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

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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 (FEV_1) [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 neuro-immunological 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 improtant 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 association with increased IL-8 and TNF-α production following microbial stimulation (e.g. Poly I:C) suggesting that prenatal

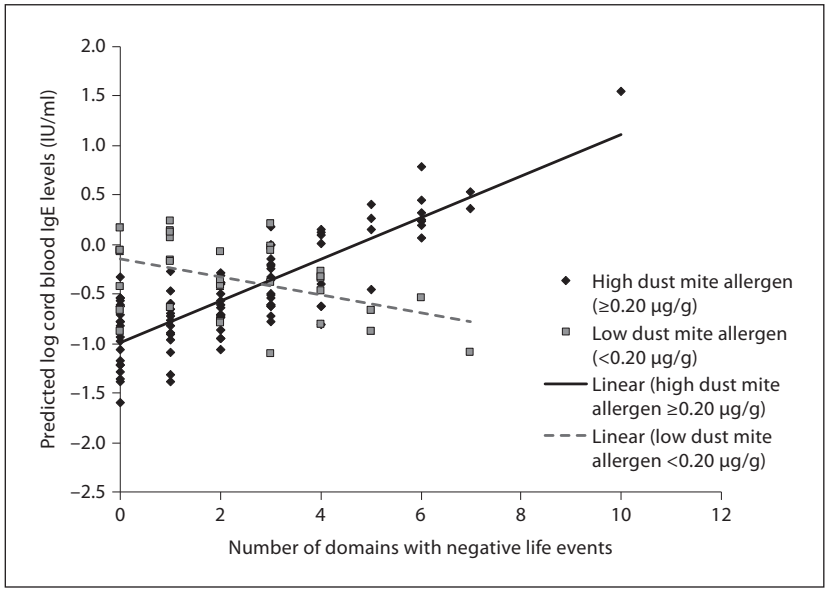

Fig. 1. Association between increasing prenatal maternal stress (negative life events) and cord blood IgE stratified by high vs. low maternal prenatal dust mite exposure.

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-methyl-cytosine (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

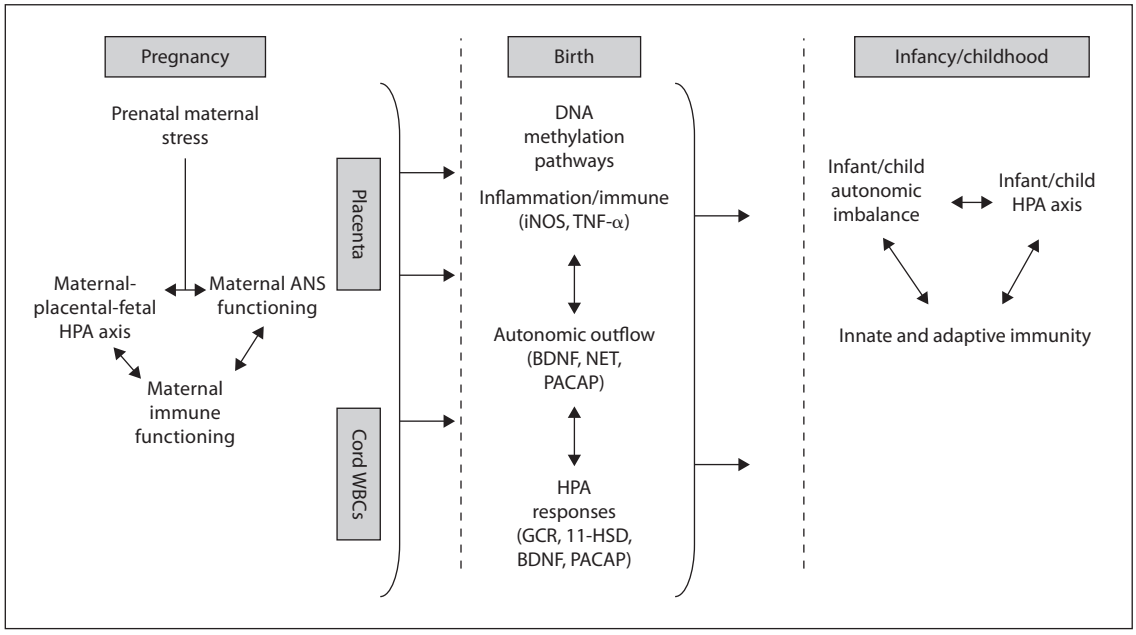

Fig. 2. Potential pathways vulnerable to stress-related methylation changes.

