Current perspectives

Stress and asthma: Novel insights on genetic, epigenetic and immunologic mechanisms

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In the United States the economically disadvantaged and some ethnic minorities are often exposed to chronic psychosocial stressors and disproportionately affected by asthma. Current evidence suggests a causal association between chronic psychosocial stress and asthma or asthma morbidity. Recent findings suggest potential mechanisms underlying this association, including changes in the methylation and expression of genes that regulate behavioral, autonomic, neuroendocrine, and immunologic responses to stress. There is also evidence suggesting the existence of susceptibility genes that predispose chronically stressed youth to both post-traumatic stress disorder and asthma. In this review we critically examine published evidence and suggest future directions for research in this field. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Asthma, psychosocial stress, immune system, neuroendocrine system, genetics*

Abbreviations used

ANS: Autonomic nervous system
aOR: Adjusted odds ratio
CRH: Corticotropin-releasing hormone
HA: Handling stimulation
HPA: Hypothalamic-pituitary-adrenocortical
MS: Maternal separation
PACAP: Pituitary adenylate cyclase–activating polypeptide
PTSD: Post-traumatic stress disorder
SES: Socioeconomic status
SNP: Single nucleotide polymorphism

Asthma is a major public health problem in the United States, where approximately 25.7 million children and adults are currently living with asthma.[1] In this country members of certain ethnic minority groups (eg, Puerto Rican and African American subjects) and the economically disadvantaged share a disproportionate burden of the "asthma epidemic."[2]

In the United States ethnic minorities and the economically disadvantaged are disproportionately exposed to chronic psychosocial stressors (eg, poverty, discrimination, and violence).[3] A growing body of literature supports a causal link between exposure to these stressors at the individual or community level and asthma or morbidity from asthma in children and adults (recently reviewed by Yonas et al[4]). For example, physical or sexual abuse during childhood, a major stressor, has been associated with asthma or asthma morbidity in Puerto Rican school-aged children,[5] as well as with adult-onset asthma in African American women.[6] Moreover, a birth cohort study of 145 children with a maternal history of asthma found that parental difficulties in early postnatal life (at age 3 months) were associated with asthma at 6 to 8 years of age.[7] In another birth cohort study including 708 children in Boston, prenatal exposure to community violence was associated with recurrent wheeze at age 2 years (a risk marker for asthma).[8] Current evidence also suggests that the relation between stress and asthma is complex and partially mediated and modified by environmental exposures (eg, outdoor air pollution[8] and cigarette smoking[9]), adherence to treatment, and coping mechanisms (eg, shift-and-persist strategies[10] and family support).

Yet on top of these factors, stress is likely to affect the onset and course of asthma by directly acting on pathogenic mechanisms in the airways.[11,12] Although these pathways have yet to be fully elucidated, preliminary evidence suggests a role for stress in modulating lung development, neuroendocrine and autonomic nervous system (ANS) responses, and the immune system.[4,13] Decades of research show that stressors, when perceived as threatening and unmanageable, modify the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and the ANS. HPA activation occurs when neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH). This molecule travels through the hypophyseal portal circulation to the anterior pituitary gland, which responds to its presence by secreting a pulse of adrenocorticotropic hormone. The adrenocorticotropic hormone signal is carried through the peripheral circulation to the adrenal glands, which synthesize and release cortisol in the zona fasciculata. The ANS consists of sympathetic and parasympathetic branches, the effector molecules of which include epinephrine, norepinephrine, and acetylcholine. By changing the outflow of these systems,

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stress alters the systemic balance of glucocorticoids and catecholamines, as well as concentrations of these (and other) hormones in primary and secondary lymphoid organs.[14] Macrophages and lymphocytes have functional receptors for these hormones (glucocorticoid receptors for cortisol and α- and β-adrenergic receptors for catecholamines), and ligation of those receptors alters these cells' repertoires of gene expression, with downstream implications for trafficking, signaling, proliferation and differentiation, and effector functions.[15] Through these modulatory influences, chronic stressors potentiate reactivity to asthma triggers, such as allergens and infections, and in doing so might exacerbate airway inflammation and airflow obstruction.[16,17]

More recently, mechanistic research in this area has begun to focus on the role of allelic variation in genes that regulate stress responses, as well as stress-induced changes in DNA methylation patterns and gene expression. In this report we first review recent findings on potential biologic mechanisms for stress-related asthma (summarized in Table I),[18-32] which might be modified by environmental and lifestyle factors, social support, or comorbidities, as shown in Fig 1. We then discuss future directions for research in this field.

GENETICS, GENOMICS, AND EPIGENETICS OF STRESS AND ASTHMA

As for other complex diseases, genome-wide association studies have identified common genetic variants that confer susceptibility to asthma but do not account for a large proportion of its heritability (phenotypic variation explained by genetic factors).[33] This "missing heritability" of asthma might be explained by unaccounted phenotypic heterogeneity,[34] structural variation (eg, copy number variants),[35] rare genetic variants with strong effects,[36] gene-gene interactions (epistasis),[36] gene-environment interactions,[37,38] or epigenetic mechanisms, such as DNA methylation[39] or microRNAs.[40] Few studies have examined the role of genetic or epigenetic mechanisms on stress-related asthma.

