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Stress-Related Programming of Autonomic Imbalance: Role in Allergy and Asthma

Rosalind J. Wright

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and Department of Environmental Health, Harvard School of Public Health, Boston, Mass., USA

Abstract

Evidence linking psychological stress to allergy has grown with our increased understanding of the natural history and pathophysiology of these disorders and the neurobiology of stress vulnerability. However, the specific pathways that increase vulnerability to developing allergy and associated disorders remain to be elucidated. Autonomic nervous system functioning (autonomic balance) has been implicated in allergy for some time albeit links between autonomic balance and immune function in early development have been under studied. Starting in utero, stress may influence the programming of brain neurotransmitter systems, sympathetic and parasympathetic nervous system functioning, and the hypothalamic-pituitary-adrenal axis, which in turn may alter neural regulation of immune function. Epigenetic dysregulation of gene expression may be a fundamental mechanism for programming of early neural-immune processes.

An important step toward identifying children at risk for chronic allergic and inflammatory conditions is characterizing relevant exposures and mechanisms that lead to and maintain early predisposition. Plasticity is a consequence of environmental exposures during critical life periods (e.g. periods of rapid growth and development) affecting physiological systems that orchestrate underlying developmental processes [1]. Stress experienced during early life, beginning in utero (i.e. maternal stress during fetal ontogeny) can permanently alter the responsiveness of key regulatory systems (i.e. autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis [2–4]) with consequent influences on the developing immune system and enhanced disease risk [5, 6]. Increasingly, evidence suggests that autonomic imbalance or dysfunction, independent of neuroendocrine or hormonal abnormalities [7–9] may be an understudied factor in the expression of a number of disorders, including allergy.

This chapter briefly reviews evidence linking autonomic imbalance and allergy. Given the focus here on the nervous system and allergy, the discussion will then focus more directly on what we know about stress-induced programming of neurological functioning, specifically autonomic balance, that may be related to immune function, allergy and related disorders during early childhood. While mechanisms underlying these relationships are unclear, the involvement of epigenetic dysregulation has gained particular focus and will be discussed [3, 10, 11].

Autonomic Imbalance and Allergy

The etiology of allergic disease (e.g. allergic rhinitis, atopic dermatitis, atopic asthma) is multifactorial with neurological involvement playing an important role [12, 13]. Research linking neural activity and allergy points to bidirectional influences between central and peripheral autonomic nervous system (ANS) activity and both immune responses and allergic symptomatology. Indeed, research implicating autonomic imbalance in the pathogenesis of inflammatory and hypersensitivity reactions in the nose, skin and the lung spans more than four decades [14–16]. While understanding the link between neurological functioning and allergy remains an active area of research, mechanisms operating in early development remain poorly understood.

Our understanding of how the nervous system may be involved in the organization of the immune response continues to evolve [17–20]. Overlapping evidence from various fields demonstrates the bidirectional communication between the brain and immune system with the autonomic nervous system (ANS) playing a central role [21–23]. When immune cells (i.e. T cells, mast cells, dendritic cells) are activated locally (e.g. in the airways) and release proinflammatory molecular mediators, these signals not only influence cells of the innate and adaptive immunological system in the periphery but also activate sensory pathways that relay information to the central nervous system (CNS) [13, 24, 25]. At the same time, CNS-mediated regulation of the peripheral immune response is mediated through vagal output (e.g. suppressing the innate immune defense to pathogens; altering pro-inflammatory cytokine balance). The efferent vagus nerve is proposed as an immune-to-brain pathway that may directly modulate the airway immune response to pathogenic invasion or to injury by irritants and toxins. The cholinergic vagus nerves participate in the regulation of the airway inflammatory response, in part, through efferent vagal endings present in airway smooth muscle. Cholinergic mechanisms represent the predominant constrictor neural pathway in human airways [26]. Differences in expression of muscarinic acetylcholine receptors in asthma suggest that cholinergic system may participate in the molecular framework influencing airway function in this context [27]. Conversely, inflammatory processes may exacerbate allergic cholinergic airway narrowing. A current model of airway narrowing in allergic asthma highlights inflammation-induced damage of m2-autoreceptors which downregulate cholinergic transmission at the level of the postganglionic nerve terminal and thereby limiting the constriction of airway smooth muscles [28, 29]. Notably, animal studies suggest that neural control influencing airway smooth muscle function and these irritant receptor systems are established during the perinatal period [30].