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, 11β-hydroxysteroid deydrogenase type 2 (11β-HSD2) [113, 114]. While 11β-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 11β-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. 11β-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 11βHSD2 in peripheral WBC DNA [125]. Catecholamines reduce 11β-HSD2 transcription [126] while GCs increase 11β-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, preterm 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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References

1 Bateson P, Barker D, Clutton-Brock T, et al: Developmental plasticity and human health. Nature 2004;430:419–421.
2 Thayer JF, Brosschot JF: Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 2005;30:1050–1058.
3 Harris A, Seckl J: Glucocorticoids, prenatal stress and programming of disease. Horm Behav 2011;59:279–289.
4 Young JB: Programming of sympathoadrenal function. Trends Endocrinol Metab 2002;13:381–385.
5 Wright RJ: Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. Pediatr Perinat Epidemiol 2007;21:8–14.
6 Phillips DIW: Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment? J Intern Med 2007;261:453–460.

7 Licht CMM, Breeburg SA, van Reedt Dortland AKB, et al: Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. Endocr Res 2010;95:2458–2466.
8 Yun AJ, Bazar KA, Lee PY: Autonomic dysfunction may be an under-recognized cause of female fertility disorders. Med Hypotheses 2004;63:172–177.
9 Jankowska EA, Ponikowski P, Piepoli MF, et al: Autonomic imbalance and immune acitvation in chronic heart failure – pathophysiological links. Cardiovasc Res 2006;70:434–435.
10 Heijmans BT, Tobi EW, Lumey LH, et al: The epigenome: archive of the prenatal environment. Epigenetics 2009;4:526–531.
11 Szyf M, McGowan P, Meaney MJ: The social environment and the epigenome. Envir Mol Mutagen 2008;49:46–60.
12 Canning BJ: Neurology of allergic inflammation and rhinitis. Curr Allergy Asthma Rep 2002;2: 210–215.
13 Undem BJ, Kajekar R, Hunter DD, et al: Neural integration and allergic disease J Allergy Clin Immunol 2000;106:S213–S220.
14 Milles JE, Widdicombe JG: Role of the vagus nerves in anaphylaxis and histamine-induced bronchoconstrictions in guinea-pigs. Br J Pharmacol 1970;39: 724–731.
15 Baraniuk JN, Silver PB, Kaliner MA, et al: Perrenial rhinitis subjects have altered vascular, glandular, and neural responses to bradykinin nasal provocation. Int Arch Allergy Immunol 1994;103:202–208.
16 Ko JH, Kuo TB, Lee GS: Effect of postural change on nasal airway and autonomic nervous system established by rhiinomanometry and heart rate variability analysis. Am J Rhinol Allergy 2008;22:159–165.
17 Sternberg EM: Neural-immune interactions in health and disease. J Clin Invest 1997;100:2641–2647.
18 Sternberg EM: Neuroendocrine regulation of autoimmune/inflammatory disease. J Endocrinol 2001; 169:429–435.
19 Tracey KJ: The inflammatory reflex. Nature 2002; 420:853–859.
20 Sternberg EM: Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol 2006;6:318–328.
21 Hori T, Katafuchi T, Take S, et al: The atuonomic nervous sytem as a communicator between the brain and the immune system. Neuroimmunomodulation 1995;2:203–215.
