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Maternal stress and perinatal programming in the expression of atopy

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“Studies evaluating psychophysiological stress reactivity during critical periods of development, including gestation and early childhood, are needed, as they hold particular promise in elucidating specific pathways that increase vulnerability to atopy.”

Biological hypersensitivity to environmental stimuli, a fundamental feature of atopy, contributes to a spectrum of costly pediatric disorders, including allergic rhinitis, atopic dermatitis and asthma. The increase in the prevalence of these disorders and the enormous costs involved in managing atopic patients have motivated efforts to identify early risk factors that may be amenable to intervention and prevention [1–3].

Research continues to delineate early immunophenotypes and early airway-response outcomes among children predisposed to chronic atopic disorders [4]. The development of allergic sensitization, childhood asthma and other atopic disorders run in parallel if certain hereditary and/or perinatal environmental influences prevail, rather than being stepping stones in a progressive atopic march [5]. Those with early (i.e., starting in the first year of life) sensitization to allergens are at greatest risk of subsequently developing chronic atopic disorders, airway inflammation and obstruction. Persistent reactivity throughout early childhood, high-level sensitization and polysensitization have also been more clearly linked to later atopic disease [6,7]. Even in persistently sensitized children, the risk of developing atopic disorders is particularly increased by a positive parental history of asthma/atopy, with these effects being strongest for maternal history [8]. This latter finding, together with other evidence, buttresses the concept of perinatal programming, which proposes that nongenetic factors acting early in life may permanently organize or imprint physiological systems.

The growing list of potential programming agents includes psychological stress. Evidence linking psychological stress to atopy suggests that early disruption of neuroimmunoregulatory processes are probably involved [9]. Both primate and rodent models of prenatal stress and early adverse caregiving have helped us to understand the potential consequences of similar experiences in humans and their relevance to atopy [10]. Early-life adversity shapes stress neurobiology, resulting in disturbed regulation of endocrine and autonomic processes (e.g., the

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hypothalamic–pituitary–adrenal [HPA] axis and the sympathetic–adrenal–medullary system). These disturbed patterns of stress regulation are hypothesized to subsequently modulate immune function, increasing susceptibility to asthma and related diseases. Maternal stress experienced *in utero* may influence programming of these key physiological systems in children [10]. Stressors influence pathogenesis by causing dysregulated biobehavioral states (e.g., depression and post-traumatic stress disorder [PTSD]), which, in turn, program lasting effects on physiological processes that influence disease risk. Infants of mothers who have prenatally programmed biobehavioral sequelae from stress may, thus, inherit biological vulnerabilities that alter reactivity to subsequent challenges [11]. Likewise, non-optimal early-childhood environments and care-giving experiences (e.g., maternal psychopathology or maternal insensitivity) may impact these processes [12,13]. Stress-elicited disruption of these inter-related systems – autonomic, neuroendocrine and immune – may lead to increased vulnerability to allergic sensitization and atopic risk.

The HPA axis seems particularly susceptible to early programming. Prenatal stress has been associated with early and long-term developmental effects resulting, in part, from altered maternal and/or fetal glucocorticoid exposure. Maternal and fetal stress also stimulate placental secretion of corticotrophin-releasing hormone (CRH), which in turn is elevated in the neonatal circulation. Elevated CRH may stimulate the fetal HPA axis to amplify fetal glucocorticoid excess, as well as activate additional elements of the fetal stress response (i.e., catecholamines and neurotrophins), influencing the developing immune and autonomic nervous systems [14]. For example, it has been proposed that alterations in stress-induced maternal cortisol levels may influence fetal immune system development and Th2 cell predominance, perhaps through a direct influence of stress hormones on cytokine production [15]. While these *in utero* responses may be adaptive in the short term, being geared toward coping with anticipated environmental challenges, they may exact a toll in contributing to an increased risk of atopic diseases in later life.