Growing evidence implicates a number of neurotrophins (NTs) as mediators or moderators of allergic disorders [31, 32] and shows that NT expression and signaling may be influenced by stress [33, 34]. One study in subjects with allergic asthma demonstrated that increased psychological stress was correlated with increased levels of brain-derived neurotrophic factor (BDNF) which, in turn, was negatively correlated with percent predicted forced expiratory volume in 1 s (FEV₁) [35]. Notably, stress perception was also positively correlated with the percentage of TNF- α -producing T cells in these subjects. The authors speculated that this may point to a neuroimmunological interaction given the constitutive secretion of BDNF in human peripheral blood monocytes which was enhanced when stimulated with TNF- α [36]. This group has also demonstrated stress-induced increase in tachykinin-like substance P associated with allergic airway inflammation in a mouse model [37]. Thus, it is reasonable to hypothesize that the programmed balance between functional parasympathetic and sympathetic activity in relation to stress, emotional stimuli, and immune function may be important for the expression of allergic sensitization and atopic disorders [38].

Pre- and Postnatal Stress and Physiologic Programming

This section provides an overview of how stress may be involved in the early programming of these systems.

General Stress Paradigm

Stressors are generally thought to influence pathogenesis by causing dysregulated biobehavioral states and lasting effects on physiological processes that influence disease risk [39–41]. In response to stress, physiological systems may operate at higher or lower levels than in normal homeostasis. It is the disturbed balance of these systems is most relevant to disease. Neural and immune defensive biological responses important for the short-term response to stress may produce long-term damage if not checked and terminated [42]. The detrimental cost of such accommodation is conceptualized as ‘allostatic load’ (i.e. wear-and-tear from chronic under- or overactivity).

One key regulatory system vulnerable to early life programming is the autonomic nervous system (ANS) [4]. As autonomic functioning and the HPA axis act cooperatively to maintain homeostasis, it is important to consider interactions between these systems as well. Disturbed regulation of these stress systems (e.g. ANS, HPA axis) in the mother consequent to her own stress history may modulate offspring immune function beginning in utero [43–45]. Postnatally, nonoptimal early childhood environments and caregiving experiences (e.g. maternal psychopathology, insensitivity) may impact the child’s biobehavioral stress response [46–48] with continued effects on immunomodulation.

Perinatal Programming of Autonomic Reactivity

Several animal models as well as human studies support the connection between an adverse intrauterine environment as well as experiences in early postnatal life and alterations of autonomic nervous system balance (e.g. sympathovagal balance) [30, 49–51]. Experimental rat models have shown that prenatal stress is associated with exaggerated cardiovascular reactivity to restraint stress [52]. In humans, infants’ autonomic responses show developmental changes with relative stability between 6 and 12 months of age [53]. The balance between functional parasympathetic and sympathetic activity in relation to stress, emotional stimuli, and immune function may be established during this early life period.

The placenta has increasingly been recognized as a key organ involved in fetal programming [54, 55]. Maternal and fetal stress stimulates placental secretion of corticotrophin-releasing hormone (CRH), which in turn is elevated in the neonatal circulation [56–59]. This may stimulate the fetal HPA axis to amplify fetal GC excess as well as activate additional elements of the fetal stress response (i.e. catecholamines and neurotrophins) influencing the developing autonomic nervous system and neural-immune interactions [44].

The caregiving environment is also important to early programming of stress regulatory systems in children. In humans, infants’ autonomic responses [53] and the HPA system remain highly reactive and labile in early infancy and start to become organized between 2 and 6 months of age through transactions between the child and caregiver [60]. Studies have consistently demonstrated that the quality of caregiving that the child receives during early development predicts the emergence of later self-regulation abilities, with sensitive caregiving associated with more optimal functioning of the child’s stress systems [61]. Not surprisingly then, perinatal maternal stress has been associated with poor stress regulation and other negative outcomes in both animal and human offspring [62–73].