22 Nance DM, Sanders VM: Autonomic innervation and regulation of the immune system (1987 – 2007). Brain Behav Immun 2007;21:736–745.
23 Tracey KJ: Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007;117:289–296.
24 Undem BJ, Weinreich D: Neuroimmune interactions in the lung; in Bienenstock J, Goetzle EJ, Blennerhassett MG (eds): Autonomic Neuroimmunology. New York, Taylor & Francis, 2003, pp 279–294.
25 Bienenstock J, Goetzl EJ, Blennerhassett MG (eds): Autononic Neuroimmunology. New York, Taylor & Francis, 2003.
26 Barnes PJ: Airway inflammation and autonomic control. Eur J Resp Dis 1986;69:80–87.
27 Lutz W, Sulkowski WJ: Vagus nerve participates in regulation of the airways: inflammatory response and hyperreactivity induced by occupational asthmogens. Int J Occup Med Environ Health 2004; 17:417–431.
28 Barnes PJ: Neural mechanisms in asthma. British Medical Bulletin 1992;48:149–168.
29 Fryer AD, Jacoby DB: Muscarinic receptors and control of airway smooth muscle. Am J Resp Crit Care Med 1998;158:S154–S160.
30 Card JP, Levitt P, Gluhovsky M, et al: Early experience modifies the postnatal assembly of autonomic emotional motor circuits in rats. J Neurosci 2005;25: 9102–9111.
31 Prakash YS, Thompson MA, Meuchel L, et al: Neurotrophins in lung health and disease. Expert Rev Resp Med 2010;4:395–411.
32 Gomariz RP, Juarranz Y, Abad C, et al: VIP-PACAP system in immunity: new insights for multitarget therapy. Ann NY Acad Sci 2006;1070:51–74.
33 Ueyama T, Kawai Y, Nemoto K, et al: Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. Neurosci Res 1997;28:103–110.
34 Hashimoto H, Shintani N, Tanida M, et al: PACAP is implicated in the stress axes. Curr Pharm Design 2011;17:985–989.
35 Joachim RA, Noga O, Sagach V, et al: Correlation between immune and neuronal parameters and stress perception in allergic asthmatics. Clin Exp Allergy 2008;38:283–290.
36 Schulte-Herbruggen O, Nassenstein C, Lommatzsch M, et al: Tumor necrosis factor-[alpha] and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. J Neuroimmunol 2005;160:204–209.
37 Joachim RA, Cifuentes LB, Sagach V, et al: Stress induces substance P in vagal sensory neurons innervating the mouse airways. Clin Exp Allergy 2006;36: 1001–1010.
38 Wright RJ: Stress and Atopic Disorders. J Allergy Clin Immunol 2005;116:1301–1306.

39 Cohen S, Herbert T: Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Ann Rev Psychol 1996;47:113–142.
40 Cohen S, Janicki-Deverts D, Miller GE: Psychological stress and disease. J Am Med Assoc 2007;298:1685–1687.
41 Cacioppo JT, Berntson CG, Malarkey WB, et al: Autonomic, neuroendocrine, and immune responses to psychological stress: the reactivity hypothesis. Ann NY Acad Sci 1998;840:664–673.
42 McEwen BS: Protective and damaging effects of stress mediators: the good and bad sides of the response to stress. Metab Clin Exp 2002;51:2–4.
43 de Weerth C, Buitelaar JK: Physiological stress reactivity in human pregnancy – a review. Neurosci Biobehav Rev 2005;29:295–312.
44 Arck PC, Knackstedt MK, Blois SM: Current insights and future perspectives on neuroendocrine-immune circuitry challenging pregnancy maintenance and fetal health. J Reprod Endokrinol 2006;3:98–102.
