Published in final edited form as:
Biol Psychol. 2010 April ; 84(1): 46–56. doi:10.1016/j.biopsycho.2010.01.007.

Perinatal stress and early life programming of lung structure and function

Rosalind J. Wright, MD, MPH[1,2]

[1] Channing Laboratory, Brigham & Women's Hospital, Harvard Medical School, Boston, MA

[2] Department of Environmental Health, Harvard School of Public Health, Boston, MA.

Abstract

Exposure to environmental toxins during critical periods of prenatal and/or postnatal development may alter the normal course of lung morphogenesis and maturation, potentially resulting in changes that affect both structure and function of the respiratory system. Moreover, these early effects may persist into adult life magnifying the potential public health impact. Aberrant or excessive pro-inflammatory immune responses, occurring both locally and systemically, that result in inflammatory damage to the airway are a central determinant of lung structure-function changes throughout life. Disruption of neuroendocrine function in early development, specifically the hypothalamic-pituitary-adrenal (HPA) axis, may alter functional status of the immune system. Autonomic nervous system (ANS) function (sympathovagal imbalance) is another integral component of airway function and immunity in childhood. This overview discusses the evidence linking psychological factors to alterations in these interrelated physiological processes that may, in turn, influence childhood lung function and identifies gaps in our understanding.

Keywords

maternal prenatal stress; postnatal stress; programming; hypothalamic-pituitary-adrenal axis; immunomodulation; autonomic nervous system; lung function; airway inflammation; airway hyperresponsiveness

Introduction

Respiratory disorders are a leading cause of morbidity and mortality in children (Martin et al., 2008). Childhood lung function is important to the development of chronic obstructive pulmonary disease (COPD) in later life (von Mutius, 2002) with COPD projected to be the fourth leading cause of death worldwide by the year 2020 (Mannino and Braman, 2007). Thus, understanding early childhood factors that contribute to early airway inflammation and lung function that may be amenable to prevention and intervention is an important area of research.

Corresponding author: Rosalind J. Wright, MD MPH Channing Laboratory 181 Longwood Avenue Boston, MA 02116 Phone: 617 525 0867 Fax: 617 525 2578 rosalind.wright@channing.harvard.edu.

Due to significant developmental plasticity, exposure to environmental toxins during prenatal and/or early postnatal development may alter the normal course of lung morphogenesis and maturation, resulting in changes that affect both structure and function of the respiratory system (Pinkerton and Joad, 2006). Moreover, when normal development is altered, the early effects may persist into adult life, magnifying the public health impact (von Mutius, 2002). Longitudinal studies of the natural history of lung function have shown that a number of early life risk factors including asthma, active and passive smoking prenatally and during childhood, atopy, lower respiratory infections, low socioeconomic status (SES), and perinatal factors including birth weight, gestational age, and nutrition are associated with reduced lung function over the life course (Gern, 2000; Gern, Rosenthal et al., 2005; Hanrahan et al., 1992; Jackson et al., 2004a; Jackson et al., 2004b; O'Connor et al. 1987; Shaheen, 1997). However, these factors do not fully account for observed effects suggesting that as yet unidentified risk factors need exploration.

While the mechanisms of early life environmental influences on lung function are not completely understood, evidence suggests that aberrant or excessive pro-inflammatory immune responses, both locally and systemically, are a central determinant of lung structure-function changes (Holt et al., 2005; Prescott, 2006). Regulatory pathways that involve the collaboration of innate and acquired immune responses are involved. Influences of factors outside the immune system, such as neurohormonal and autonomic nervous system functioning (phenotypes), may also be important (Buijs et al., 20088; Elenkov et al., 2008). Both glucocorticoid action and sympathovagal balance play a role in regulating lung function and airway response, including having a major role in fetal and postnatal lung development.

Overlapping research suggests that negative emotion and psychological stress influence respiratory processes and lung function, having both transient and more long-term effects (Ritz, 2004; Ritz and Kullowatz, 2005). It has been estimated that between 20-40% of asthmatic subjects have significant changes in lung function induced by emotional stimuli (Isenberg et al., 1992). In one study, Ritz and Steptoe (2000) demonstrated clinically significant changes in forced expiratory volume in the first second (ΔFEV1) (i.e., ΔFEV1 > 15%) in association with negative mood states in 25% of the adult asthmatic subjects with mild to moderate disease. In another series of studies, Ritz and colleagues examined the effects of affective states on respiratory resistance (in both healthy and asthmatic subjects) using the forced oscillation technique during viewing of pictures, imagery, and films (for an overview of studies see Ritz, 2004). Collectively the findings from these studies showed the greatest effect was induced by negative states with within-individual effect sizes for an increase in respiratory resistance (relative to prestimulus levels) ranging between $d = 0.37$ and 1.02 depending on the stimulus material. Cross-sectional (Jackson et al., 2007) and longitudinal epidemiological studies in adults (Kubzansky et al., 2006; Kubzansky et al., 2002) have linked negative emotion to reductions in maximally attained lung function as well as a more accelerated rate of lung function decline. While studies examining stress in the prenatal period are not available, one study in urban children found a relationship between exposure to chronic stress (violence) in early childhood and reduced lung function at age 6 years (Franco Suglia et al., 2007). Moreover, overlapping evidence demonstrating that psychological factors influence neurohormonal, and consequently, immune inflammatory processes, starting *in utero* suggest their possible role in early lung growth and development (Wright, 2007). Animal studies, and some early work in humans, have advanced our understanding of how perinatal stress may be linked to evolving immunocompetence and airway responses in early life, albeit research in humans remains sparse. In the discussion that follows, we review the evidence suggesting that stress elicited disruption of interrelated systems - neuroendocrine, autonomic, and immune – during the perinatal period, may lead to increased vulnerability to airway inflammation and reactivity