Perinatal Stress and Immunomodulation

Prenatal stress increases allergen-induced airway inflammation [74, 75] and airway hyperresponsiveness (AHR) [76] in mice offspring. Prenatally stressed mice also show dysregulated cellular and humoral immune response upon antigen challenge (e.g. Th2 adaptive response and increased IgE) [76]. In primates, prenatal stress impacts the newborn's antigen response [77]. While these data are suggestive, human studies examining the effects of prenatal stress on airway responses or the developing atopic phenotype in infancy and early childhood are sparse.

While no prospective human study has measured prenatal maternal stress directly in association with child wheeze or other early atopic phenotypes, a few have considered maternal psychological functioning, as a correlate of stress exposure. Lin et al. [78] reported an association between maternal self-reported nervousness during pregnancy and elevated cord blood total IgE and the Avon Longitudinal Study of Parents and Children (ALSPAC) showed associations between maternal anxiety during pregnancy and asthma development in preadolescent children [79]. Reyes et al. [80] reported an association between a composite measure of psychological functioning in pregnancy (maternal demoralization) and increased risk of transient and persistent wheeze in a high-risk New York City sample adjusting for maternal (age, ethnicity, education, history of asthma, and IgE) and child (gender, tobacco smoke exposure) factors.

In a prospective urban pregnancy cohort in Boston [the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) study], my group has documented evidence that prenatal maternal stress is associated with increased cord blood IgE expression in the children [81, 82] and enhanced reactivity to low-dose prenatal allergen exposure as indexed by elevated IgE in cord blood [83] (fig. 1). My group has also prospectively linked early life caregiver stress to dysregulation of immune function in another Boston birth cohort predisposed to allergy [84]. We found the increased maternal caregiving stress was associated with greater antigen-specific TNF- α production in particular. A number of studies have found that stress induces the release of pro-inflammatory cytokines including TNF- α as well as others (e.g., IL-6) [85–87] and that TNF- α is important in asthmatic airway inflammation. Continued follow-up of these prospective studies will examine whether stress-induced perinatal immunomodulation impacts the expression of allergic disease in these children.

Factors, including psychological stress, that alter the maturation of local immune networks (e.g. dendritic cells, epithelial cells (ECs), regulatory T cells) may predispose to a Th2 phenotype [88]. Psychological stress has been associated with increased proportions of both natural killer (NK) and NKT cells as well as the altering their functional mechanisms [89, 90].

Chronic psychological stress is known to alter innate- and adaptive-immune responses to a variety of pathogenic challenges with Toll-like receptors (TLRs) playing a key role. Evidence in murine models suggests that psychological stress may operate in a TLR4-dependent manner. Powell et al. [91] have demonstrated that stress modulates Toll-like receptor cytokine secretion in response to unmethylated CpG motif in bacterial deoxyribonucleic acid (DNA) and polyinosinic-polycytidylic acid (Poly I:C) in splenic DCs rendering them resistant to glucocorticoids. Zhang et al. [92] have demonstrated an association between stress and TLR4-mediated P13K/Akt signaling in mice. Notably, recent data from a human pregnancy cohort showed that higher levels of prenatal maternal stress was associated with increased IL-8 and TNF- α production following microbial stimulation

(e.g. Poly I:C) suggesting that prenatal stress may modify the neonatal immune response through Toll-like receptor (TLR)-dependent pathways [93].

Integration of Systems

Given well documented interactions between the central and peripheral autonomic nervous system, the endocrine system and the immune system starting in early development, future research needs to understand how these systems function in the mothers during pregnancy and in early childhood [94, 95]. For example, no studies to date have examined the influence of prenatal and early life stress on the expression of neuropeptides and their possible role on allergic sensitization and/or airway inflammation and response in early development.

Moreover, as we know that these systems likely act cooperatively to maintain homeostasis, the majority of existing studies examining the impact of stress on physiological systems and subsequent health have examined one system in isolation from others. Recent findings related to HPA axis and ANS functioning highlight the need to consider these systems simultaneously due to their interactive influences on outcomes. Specifically, two recent studies have shown a modifying effect of high vs. low salivary alpha-amylase (as a surrogate marker of sympathetic nervous system functioning) on the influence of high vs. low cortisol on behavioral outcomes in young children [96] and adolescents [97].