45 Yehuda R, Bierer LM: Transgenerational transmission of cortisol and PTSD risk. Prog Brain Res 2008;167:121–134.
46 Vallee M, Mayo W, Dellu F, et al: Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. J Neurosci 1997;17:2626–2636.
47 Liu D, Diorio J, Tannenbaum B, et al: Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal response to stress. Science 1997;277:1659–1662.
48 Anisman H, Zaharia MD, Meaney MJ, et al: Do early-life events permanently alter behavioral and hormonal responses to stressors? Int J Dev Neurosci 1998;16:149–164.
49 Jansson T, Lambert GW: Effect of intrauterine growth restriction on blood pressure, glucose tolerance and sympathetic nervous system activity in the rat at 3–4 months of age. J Hypertens 1999;17:1239–1248.
50 Pryce CR, Ruedi-Bettschen D, Dettling AC, et al: Early life stress: long-term physiological impact in rodents and primates. News Physiol Sci 2002;17:150–155.
51 Herlenius E, Lagercrantz H: Development of neurotransmitter systems during critical periods. Exp Neurol 2004;190:S8–S21.
52 Igosheva N, Klimova O, Anishchenko T, et al: Prenatal stress alters cardiovascular responses in adult rats. J Physiol 2004;557:273–285.
53 Alkon A, Lippert S, Vujan N, et al: The ontogeny of autonomic measures in 6- and 12-month-old infants. Dev Psychobiol 2006;48:197–208.
54 Longtine MS, Nelson DM: Placental dysfunction and fetal programming: the importance of placental size, shape, histopathology, and molecular composition. Semin Reprod Med 2011;29:187–196.
55 Jansson T, Powell TL: Role of the placenta in fetal programming: underlying mechanisms and potential interventional approaches. Clin Sci 2007;113:1–13.
56 Seckl J: Glucocorticoids, feto-placental 11-beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. Steroids 1997;62:89–94.
57 Seckl JR: Glucocorticoid programming of the fetus: adult phenotypes and molecular mechanisms. Mol Cell Endocrinol 2001;185:61–71.
58 Reinisch JM, Simon NG, Karwo WG, et al: Prenatal exposure to prednisone in humans and animals retards intra-uterine growth. Science 1978;202:436–438
59 Goland RS, Jozak S, Warren WB, et al: Elevated levels of umbilical cord plasma corticotropin-releasing hormone in growth-related fetuses. J Clin Endocrinol Metab 1993;77:1174–1179.
60 Wright R, Bosquet EM: Maternal stress and perinatal programming in the expression of atopy. Expert Rev Clin Immunol 2008;4:535–538.
61 Lyons-Ruth K, Block DE: The disturbed caregiving system: Relations among childhood trauma, maternal caregiving, and infant affect and attachment. Infant Mental Health J 1996;17:257–275.
62 Caldji C, Diorio J, Meaney MJ: Variations in maternal care in infancy regulate the development of stress reactivity. Biol Psychiatry 2000;48:1164–1174.
63 Coplan J, Andrews MW, Rosenblum LA, et al: Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci USA 1996;93:1619–1623.
64 Francis DD, Caldji C, Champagne F, et al: The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol Psychiatry 1999;46:1153–1166.
65 Gunnar MR, Donzella B: Social regulation of the cortisol levels in early human development. Psychoneuroendocrinology 2002;27:199–220.
66 Cicchetti D, Rogosch FA: Diverse patterns of neuroendocrine activity in maltreated children. Dev Psychopathol 2001;13:677–693.

67 DeBellis MD, Baum AS, Birmaher B, et al: Developmental traumatology. 1. Biological stress systems. Biol Psychiatry 1999;9:1259–1270.
68 Heim C, Newport DJ, Heit S, et al: Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 2000;284:592–597.
69 Kaufman J, Birmaher B, Perel J, et al: The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biol Psychiatry 1997;42:669–679.
70 Gunnar MR, Bruce J, Hickman SE: Salivary cortisol response to stress in children. Adv Psychosom Med 2001;22:52–60.
71 Field T: The Effects of Mother's Physical and Emotional Unavailability on Emotions Regulation. Chicago, University of Chicago Press, 1994.