as well as reduced lung function in later life. Evidence is also reviewed suggesting that programming of early lung development may occur through epigenetic influences on gene regulation in critical periods of development starting prenatally.

Developmental Plasticity of the Respiratory System

Plasticity is a consequence of environmental exposures during critical life periods affecting key physiological systems that operate in orchestrating underlying developmental processes (Feinberg, 2007). Lung development commences *in* utero and progresses through to adolescence and young adulthood when maximally attained lung function is achieved. Due to rapid growth and plasticity of physiological characteristics during gestation and early childhood, the fetus and young children may be particularly vulnerable to environmental toxins (Kajekar, 2007). Adolescence is another period of rapid growth in lung function and also warrants attention in this regard.

Epidemiological studies demonstrate that prenatal factors that contribute to intrauterine growth restriction (IUGR) and low birth weight increase the risk of respiratory problems and reduced lung function in infants, children and adults as noted above. Factors that play a role include maternal prenatal stress and maternal-fetal cortisol disruption (e.g., Kivlighan et al., 2008). In animal models, restrictive growth *in utero* has been linked to reduction of internal surface area relative to lung volumes (Harding et al., 2000) and also airway development – specifically, impaired growth of bronchial walls which may have implications for airway compliance in later life (Wignarajah et al., 2002). The mechanisms underlying such structural changes are not completely elucidated.

While the origins of chronic lung diseases are multi-factorial, the central underlying mechanisms leading to reduced lung function and exaggerated responsiveness to bronchoconstrictor stimuli involve chronic airway inflammation associated with a cycle of injury, repair and remodeling (Holgate, 1997; Holt et al., 2005). The fundamental cause of the underlying airway inflammation is aberrant and/or excessive immune responses to various environmental agents (Holt et al., 2005). While such changes have been well documented in older children with clinical manifestations of asthma and reactive airways disease, it has become evident that airway inflammation and early remodeling occur and progress even in the presymptomatic and/or subclinical state (Pohunek et al., 2005; van den Toorn et al., 2001). This further underscores the importance of the early childhood period as lung function may be programmed or ‘set’ in the first years of life (Bush, 2008; Morgan et al., 2005; Rasmussen et al., 2002). Other research has focused on the role of the nervous system and neuropeptides in airway inflammation and response (Undem and Weinreich, 2003). Studies have also documented autonomic nervous system (ANS) dysregulation (increased heart rate variability, increased vagal tone) in asthmatic children (Anthracopoulos et al., 2005; Kazuma et al., 2000; Miller and Wood, 1997; 2003). Recent advances in methodology allow for the assessment of autonomic measures in even young infants suggesting that the disruption of cardiorespiratory regulation may be evident in the first year of life (Alkon et al., 2006; Bosquet-Enlow et al., 2009) and vulnerable to *in utero* and early postnatal programming related to environmental factors (Cohen et al., 2008; Propper et al., 2008).

Taken together, these data suggest that the developmental origins of the structural and functional organization of the lungs involve, in part, the coordinated maturation of the immune, neural, and endocrine systems. Environmental toxins that disrupt these interrelated systems during prenatal and/or early postnatal development may thus alter the normal course of lung morphogenesis and maturation, potentially resulting in long-term changes in the respiratory system (Kajekar et al., 2007; Bavis and Mitchell, 2008; Mitchell and Johnson,

2003). Psychological stress is an important candidate for such environmental programming although this remains virtually unexplored in human studies.