In a study of more than 1200 (predominantly African American) adults exposed to traumatic events, Ressler et al[41] implicated the pituitary adenylate cyclase–activating peptide (PACAP)–PAC1 receptor pathway on the pathogenesis of post-traumatic stress disorder (PTSD).[41] In this study both PACAP38 (PACAP peptide containing 38 residues) blood levels and the C allele of a functional single nucleotide polymorphism (SNP; rs2267735) in an estrogen-receptor element of the gene for the PAC1 receptor *(ADCYAP1R1)* were significantly associated with PTSD or more PTSD symptoms in female but not male subjects. For example, the correlation coefficient *(r)* for PACAP38 blood level and PTSD symptoms was 0.497 ($P < .005$) in female subjects but nonsignificant in male subjects ($P > .5$). In contrast to these sex-specific associations, methylation of a CpG site in the promoter of *ADCYAP1R1* (assessed in DNA from white blood cells) was shown to be associated with PTSD or more PTSD symptoms (r for symptoms = 0.35, $P < .0005$). *ADCYAP1R1* mRNA was shown to be inducible after fear conditioning in rodents, which further supports the plausibility of the human findings.[41] A female-specific association between the C allele of rs2267735 and PTSD or PTSD symptoms has been replicated in studies of highly traumatized Chinese[42] and African American[43] adults but not in a study of adults of European or African American descent who were not selected on the basis of traumatic exposures.[44] By using magnetic resonance imaging, the C allele of rs2267735 was recently shown to affect fear responses in the amygdala and hippocampus of women with lifetime history of exposure to traumatic events.[45] Of interest, the C allele of rs2267735 was associated with anxiety in school-aged boys and girls, suggesting that any sex-specific effects of this SNP are not present before puberty.[46] In contrast to the published work replicating an association between SNP rs2267735 and PTSD, findings for *ADCYAP1R1* methylation have yet to be replicated for PTSD. Given that PTSD has been associated with asthma or asthma symptoms,[47,48] there has been recent interest in studying both methylation and genetic variants in *ADCYAP1R1* and asthma.

Puerto Ricans are disproportionately affected by asthma in the United States[49-52] and often exposed to violence, both in the household and in the community.[53-55] Our group has shown that physical/sexual abuse and parental stress are associated with asthma in Puerto Rican children.[5,56] Given these findings, known increased susceptibility of Puerto Rican adults to having PTSD after exposure to traumatic events, and experimental evidence suggesting a potential role of *ADCYAP1R1* on regulating expression of the glucocorticoid receptor gene,[57] we examined exposure to violence (assessed by using a validated scale), *ADCYAP1R1*, and asthma in 516 Puerto Rican children aged 6 to 14 years.[18] In this study we demonstrated that exposure to violence is associated with methylation of a CpG site in the promoter of *ADCYAP1R1* (adjusted β value per each 10-point increment in the ETV scale obtained from a linear regression model, 0.5%; 95% CI, 0.1% to 0.9%; $P = .02$) and that such methylation is associated with asthma in Puerto Rican children (adjusted odds ratio [aOR] per each 1% increment in methylation obtained from a logistic regression model, 1.3; 95% CI, 1.0-1.6; $P = .03$). Moreover, we showed that the C allele of SNP rs2267735 (previously implicated in PTSD and anxiety) is associated with 30% increased odds of asthma (95% CI for aOR, 1.0-1.7; $P = .03$) in these children.

Our findings for *ADCYAP1R1* have yet to be replicated, and we cannot exclude reverse causation for the methylation findings (eg, asthma leading to increased DNA methylation) in a cross-sectional study. However, the biological plausibility of our results is supported by experimental models showing that PACAP acts as an endogenous bronchodilator, relaxing airway smooth muscle.[58,59] Moreover, PACAP protects against endotoxin-induced allergic airway inflammation in rodents,[60] in which the PAC1 receptor mediates anti-inflammatory effects in allergic airway inflammation.[61] Together with these experimental findings, our results suggest that genetic and epigenetic variation in a susceptibility gene for PTSD and childhood anxiety *(ADCYAP1R1)* is implicated in the pathogenesis of asthma in children disproportionately exposed to violence or traumatic events, such as Puerto Ricans.

CRH, along with signaling of PACAP, regulates anxiety-related behavior[41] and is thus in a candidate pathway for stress-related asthma. SNPs in the gene encoding the main receptor for CRH *(CRHR1)* have been associated with change in lung function in response to inhaled corticosteroids in patients with asthma or chronic obstructive pulmonary disease in some studies[19-22] but not in others.[23]

Few studies have examined the effects of psychosocial stress on genome-wide expression in tissues relevant to asthma. In a