72 Hessl D, Dawson G, Frey K, et al: A longitudinal study of children of depressed mothers: psychobiological findings related to stress; in Hann DM, Huffman LC, Lederhendler KK, et al (eds): Advancing Research on Developmental Plasticity: Integrating the Behavioral Sciences and the Neurosciences of Mental Health. Bethesda, National Institutes of Mental Health, 1998, p 256.
73 Essex MJ, Klein MH, Cho E, et al: Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biol Psychiatry 2002;52:776–784.
74 Nogueira PJ, Ferreira HHA, Antunes E, et al: Chronic mild prenatal stress exacerbates the allergen-induced airway inflammation in rats. Mediat Inflamm 1999;8:119–122.
75 Quarcoo D, Pavlovic S, Joachim RA: Stress and airway reactivity in a murine model of allergic airway inflammation Neuroimmunomodulation 2009;16:318–324.
76 Pincus-Knackstedt MK, Joachim RA, Blois SM, et al: Prenatal stress enhances susceptibility of murine adult offspring toward airway inflammation. J Immunol 2006;177:8484–8492.
77 Coe CL, Lubach GR, Karaszewski JW: Prenatal stress and immune recognition of self and nonself in the primate neonate. Biol Neonate 1999;76:301–310.
78 Lin YC, Wen HJ, Lee YL, et al: Are maternal psychosocial factors associated with cord immunoglobulin E in addition to family atopic history and mother immunoglobulin E? Clin Exp Allergy 2004;34:548–554.
79 Cookson H, Granell R, Joinson C, et al: Mother's anxiety during pregnancy is associated with asthma in their children. J Allergy Clin Immunol 2009;123:847–853.
80 Reyes M, Perzanowski MS, Whyatt RM, et al: Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. Ann Allergy Asthma Immunol 2011;107:42–49.
81 Sternthal MJ, Bosquet Enlow M, Cohen S, et al: Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort. A life-course perspective. J Allergy Clin Immunol 2009;124:954–960.
82 Sternthal MJ, Coull BA, Chiu Y-HM, et al: Associations among maternal childhood socioeconomic status, cord immunoglobulin E, and repeated wheeze in urban children. J Allergy Clin Immunol 2011;128:337–345.
83 Peters JL, Cohen S, Staudenmayer J, et al: Prenatal negative life events increase cord blood IgE: interactions with dust mite allergen and maternal atopy. Allergy 2012;67:545–551.
84 Wright RJ, Finn PW, Contreras JP, et al: Chronic caregiver stress and IgE expression, allergeninduced proliferation and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol 2004;113:1051–1057.
85 Nakano M, Onozuka K, Yamasu H, et al: Protective effects of cytokines in murine Salmonella. Adv Exp Med Biol 1992;319:89–95.
86 Yamasu K, Shimada Y, Sakaizumi M, et al: Activation of the systemic production of tumor necrosis factor after exposure to acute stress. Eur Cytokine Network 1992;3:391–398.
87 LeMay LG, Vander AJ, Kluger MJ: The effects of pentoxifylline on lipopolysaccharide (LPS) fever, plasma interleukin 6 (IL-6), and tumor necrosis factor (TNF) in the rat. Cytokine 1990;2:300–306.
88 Joachim RA, Handjiski B, Blois SM, et al: Stress-induced neurogenic inflammation in murine skin skews dendritic cells towards maturation and migration. Key role of intercellular adhesion molecule-1/leukocyte function-associated antigen interactions. Am J Pathol 2008;173:1379–1388.
89 Lutgendorf SK, Moore MB, Bradley S, et al: Distress and expression of natural killer receptors on lymphocytes. Brain Behav Immun 2005;19:185–194.
90 Oya H, Kawamura T, Shimizu T, et al: The differential effect of stress on natural killer T (NKT) and NK cell function. Clin Exp Immunol 2000;121:384–390.