Key Physiological Systems Linked to Lung Development and Airway Responses

Immune function

Research continues to delineate the relationships among early environmental influences, immunodeviations, and developmental outcomes in the lungs (Heaton et al., 2005; Prescott, 2006). Immunophenotypes linked to airway inflammation and reactivity show significant interindividual variability and are dependent on the particular environmental challenge as well as timing of exposure(s). The most common cause of chronic airway inflammation in early childhood is asthma. Although diverse pathogenic mechanisms are likely involved in different forms of asthma and the resulting airway changes [i.e., airway hyperreactivity (AHR), which is thought to be present in all patients with asthma (Wills-Karp, 1999)], over the past 10 years there has been much focus on the influence of the systemic propensity for type 2 T-helper (Th2) allergic responses and eosinophils (Umetsu et al., 2002). Since the description of Th1 and Th2 clones, characterized by different patterns of cytokine secretion (Mossman and Coffman, 1989; Mossman and Sad, 1996), it has become evident that chronic airway inflammation and associated clinical syndromes (e.g., allergic asthma) are associated with a systemic Th2-biased response (Robinson et al., 1992). The Th2 paradigm involves a complex interaction of T and B lymphocytes, and antigen presenting cells, resulting in the production of higher levels of cytokines, such as interleukin-4 (IL-4) or IL-13, lower levels of interferon gamma (IFN-γ) and increased immunoglobulin E (IgE) production. These mechanisms have their roots in early life with an immunological bias towards a Th2 phenotype *in utero* (Devereux et al., 2002; G Devereux et al., 2001; Liao et al.,1996; Miles et al., 1996; Prescott et al., 1998; Tang et al., 1994). Epidemiological studies suggest that perinatal environmental conditions determine whether this propensity persists or is redirected toward Th1 and/or T cell regulatory (Treg) pathways, even in those with a genetic predisposition to allergy (Garn and Renz, 2007; Ownby et al., 2002; Taussig et al., 2003; Wang and McCusker, 2006; Willwerth et al., 2006). Experimental findings suggest that perinatal stress may influence the evolving systemic propensity for type Th2 responses (i.e., enhanced adaptive immunity) as discussed below.

While the Th2 paradigm has been useful in understanding the subjects with allergic asthma and airway inflammation, this is clearly not able to explain all forms. Early wheeze and asthma is increasingly understood to be a heterogeneous syndrome associated with diverse factors that involve not only allergen sensitization, but also infection, air pollution, tobacco smoke, and perinatal stress (Gold and Wright, 2005; Pinkerton and Joad, 2006). These pathways may be relevant to atopic wheeze and asthma, however a significant proportion of recurrent airway obstruction in the preschool years is nonatopic wheeze (Bush, 2008). These children often do not have a family or personal history of atopy. Airway changes are marked by neurtophilic inflammation (Wenzel and Busse, 2007) albeit increased eosinophilia and IgE production are common to both atopic and nonatopic wheeze (Turato et al., 2008).

It is also evident that non-Th2 factors, e.g., IFN-γ (a Th1 cytokine) and neutrophils, are frequently found in the lungs of many patients with asthma, particularly in those with more severe disease (Wenzel and Busse, 2007). Indeed, Th1 cells also play a role in allergic inflammation (Hansen et al., 1999). It is now accepted that the Th2 biased polarization of adaptive immunity may be only one of several axes that result in enhanced susceptibility to airway inflammation and altered reactivity. Antigen-independent responses including innate immune cells [e.g., bronchial epithelial cells, alveolar macrophages, and dendritic cells

(DCs)] may also be important in modifying airway inflammation (Suarez et al., 2008). Environmental influences may impact maturation process of dendritic cells, thus determining their phenotype and function.

Still other evidence has identified a novel T cell subset associated with pulmonary inflammation as a result of particular environmental exposures (e.g., cigarette smoke exposure, ozone) (Harrison et al., 2008; Miossec et al., 2009). A number of investigators have examined several distinct mouse models of asthma and AHR, including allergic and non-allergic forms, searching for common disease mechanisms. What has been found is that a component of innate immunity, natural killer T (NKT) cells, are required for the development of multiple forms of AHR, induced with allergen (Akbari et al., 2003), exposure to ozone (a component of air pollution) (Pichavant et al., 2008), and exposure to respiratory viruses (Kim et al., 2008). Moreover, different subsets of NKT cells are involved in these different forms of AHR. It has also been demonstrated that NKT cells produce IL-17A in the context of oxidative stress, and it is known that oxidative stress can exacerbate allergen induced AHR (Rangasamy et al., 2005).

