burden of allergic disease and this should be explored in future research. Interventions to lower stress and anxiety may be particularly relevant to allergic diseases when allergen avoidance is difficult or impossible. Interventions that can partly decrease symptom severity may be of significant benefit to those with allergic rhinitis or asthma and improve quality of life on many fronts. In the context of food or venom allergy, lowering stress and anxiety is unlikely to make allergen exposure safe but may help to decrease adverse symptoms in response to allergen immunotherapy, which also would be of significant benefit to patients.

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