91 Powell ND, Bailey MT, Mays JW, et al: Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. Brain Behav Immun 2009;23:225–231.
92 Zhang Y, Zhang Y, Miao J, et al: Chronic restraint stress promotes immune suppression through toll-like receptor 4-mediated phosphoinositide 3-kinase signaling. J Neuroimmunol 2008;204:13–19.

93 Wright RJ, Visness CM, Calatroni A, et al: Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city population. Am J Resp Crit Care Med 2010;182:25–33.
94 Wrona D: Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems. J Neuroimmunol 2006;172:38–58.
95 Butts CL, Sternberg EM: Neuroendocrine factors alter host defense by modulating immune function. Cell Immunol 2008;252:7–15.
96 El-Sheikh M, Erath SA, Buckhalt JA, et al: Cortisol and children's adjustment: the moderating role of sympathetic nervous system activity. J Abnorm Child Psychol 2008;36:601–611.
97 Gordis EB, Granger DA, Susman EJ, et al: Asymmetry between salivary cortisol and alpha-amylase reactivity to stress: relation to aggressive behavior in adolescents. Psychoneuroendocrinology 2006;31:976–987.
98 Gluckman PD, Hanson MA, Cooper C, et al: Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61–73.
99 Jaenisch R, Bird A: Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;35:245–254.
100 Baccarelli A, Bollati V: Epigenetics and environmental chemicals. Curr Opin Pediatr 2009;21:243–251.
101 Levenson JM, Sweatt JD: Epigenetic mechanisms: a common theme in vertebrate and invertebrate memory formation. Cell Mol Life Sci 2006;63:1009–1016.
102 Meaney MJ, Szyf M: Maternal care as a model for experience-dependent chromatin plasticity? Trends Neurosci 2005;28:456–463.
103 Feinberg AP: Phenotypic plasticity and the epigenetics of human disease. Nature 2007;447:433–440.
104 Weaver IC, Cervoni N, Champagne FA, et al: Epigenetic programming by maternal behavior. Nat Neurosci 2004;7:847–854.
105 Heijmans BT, Tobi EW, Stein AD, et al: Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci 2008;105:17046–17049.
106 McGowan PO, Sasaki A, D'Alessio AC, et al: Epigenetic regulation of the glucocorticoid receptor in human brain associated with childhood abuse. Nat Neurosci 2009;12:342–348.
107 Oberlander TF, Weinberg J, Papsdorf M, et al: Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;3:97–106.
108 Sanchez MM: The impact of early adverse care on HPA axis development: nonhuman primate models. Horm Behav 2006;50:623–631.
109 Sanchez MM, Noble PM, Lyon CK, et al: Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biol Psychiatry 2005;15:373–381.
110 Turner JD, Alt SR, Cao L, et al: Transcriptional control of the glucocorticoid receptor: CpG islands, epigenetics and more. Biochem Pharmacol 2010;80:1860–1868.
111 Turner JD, Pelascini LP, Macedo JA, et al: Highly individual methylation patterns of alternative glucocorticoid receptor promoters suggest individualized epigenetic regulatory mechanisms. Nucl Acids Res 2008;36:7207–7218.
112 Radley JJ, Kabbaj M, Jacobson L, Heydendael W, Yehuda R, Herman JP: Stress risk factors and stress-related pathology: europlasticity, epigenetics, and endophenotypes. Stress 2011;14:481–497.
113 Alikhani-Koopaei R, Fouladkou F, Frey FJ, et al: Epigenetic regulation of 11 beta-hydroxysteroid dehydrogenase type 2 expression. J Clin Invest 2004;114:1146–1157.
114 Waddell BJ, Benediktsson R, Brown RW, et al: Tissue-specific messenger ribonucleic acid expression of 11-beta-hydroxysteroid dehydrogenase types 1 and 2 and the glucocorticoid receptor within rat placenta suggests exquisite local control of glucocorticoid action. Endocrinology 1998;139:1517–1523.