Neuroendocrine function

Influences of factors outside the immune system, such as neurohormonal phenotypes, may also influence these processes (Buijs et al., 2008; Elenkov and Chrousos, 1999; Elenkov et al., 2008) albeit such relationships are virtually unexplored in human early life respiratory disorders, at least directly. Glucocorticoids play a major role in regulating fetal and postnatal lung development (Grier and Halliday, 2004). Many studies have demonstrated that fetal and early postnatal exposure to endogenous or exogenous corticosteroids affect lung development and that resulting structural alterations persist (Harding et al., 2000). Evidence also links hormonal imbalances (in particular, cortisol) with altered cytokine and Th1/Th2 balance. For example, glucocorticoids (GCs) are known to inhibit the production of IL-12, IFN-γ, by antigen presenting cells and Th 1 cells, but up-regulate the production if IL-4, IL-10, and IL-13 by Th2 cells (Wonnacott and Bonneau, 2002), and to prevent the development of regulatory T cells (Stock et al., 2004). This may induce selective suppression of the Th1-mediated cellular immunity and trigger a shift towards Th2-mediated humoral immunity (Elenkov and Chrousos, 1999; Elenkov et al., 2005). It has been proposed that alterations in maternal cortisol levels *in utero* may influence fetal immune system development and Th2 cell predominance, perhaps through direct influence of stress hormones on cytokine production (von Hertzen, 2002; Wright, 2005). In addition, glucocorticoid resistance may be an important determinant of lung development and function (Barnes, 2004; McKinley et al., 2008).

Autonomic nervous system

Our understanding of how the nervous system may be involved in the organization of the immune response continues to evolve (Sternberg, 1997, 2001; Sternberg, 2006; Tracey, 2002). 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 the airway smooth muscles. Cholinergic mechanisms represent the predominant constrictor neural pathway in human airways (Barnes, 1986). 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 (Lutz and Sulkowski, 2004). Conversely, inflammatory processes could exacerbate allergic cholinergic

airway narrowing. A current model of excessive airway narrowing in allergic asthma highlights inflammation-induced damage of m2-autoreceptors which downregulate cholinergic transmission at the level of the postganglionic nerve terminal in health and thereby limit the constriction of airway smooth muscles (Barnes, 1992; Fryer and Jacoby, 1998). Notably, a number of animal studies suggest that neural control of airway smooth muscle and the irritant receptor systems is established during the perinatal period (Card et al., 2005). It thus seems reasonable to suggest that disruption of the vagal anti-inflammatory pathway may predispose some individuals to excessive inflammatory responses in early life.

Integration of systems

A bidirectional network of interactions between the central nervous system, the endocrine system and the immune system is well documented (Butts and Sternberg, 2008; Wrona, 2006). The immune and nervous system are closely related in both physiological and pathological reactions in the lung. For example, extensive communications between neurons and immune cells are responsible for the magnitude of airway inflammation and the development of airway hyperreactivity, a consequence of neuronal dysregulation (Nockher and Renz, 2006; Veres et al., 2007). These systems likely act cooperatively to maintain homeostasis. To date, the majority of studies examining the impact of stress on physiological systems and subsequent health have examined one system in isolation from others. However, research increasingly suggests that it is the disturbed balance of these systems that predicts susceptibility to disease. For example, recent findings related to hypothalamic-pituitary-adrenal (HPA) axis and ANS functioning highlight the need to consider these systems simultaneously due to their interactive influences in predicting 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 (El-Sheikh et al., 2008) and adolescents (Gordis et al., 2006).

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

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 that is relevant to disease. Immune and neuroendocrine defensive biological responses important for the short-term response to stress, may produce long term damage if not checked and eventually terminated (McEwen, 2002). Disturbed regulation of stress systems [e.g., HPA axis, sympathetic-adrenal-medullary (SAM) system] due to maternal stress may, in turn, modulate immune function in the offspring beginning *in utero* (Arck et al., 2006; de Weerth and Buitelaar, 2005). That is, offspring of mothers with biobehavioral sequelae may inherit a biological vulnerability to disrupted stress regulatory systems altering their reactivity to subsequent challenges (Yehuda and Bierer, 2008). Likewise, non-optimal early childhood environments and caregiving experiences may also impact these processes (e.g., maternal psychopathology, maternal insensitivity) (Anisman et al., 1998; Liu et al., 1997; Vallee et al., 1997). Developmental findings show that the acquisition of the ability to regulate one's response to stress (“self-regulation”) progresses through several stages in the early years of development. Neonates and young infants are highly dependent on their caregivers as regulators. The HPA axis and ANS seem particularly susceptible to early-life programming.

Perinatal Programming of the HPA Axis

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 stimulates placental secretion of corticotrophin-releasing hormone (CRH), which in turn is elevated in the neonatal circulation (Goland et al., 1993; Reinisch et al., 1978; J. Seckl, 1997; Seckl, 2001). 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 immune and autonomic nervous systems (Arck et al., 2006). While these *in utero* responses may be adaptive in the short term, geared toward coping with anticipated environmental challenges, ultimately they may exact a toll in contributing to increased risk of inflammatory diseases in later life.