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In humans, both the HPA system and the autonomic nervous system show significant developmental changes in infancy, shaped by interactions with the environment. The HPA axis starts to become organized between 2 and 6 months of age [16], and the autonomic nervous system demonstrates relative stability in resting measures by 6–12 months of age while stability in reactivity measures in response to challenge likely occurs later in development [17]. The HPA axis in particular has been shown to be highly responsive to child–caregiver interactions, with sensitive caregiving programming the HPA axis to become an effective physiological regulator of stress, and insensitive caregiving, promoting hyper- or hyporeactive HPA responses [18]. Several animal models, as well as human studies, also support the connection between caregiving experiences in early postnatal life and alterations of autonomic nervous system balance [17,19,20]. Furthermore, children who have a history of sensitive caregiving are more likely to demonstrate optimal affective and behavioral strategies for coping with stress [13]. Therefore, children with a history of supportive, sensitive caregiving in early development may be better able to cope with environmental stressors and, consequently, less likely to manifest disturbed HPA and autonomic reactivity that put them at risk for stress-related illnesses, such as asthma.

As yet, the specific pathways of an increased vulnerability to atopy in response to perinatal stress is largely unknown in humans. Data regarding the development of allergic sensitization in inner-city minority populations in the USA suggest that new models for understanding the developmental etiology of asthma and other atopic disorders are needed. There is a paradox between the prevalence of atopy in the US inner-city and the currently proposed hygiene

hypothesis – if the hygiene hypothesis is correct, early exposure to microbial products in the inner city should markedly reduce the incidence of allergic sensitization and atopic diseases compared with other US locales [3]. The converse, however, is the reality. In a cross-sectional study of 4164 children in the Third National Health and Nutrition Examination Survey (NHANES), African-American and Hispanic ethnicity was associated with an increased risk of sensitization to cockroaches, dust mites and mold [21]. Stevenson and colleagues have found that allergic sensitization is prevalent in a lower socioeconomic status sample, even among children who do not have a family history of atopy [22]. While impoverished households are more likely to be reservoirs for allergens in higher concentrations than more affluent settings, this does not completely explain the observed differences [23]. Sensitization to multiple allergens is also more prevalent in urban homes, suggesting that some other factor may be enhancing response to allergens in these urban populations. Differential exposure to stress, and variability in stress responses, occurring in these early critical periods, may be factors that augment the likelihood of early atopy by enhancing the immune response to allergen exposure [24]. One intriguing mechanism gaining support in the literature is environmental influences on epigenetic regulation and atopic risk [25]. New data from behavioral studies link the social environment (stress and caregiving) with epigenetic programming. One line of evidence comes from studies of epigenetic changes during long-term potentiation and fear conditioning by Sweat's group [26], and another comes from a study of epigenetic programming related to maternal care [27].

The nature of the stressor(s) that are likely to have a measurable impact on atopic risk is currently unknown. Emerging evidence suggests that exposure to trauma may be a particularly robust potentiator of the cascade of biological events that increase vulnerability to atopy and may help explain the increased risk found in low-income urban populations [28]. The Diagnostic and Statistical Manual of Mental Health Disorders (DSM)-IV-TR defines a traumatic event as one that involves experiencing, being threatened with, witnessing or learning about death or serious injury to self or others and a resultant feeling of intense fear, helplessness or horror (criterion A traumatic event) [29]. Low-income, urban, minority women experience interpersonal violence (e.g., child abuse, intimate partner violence, community violence) and other traumas over their lives at rates markedly above national samples in the USA [30–32]. Numerous studies have demonstrated that victims of trauma experience a host of physiological, affective and behavioral responses, with PTSD and/or major depression emerging in a significant minority, often concomitantly [33,34]. Therefore, not surprisingly, low-income and ethnic-minority mothers, particularly in the perinatal period, demonstrate elevated rates of PTSD and depression [35,36]. These psychological conditions during pregnancy have been repeatedly linked to disruptions in the maternal–fetal HPA axis and, later, the infant HPA axis and autonomic reactivity [11,37]. Furthermore, extensive literature documents associations between maternal traumatic stress, anxiety and depression and serious difficulties in maternal caregiving. Such caregiving difficulties have, in turn, been associated with disruptions in child endocrine, autonomic, affective and behavioral regulation [13]. Consequently, trauma influences on perinatal maternal–child interactions may disrupt infant neuroimmune development through its impact on child stress neurobiology, setting the stage for the altered reactivity characteristic of atopy [10].

Studies evaluating psychophysiological stress reactivity during critical periods of development, including gestation and early childhood, are needed, as they hold particular promise in elucidating specific pathways that increase vulnerability to atopy. Exploring links between maternal trauma and atopic risk may be particularly relevant in urban, high-risk US populations that are disproportionately burdened by both phenomena.

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