115 Benediktsson R, Lindsay R, Noble J, et al: Glucocorticoid exposure in utero: a new model for adult hypertension. Lancet 1993;341:339–341.
116 Edwards C, Benediktsson R, Lindsay R, et al: Dysfunction of placental glucocorticoid barrier – link between fetal environment and adult hypertension. Lancet 1993;341:355–357.
117 Condon J, Gosden C, Gardener D, et al: Expression of type 2 11-beta-hydroxysteroid dehydrogenase and corticosteroid hormone receptors in early human fetal life. J Clin Endocrinol Metab 1998;83:4490–4497.
118 Speirs HJ, Seckl JR, Brown RW: Ontogeny of glucocorticoid receptor and 11 hydroxysteroid dehydrogenase type 1 gene expression identifies potential critical periods of glucocorticoid susceptibilty during development. J Endocrinol 2004;181:105–116.
119 Brown RW, Diaz R, Robson AC, et al: Ontogeny of 11-beta-hydroxysteroid dehydrogenase type 2 and mineralcorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology 1996;137:794–797.

120 McTernan CL, Draper N, Nicholson H, et al: Reduced placental 11-beta-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. J Clin Endocrinol Metab 2001;86:4979–4983.
121 Takeda Y: Pathophysiological roles of vascular 11-beta-hydroxysteroid dehydrogenase and aldosterone. J Steroid Biochem Mol Biol 2003;85:443–447.
122 Takeda Y, Miyamori I, Yoneda T, et al: Gene expression of 11 beta-hydroxysteroid dehydrogenase in the mesenteric arteries of genetically hypertensive rats. Hypertension 1994;23:577–580.
123 Ferrari P, Sansonnents A, Dick B, et al: In vivo 11 beta-HSD-2 activity: variability, salt sensitivity, and effect of licorice. Hypertension 2001;38:1330–1336.
124 Ferrari P: The role of 11 beta-hydroxysteroid dehydrogenase type 2 in human hypertension. Biochim Biophys Acta 2010;1802:1178–1187.
125 Friso S, Pizzolo F, Choi SW, et al: Epigenetic control of 11-beta-hydroxysteroid dehydrogenase 2 gene promoter is related to human hypertension. Atherosclerosis 2008;199:323–327.
126 Sarkar S, Tsai SW, Nguyen TT, et al: Inhibition of placental 11 beta-hydroxysteroid dehydrogenase type 2 by catecholamines via alpha-adrenergic signaling. Am J Physiol Regul Integr Comp Physiol 2001;281:R1966–R1974.
127 van Beck JP, Guan H, Julan L, et al: Glucocorticoids stimulate the expression of 11 beta-hydroxysteroid dehydrogenase type 2 in cultured human placental trophoblast cells. J Clin Endocrinol Metab 2004;89:5614–5621.
128 Roth TL, Lubin FD, Funk AJ, et al: Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;65:760–769.
129 Givalois L, Arancibia S, Alonso G, et al: Expression of brain-derived neurotrophic factor and its receptors in the median eminence cells with sensitivity to stress. Endocrinology 2004;145:4737–4747.
130 Yang JT, Chang CN, Lee TH, et al: Effect of dexamethasone on the expression of brain-derived neurotrophic factor and neurtotrophin-3 messenger ribonucleic acids after forebrain ischemia in the rat. Crit Care Med 2002;30:913–918.
131 Mayeur S, Silog M, Moitrot E, et al: Placental BDNF/TrkB signaling system is modulated by fetal growth disturbances in rat and human. Placenta 2010;31:785–790.
132 Gilmore JH, Jaskog LF, Vadlamudi S: Maternal poly I:C exposure during pregnancy regulates TNF alpha, BDNF, and NGF expression in neonatal brain and the maternal-fetal unit of the rat. J Neuroimmunol 2005;159:106–112.