The HPA system remains highly reactive and labile in early infancy and becomes organized between 2 and 6 months of age through transactions between the child and caregiver (Wright and Bosquet, 2008). 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 adaptive self-regulatory abilities and more optimal functioning of the child's HPA system (Lyons-Ruth and Block, 1996). Increased maternal stress has been associated with lower levels of parenting sensitivity and higher levels of negative parenting behaviors (e.g. abuse, hostility) (Belsky, 1984). Not surprisingly then, perinatal maternal stress has been associated with poor stress regulation and other negative outcomes in both animal and human offspring. (Caldji et al., 2000; Cicchetti and Rogosch, 2001; Coplan et al., 1996; DeBellis et al., 1999; Essex et al., 2002; Field, 1994; Francis et al., 1999; M.R. Gunnar et al., 2001;. Gunnar and Donzella, 2002; Heim et al., 2000; Hessl et al., 1998; Kaufman et al., 1997).

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) (Card et al., 2005; Herlenius and Lagercrantz, 2004; Jansson and Lambert, 1999; Pryce, Ruedi-Bettschen, Dettling, and Feldon, 2002). Experimental rat models have shown that prenatal stress is associated with exaggerated cardiovascular reactivity to restraint stress (Igosheva et al., 2004). In humans, infants' autonomic responses show developmental changes with relative stability between 6 to 12 months of age (Alkon et al., 2006). The balance between functional parasympathetic and sympathetic activity in relation to stress, emotional stimuli, and immune function may also be important for the expression of allergic sensitization and atopic disorders as well as early airway inflammation and reactivity (Wright, 2005). Finally, a number of animal studies suggest that neural control of airway smooth muscle and the irritant receptor systems are established during this early life period and sensitive to environmental programming (Card et al., 2005).

Linking stress, immunomodulation, respiratory function, and airway responses

The preceding discussion suggests that individuals may be susceptible to the development of immunologic deviations that contribute to both systemic and localized inflammation in the airways and/or airway hyperresponsiveness through a number of pathways linked to stress. Moreover, evidence suggests a role for imbalance in sympathovagal activity in airway responses and lung function which may also be influenced by stress and negative affect. The evidence linking these processes to respiratory function is summarized below.

Perinatal Stress and Early Immunomodulation

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 (Joachim et al., 2008). Psychological stress has been associated with increased proportions of both natural killer (NK) and NKT cells as well as the altering their functional mechanisms (Lutgendorf et al., 2005; Oya et al., 2000). These effects have been shown by others to be correlated with changes in cortisol and sympathetic nervous system input (Sagiyama et al., 2004). Evidence in rhesus monkeys suggests that prenatal stress impacts the infant monkey's response to antigens at birth (Coe et al., 1999). Others have documented dysregulated pathways of the cellular and humoral immune response upon antigen challenge in prenatally stressed adult mice, reflected by a Th2 greater than Th1 adaptive immune response and increased IgE levels in vivo (Pincus-Knackstedt et al., 2006). In a prospective urban pregnancy cohort in Boston [the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) study], my laboratory has documented evidence that prenatal maternal stress is associated with increased cord blood IgE expression in the children (Sternthal et al., 2009) and enhanced reactivity to low-dose prenatal allergen exposure as indexed by elevated IgE in cord blood (Peters et al., 2008). Recent analyses in the Urban Environment and Childhood Asthma (URECA) study, demonstrated an association between increasing levels of cumulative maternal stress assessed prenatally and altered innate and adaptive immune responses in cord blood mononuclear cells (Wright et al., in press). My group has also prospectively linked early life caregiver stress to dysregulation of immune function in another Boston birth cohort predisposed to allergy (Wright et al., 2004). We found that increased maternal caregiving stress was associated with greater antigen-specific tumor necrosis factor (TNF)-alpha production in particular. A number of studies have found that stress induces the release of pro-inflammatory cytokines including TNF-alpha as well as others (e.g.,IL-6) (LeMay et al., 1990; Nakano et al., 1992; Yamasu et al., 1992) and that TNF-alpha 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.

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 and colleagues 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 (Powell et al., 2009). Zhang and others have demonstrated an association between stress and TLR4-mediated P13K/Akt signaling in mice (Zhang et al., 2008). Notably, recent data from a human pregnancy cohort showed that higher levels of prenatal maternal stress was associated with increased IL-8 and TNF-alpha production following microbial stimulation (e.g., polyinosinic-polycytidylic acid, Poly I:C) suggesting that prenatal stress may modify the neonatal immune response through Toll-like receptor (TLR)-dependent pathways (Wright et al., in press).