Epigenetics – A Fundamental Programming Mechanism

Mechanisms underlying early life programming of neural-immune processes are still not well understood. Growing attention has focused on epigenetic dysregulation of gene expression (i.e. long-lasting changes in gene expression that result from environmental influences) as a programming mechanism [98]. Epigenetics may be at the roots of developmental plasticity in infant stress systems [3, 10, 11]. DNA methylation, the most widely studied epigenetic mechanism, is an adaptable epigenetic mechanism that modifies genome function through the addition of methyl groups to cytosine to form 5-methylcytosine (5mC). Increased methylation silences expression. Gene specific DNA methylation changes in response to environmental signals including chemical exposures such as diet and toxins [99, 100]. Recent findings also implicate psychological stress with behavioral studies demonstrating epigenetic changes during fear conditioning [101] and evidence for epigenetic programming related to maternal care [11, 102]. Methylation marks are largely established early in life [98, 103] and may mediate persistent changes in biological and behavioral phenotypes over the lifespan [104]. This is buttressed by human studies demonstrating that prenatal and early life environmental conditions lead to epigenetic changes that may persist throughout life. For example, individuals exposed prenatally to the Dutch famine have reduced DNA methylation of the maternally imprinted insulin-like growth factor II (IGF2) gene compared to their unexposed same-sex siblings when assessed six decades later [105]. In another study, early life experiences of severe psychosocial stress (child abuse) was linked to increased methylation of the hippocampal glucocorticoid receptor (GR) gene (NR3C1 exon 1_F) and reduced GR messenger RNA (i.e. reduced expression) compared to control subjects not exposed to such early stress [106].

As summarized earlier, stress-elicited disruption of interrelated systems – autonomic, neuroendocrine, and immune systems – in mothers prenatally may lead to increased vulnerability in their children. Epigenetics may be at the roots of developmental plasticity in infant stress systems. Given the complexity of these interrelationships, a major challenge will be selecting specific gene pathways through which effects are operating. This brief overview focuses on those pathways that have been identified that may be involved in programming of neural-immune pathways in general and autonomic balance more specifically as summarized in figure 2.

While epigenetics has been proposed as a mediator between prenatal stress and programming of the infant stress response [3], prospective epidemiological studies designed to examine these relationships are sparse. Oberlander et al. [107] reported an association between maternal depression (a correlate of stress) assessed in the 3rd trimester of pregnancy and increased methylation of a region in the GR gene (NR3C1 promoter) – the same region examined in the suicide study [106] and the human homologue of the region Weaver et al. [104] studied in a rodent model of maternal care and programming of the offspring HPA response. Cord blood DNA was used in this sample including 82 subjects. Increased methylation of NR3C1 was also associated with increased salivary cortisol responses to a standardized stressor (habituation-information processing task) in the 3-month-old infants. The stress response was indexed by a direction of change score between a baseline cortisol and a poststress recovery sample. Infants with an increased cortisol response had significantly higher NR3C1 methylation compared to infants whose cortisol levels declined.

Studies examining the influence of autonomic imbalance in mothers in this context or considering ANS stress reactivity in early life/infancy as well as the infant HPA response as they subsequently relate to early childhood immunophenotypes is needed. Future research should evaluate methylation marks in genes known to control functions modified by stress which are expressed in the target tissues (fig. 2). Some examples from the extant literature are summarized below.

Early life programming of the HPA axis [108–110] may be reflected in the GR gene [111, 112]. In pregnancy, maternal-to-fetal transfer of GCs is regulated by a placental enzyme, 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) [113, 114]. While 11 β -HSD2 provides a protective barrier, approximately 10–20% of maternal GC crosses intact to the fetus [114, 115]. As maternal GC levels are higher than those of the fetus, even subtle changes in placental 11 β -HSD2 activity may affect fetal GC exposure [116]. GC receptors are expressed in most fetal tissues from early embryonic stages [117–119] including the placenta where they mediate metabolic and anti-inflammatory effects. 11 β -HSD2 is also expressed in the placenta [120], vasculature [121, 122] and peripheral WBCs [123, 124]. Notably, changes in epigenetic marks in DNA from peripheral WBCs may inform links to adverse outcomes even when the ultimate target tissue is not available. For example, an epigenetic regulatory relationship to hypertension is reported for 11 β HSD2 in peripheral WBC DNA [125]. Catecholamines reduce 11 β -HSD2 transcription [126] while GCs increase 11 β -HSD2 activity [127] in cultured trophoblasts.