One notable challenge to linking stress-induced changes in immunity to lung function outcomes is assessing and understanding the complex relationships between local airway inflammation and systemic inflammatory processes in this context. While quantifying inflammation in the lungs is most directly accomplished through invasive methods including the analysis of bronchoalveolar lavage (BAL) fluid or bronchial biopsy obtained through bronchoscopy or semi-invasive methods including sputum induction (Montuschi, 2007), this is not always practical in human research studies. Less invasive techniques for assessing either the gaseous phase of exhaled breath (e.g., nitic oxide, carbon monoxide, hydrocarbons) or the liquid phase known as exhaled breath condensate (EBC) are being

developed. While measurement of exhaled nitric oxide (NO) has been standardized and validated for subjects as young as 4 years (Beydon et al., 2007), methods for EBC analysis in these younger age groups is still being worked out (Montuschi, 2007; Hoffmeyer et al., 2009). Other studies incorporate the measurement of inflammatory biomarkers in plasma [e.g., high sensitivity C-reactive protein (hs-CRP)]. While CRP from peripheral blood may be more reflective of systemic inflammation, there is correlational evidence that such markers may serve as a reasonable surrogate of airway inflammation. High sensitivity CRP, a systemic marker of low-grade inflammation has been negatively correlated with pulmonary function tests (FEV1) ($r = -0.49$, $p = 0.01$) and positively associated with percent eosinophils ($r = 0.44$, $p=0.03$) in induced sputum from asthmatics (Allam et al., 2009) as well as an increased frequency of airway hyperresponsiveness (Ridker et al., 1997). While some studies in adult asthmatics demonstrate that hs-CRP in serum is correlated with hs-CRP in EBC ($r = 0.74$ in stable asthma treated with inhaled corticosteroids, $p=0.0003$) as well as exhaled nitric oxide ($r = 0.62$, $p = 0.004$) (Zietkowski et al., 2009), other studies do not find this relationship (Sutherland et al., 2007). Overlapping lines of evidence in asthmatics (Navratil et al., 2009; Takemura et al., 2006) and those with chronic obstructive pulmonary disease (Sin and Man, 2006; Dahl et al., 2001) suggest that while systemic and airway inflammation may be correlates of one another, they may also operate independently in influencing lung structure and function. In a recent prospective study of young adults, increased levels of hs-CRP in blood predicted a greater decline in FEV1 over a 9-year follow-up period [23 ml/yr vs. 1.6 ml/yr decline in men; 6.2 ml/yr decrease vs. 1.6 ml/yr increase in women (highest quartile hs-CRP vs. lowest quartile, respectively)] (Rasmussen et al., 2009). These differences remained significant when adjusted for a number of potential confounding factors including body mass index (BMI), cardiorespiratory fitness, smoking, asthma, AHR, and serum eosinophil cationic protein (ECP), an indicator of eosinophilic inflammation. Moreover, studies demonstrating an association between CRP genotype and lung function further support a primary role of systemic inflammation in airway disease. Thus, going forward, studies should examine interrelationships among stress-induced changes in both localized and systemic inflammation, lung growth and development, and lung function measures, extending what we have learned in these studies of older children with asthma and adult asthmatics to earlier developmental periods (at birth, in infancy, and early childhood).

Perinatal Stress and Airway Pathophysiology

Perinatal stress and emotional arousal may influence airway narrowing through inflammatory pathways as well as neuronal activity (Quarcoo et al., 2009; Joachim et al., 2008; Pincus-Knackstedt et al., 2006). Nogueira and colleagues (Nogueira et al., 1999) were first to demonstrate that prenatal stress increased allergen-induced airway inflammation in adult mice offspring. Similarly, allergen aerosol challenge has been associated with increased airway hyperresponsiveness in mice exposed to prenatal stress (Pincus-Knackstedt et al., 2006). Moreover, total serum IgE was significantly increased in ovalbumin (OVA)-sensitized adult offspring in response to prenatal stress. Mice exposed to prenatal stress were also more likely to express a Th2 adaptive immune response. Additional studies have demonstrated exacerbations in airway inflammation in OVA-sensitized rats following chronic or repeated psychosocial challenge (Datti et al., 2002; Forsythe et al., 2004; Joachim et al., 2003; Joachim et al., 2004; Okuyama et al., 2007). 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 second (FEV_1) (Joachim et al., 2008). Notably, stress perception was also positively correlated with the percentage of TNF-alpha-producing T cells in these subjects. The authors speculated that this may point to a neuro-immunological interaction given evidence demonstrating the constitutive secretion of BDNF

in human peripheral blood monocytes which is enhanced when stimulated with TNF-alpha (Schulte-Herbruggen et al., 2005). This group has also demonstrated stress-induced increase in tachykinin-like substance P associated with allergic airway inflammation in a mouse model (Joachim et al., 2006). No studies to date have examined the influence of prenatal and early life stress on the expression of neuropeptides and their possible role on airway inflammation and response in early development.

Stress and acquired glucocorticoid resistance

An alternative hypothesis linking stress, neuroendocrine and immune function considers a glucocorticoid resistance model (Miller et al., 2002). Gloucocorticoid sensitivity plays a role in the developmental regulation of the lung (Ganalingham et al., 2006). Insight into the cellular and molecular mechanisms underlying stress-induced steroid resistance is provided in a number of recent studies. Oxidative stress pathways have been implicated in the link between psychosocial stress and asthma (Wright, 2005) as well as steroid resistant asthma (Adcock and Barnes, 2008; Marwick et al., 2008). This may particularly be relevant in airway inflammation where neutrophilc rather than eosinophilic inflammation predominates (Bush, 2008; Wenzel et al., 1999). 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 (Ito et al., 2008). Notably, psychological stress is also an oxidant and may thus operate through these same pathways (Wright, 2005). While human data in the context of lung disease are sparse in this regard, one recent cross-sectional analysis in adolescents demonstrated that peripheral blood mononuclear cells harvested from asthmatics who perceived low parental support (i.e., greater stress) were more resistant to hydrocortisone's effects on cytokine expression (IL-5, IFN-γ) and activation of eosinophils relative to asthmatics reporting higher parental support (Miller et al., 2009). Examination of mechanisms contributing to steroid resistance in relation to perinatal stress may provide insight into the link between stress and reduced lung function or airway hyperresponsiveness over subsequent development.

Epigenetics – A Fundamental Programming Mechanism

Programming effects of stress on respiratory outcomes may operate at a more fundamental molecular level, i.e., through epigenetic programming. Determining the range of environmental exposures that impact the epigenome during development was a research priority identified at the recent National Heart, Lung, and Blood Institute (NHLBI) Pediatric Pulmonary Disease Strategic Planning Workshop (Castro et al., 2009*)*. DNA methylation is an adaptable epigenetic mechanism that, in mammals, modifies genome function through the addition of methyl groups to cytosine to form 5-methyl-cytosine. DNA methylation marks are largely established early in life (Feinberg, 2007; Gluckman et al., 2008) and may ensure stable regulation that mediates persistent changes in biological and behavioral phenotypes over the lifespan (Miller and Ho, 2008; Weaver et al., 2002). DNA methylation of many genes changes with disease status and in response to environmental signals including chemical exposures such as diet, drugs and toxins (Baccarelli et al., 2009; Jaenisch and Bird, 2003; Li et al., 2003). Recent findings also implicate psychological stress given behavioral studies demonstrating epigenetic changes during fear conditioning (Levenson and Sweatt, 2006; Miller et al., 2007) and evidence for epigenetic programming related to maternal care (Meaney ajd Szyf, 2005; Szyf et al., 2008).

Genes involved in HPA axis functioning seem particularly susceptible to stress-related programming (Wright and Bosquet, 2008). These include glucocorticoid receptor expression, the activation of which alters HPA activity through negative feedback inhibition (De Kloet, 2004). The human glucocorticoid receptor (GR) promoter region is extensively methylated with diverse methylation profiles demonstrated in a nonclinical sample of

subjects (Turner et al., 2008). The intracellular access of glucocorticoids to their receptors is also modulated by the 11 beta-hydroxysteroid dehydrogenase (11βHSD) enzymes, which interconvert biologically active 11 β-hydroxyglucocorticoids and inactive 11-ketosteroids (Krozowski et al., 1994). While compromised 11βHSD2 activity can be caused by loss of function mutations of the gene encoding 11βHSD2, the frequency of such mutations is extremely low (Zaehner et al., 2000). Thus, other mechanisms accounting for the inter-individual variability in 11βHSD2 enzyme activity should be considered (Alikhani-Koopaei et al., 2004). The 11βHSD2 promoter comprises a highly G + C-rich (or GC-rich) core, contains more than 80% GC, lacks a TATA-like element, and has two typical CpG islands raising the possibility that methylation may play a role in the epigenetically determined inter-individual variable expression of 11βHSD2. One candidate pathway implicated in both airway inflammation (Esposito and Cuzzocrea, 2007) and autonomic response(Danson et al., 2009) is the nitric oxide (NO) signaling pathways. Alterations of NO expression occur in the context of psychological stress and stress-related behaviors (McLeod et al., 2001). The inducible nitric oxide synthase (NOS) genes are also susceptible to epigenetic programming (Tarantini et al., 2009).

The notion that variability in methylation between subjects may reflect an important epigenetic mechanism is suggested by recent studies in both animals and humans. Epigenetic modulation of the 11βHSD2 gene has been recently demonstrated in a rodent model and cultured cell lines (Alikhani-Koopaei et al., 2004), albeit epigenetic regulation of this gene is not well characterized in humans. Weaver and colleagues have demonstrated differential methylation patterns of the Ngfi-A-binding site in GR promoter 1_7 in the rat brain in offspring that had received poor maternal care versus those that had received better maternal care (Weaver et al., 2004). When pups were cross-fostered between mothers providing good or poor post-natal care (i.e., pups who had received poor caregiving from their biological mother were switched to the caregiving of the foster mothers who now provided positive caregiving), the pups developed the epigenome of the foster mother. This same group recently reported increased methylation in a neuron-specific GC receptor (NR3C1) promoter as well as decreased levels of GC receptor mRNA from hippocampus tissue obtained from suicide victims with a history of childhood abuse (McGowan et al., 2009). Recent human data demonstrates that methylation of exon 1F in fetal cord blood was sensitive to maternal mood in the perinatal period and the infants HPA stress reactivity (Oberlander et al., 2008). Whether alterations in DNA methylation underlie stress-induced altered phenotypic plasticity related to lung structure and function remains largely unexplored.