Brain-derived neurotrophic factor (BDNF) may be an interesting target gene given animal studies showing that this gene is regulated by methylation and is sensitive to early adverse life experiences, stress [128, 129] and exposure to GCs [130]. Despite its name, BDNF has diverse functions during development and is expressed in a number of tissues including the placenta and peripheral WBCs [131–133]. BDNF is an important component of the HPA pathway and in sympathovagal balance [134, 135]. It is proposed that stress-induced increased cortisol results in the reduced expression and impaired function of BDNF [136]. This gene has been linked to nitric oxide (NO) production [137] and may play a role in the inflammatory stress response as well.

Given increasing evidence that neurotrophins (NTs) may be mediators or moderators of allergic disorders [31, 32] and that NT expression and signaling may be influenced by stress [33, 34] in early development this may be another important pathway. Other research shows that certain NTs involved in the stress axes (e.g. pituitary adenylate cyclase-activating polypeptide; PPACAP) regulates autonomic function by maintaining sympathetic-

parasympathetic balance and contributes to peripheral homeostatic maintenance, particularly under stress conditions [138] and are involved in immunity [139].

Inducible nitric oxide synthase (iNOS) is developmentally regulated in the fetus and is likely important in regulating fetal blood flow and sympathetic nerve activity [140–142]. NO is produced in the vasculature, placenta, and peripheral WBCs [143]. NO expression has been linked to arterial reactivity in pregnancy [144]. Emerging evidence suggests oxidative stress and reactive oxygen species (such as NO) play important roles in the modulation of autonomic balance [145], including in pregnancy [146]. NO production is modulated by hormones including cortisol [147]. Stress may influence expression of iNOS through effects on transcription factors such as nuclear factor kappa B which is strongly counterregulated by GR-dependent mechanisms [148].

Norepinephrine transporters (NETs) are membrane proteins that conserve neurotransmitters by transporting them back into the presynaptic neuron. Methylation, and therefore silencing of this gene, may result in increased co-release of epinephrine and decreased norepinephrine reuptake thus creating a mechanism for increasing synaptic and circulating levels of catecholamines. NET expression in peripheral tissues is associated with autonomic outflow [149, 150]. NET is expressed in the placenta [151].

Correlates of stress have also been associated with up-regulation of inflammatory signaling pathways and cytokine expression including TNF- α in the placenta [152]. Elevated proinflammatory cytokines (e.g. TNF- α) assessed systemically or in the placenta have been associated with adverse outcomes including low birth weight, pre-term delivery, and effects on the umbilical circulation [153, 154]. Inflammation is considered a central mediator of stress effects on cardiorespiratory and autonomic responses [155]. Based on preliminary studies in our lab, we focus on TNF- α . We have shown an association between maternal stress prenatally and increased expression of TNF- α in stimulated cord blood lymphocytes [93].

Conclusion

Plasticity is a consequence of environmental exposures during critical life periods affecting physiological systems orchestrating underlying developmental processes. The ANS is a putative key regulatory system vulnerable to perinatal stress-related programming toward trajectories of enhanced pediatric and adult disease risk. Given the generalized integration of ANS functioning (e.g. involvement in the modulation of the immune system, disruption of autonomic balance in early development may have long-term health implications for allergic and inflammatory diseases.

Further studies are required to establish the exact contribution of the ANS in the initiation and perpetuation of allergy. Epigenetics may be a fundamental mechanism involved in programming of autonomic balance in early life with implications for the developing immune system and thus should be a focus of research going forward in this area.

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Fig. 1.

Association between increasing prenatal maternal stress (negative life events) and cord blood IgE stratified by high vs. low maternal prenatal dust mite exposure.

Fig. 2.
Potential pathways vulnerable to stress-related methylation changes.