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 may, in turn, lead to increased vulnerability to asthma (Wright, 2007). It will be important to begin to understand factors related to developmental programming of glucocorticoid sensitivity during critical periods of development which may play a role in disease etiology as well as subsequent morbidity.

Influence of Modifying Factors

A number of factors have been shown to modify the effects of perinatal stress on the early child developmental processes discussed here that may, in turn, influence lung function. While an in-depth discussion is beyond the scope of this review, it is worth acknowledging those factors that may be considered in research going forward. These include genetic susceptibility of the index child, family context (Morris et al., 2007), race/ethnicity (Cunningham et al., 2009), developmental stage (Boyce and Ellis, 2005), child's gender

(Hatzinger et al., 2007) and temperament (Talge et al., 2008). For example, data from my laboratory has shown gender differences in the relationships between family and community violence exposure and early childhood lung function (Franco Suglia et al., 2007).

Influence of Stress on Prospective Development of Wheeze Phenotypes

In order to disentangle whether stress has a greater effect on lung architecture and growth versus processes involved in airway response and inflammation, it may be useful to examine the influence of stress on early wheeze phenotypes in childhood in a prospective design. While our understanding of the natural history of childhood wheezing is still evolving, epidemiological studies have characterized distinct patterns of wheezing based on age of onset, remission, and persistence with further classification based on allergic, immunologic and physiological parameters (Taussig et al., 2003). Wheeze phenotypes (transient, atopic, nonatopic) evolve over early childhood and are more clearly delineated by age 6 to 7 years. These distinctive patterns of wheezing may reflect differences in etiology and prognosis for asthma development as well as having differential relationship to lung function (Martinez et al., 1995). Typically, studies discriminate between transient wheezing (nonatopic children who wheeze during the first 3 years of life but not thereafter), nonatopic persistent wheezing [nonatopic children who wheeze beyond the third year of life after having a lower respiratory illness (LRI)], and atopic wheezing (atopic children with wheezing during the first 6 years of life). This latter group can be further divided into early atopic or persistent wheezers (those whose symptoms started during the first 3 years and wheezed at age 6) and late atopic wheezers (those who did not wheeze before age 3 but did have wheezing by age 6) albeit the latter group is relatively rare. These wheezing phenotypes, in turn, have been differentially associated with lung function changes (Lowe et al., 2009; Stern et al., 2007) including airway resistance (Brussee et al., 2004). Wheezing phenotypes, particularly persistent wheezing, are predictors of lung function by age 6 years. Stress may operate through different pathways to influence wheeze risk and lung growth and development including altered somatic growth (prematurity, birth weight), altered intrinsic airway responses, and immunomodulation beginning *in utero* that impacts consequent airway inflammation. Specifically, stress-elicited disruption of interrelated systems – neuroendocrine, autonomic, and immune – during the prenatal and early childhood periods may contribute to an increased risk for wheezing syndromes as well as potentiate an increased vulnerability to airway inflammation and reactivity resulting in altered childhood lung function. How stress influences distinct wheeze phenotypes may vary based on timing of exposure (prenatal, early postnatal, cumulative) underscoring the need to examine associations prospectively. For example, in prospective studies one could examine the influence of prenatal maternal stress on maternal cortisol disruption *in utero* and subsequent effects on subsequent wheeze phenotypes and childhood lung function. One could also examine whether this relationship is mediated through IUGR and low birth weight.

Summary and Conclusion

Evidence that psychological factors influence neurohormonal and consequently immune inflammatory processes starting *in utero* suggest their possible role in lung growth and development albeit research on the influence of stress on childhood lung function outcomes remains sparse. Stress-elicited disruption of interrelated systems - neuroendocrine, autonomic, and immune - during perinatal development may lead to increased vulnerability to airway inflammation and reactivity as well as reduced lung function in later childhood and even into adulthood. Future studies need to examine how fetal exposure to maternal stress may influence programming of these interrelated systems and how such effects are independent of and moderated by postnatal stress as well as other environmental toxins. That is, stress-induced disruption of these interrelated systems may have important

independent effects on lung growth and development, but also may enhance vulnerabililty to other known lung toxins (i.e., air pollution, tobacco smoke) (Wright et al., 2005). An important step toward identifying children at risk for costly pediatric disorders is the identification of mechanisms that may lead to and maintain early predisposition. Identifying programming agents that help to shape functional competence of the immune system and interrelated systems may give new insights into the mechanisms by which they exert their effects on lung function growth and development.

Acknowledgments

During preparation of this manuscript, R Wright was supported by R01 HL080674.

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