133 Devlin AM, Brain U, Austin J, et al: Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. PLoS One 2010;5:e12201.
134 Kohn J, Aloyz RS, Toma JG, et al: Functionally antagonistic interactions between the TrkA and p75 neurotrophin receptors regulate sympathetic neuron growth and target innervation. J Neurosci 1999;19:5393–5408.
135 Yang AC, Chen TJ, Tsai SJ, et al: BDNF Val66Met polymorphism alters sympathovagal balance in healthy subjects. Am J Med Genet Neuropsychiatr Genet 2010;153B:1024–1030.
136 Kunugi H, Hori H, Adachi N, et al: Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. Psychiatry Clin Neurosci 2010;64:447–459.
137 Benedick Kahn L, Gustafsson LE, Olgart Hoglund C: Brain-derived neurotrophic factor enhances histamine-induced airway responses and changes levels of exhaled nitric oxide in guinea pigs in vivo. Eur J Pharmacol 2008;595:78–83.
138 Tanida M, Shintani N, Morita Y, et al: Regulation of autonomic nerve activities by central pituitary adenylate cyclase-activating polypeptide. Regul Peptides 2010;161:73–80.
139 Ganea D, Rodriguez R, Delgado M: Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: players in innate and adaptive immunity. Cell Mol Biol 2003;49:127–142.
140 Kumagai H, Averill DB, Khosia MC, et al: Role of nitric oxide and angiotensin II in the regulation of sympathetic nerve activity in spontaneously hypertensive rats. Hypertension 1992;21:476–484.
141 Weiner CP, Thompson LP: Nitric oxide and pregnancy. Semin Perinatol 1997;21:367–380.
142 Brooks VL, Dampney AL, Heesch CM: Pregnancy and the endocrine regulation of the baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol 2010;299:R439–R451.
143 McLaughlin MK, Conrad KP: Nitric oxide biosynthesis during pregnancy: implications for circulatory changes. Clin Exp Pharmacol Physiol 1995;22:164–171.
144 Barron C, Mandala M, Osol G: Effects of pregnancy, hypertension and nitric oxide inhibition on rat uterine artery reactivity. J Vasc Res 2010;47:463–471.
145 Danson EJ, Li D, Wang L, et al: Targeting cardiac sympatho-vagal imbalance using gene transfer of nitric oxide synthase. J Mol Cell Cardiol 2009;46:482–489.
146 Myatt L: Review: Reactive oxygen and nitrogen species and functional adaptation of the placenta. Placenta 2010;31(suppl):S66–S69.

147 Duckles SP, Miller VM: Hormonal modulation of endothelial NO production. Pflügers Arch 2010; 459:841.
148 Miller GE, Chen E, Sze J, et al: A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. Biol Psychol 2008;64:266–272.
149 Shannon JR, Flattem NL, Jordan J, et al: Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. N Engl J Med 2000;342:541–549.
150 Esler M, Eikelis N, Schlaich M, et al: Human sympathetic nerve biology: parallel influences of stress and epigenetics in essential hypertension and panic disorder. Ann NY Acad Sci 2008;1148:338–348.
151 Bottalico B, Larsson I, Brodszki J, et al: Norepinephrine transporter (NET), serotonin transporter (SERT), vesicular monoamine transporter (VMAT2) and organic cation transporters (OCT1, 2 and EMT) in human placenta from preeclamptic and normotensive pregnancies. Placenta 2004;25:518–529.
152 Zhu MJ, Du M, Hathanielsz PW, et al: Maternal obesity up-regulates inflammatory signaling pathways and enhances cytokine expression in the midgestation sheep placenta. Placenta 2010;1:387–391.
153 Wang X, Athayde N, Trudinger B: A proinflammatory cytokine response is present in the fetal placental vasculature in placental insufficiency. Am J Obstet Gynecol 2003;189:1445–1451.
154 Challis JR, Lockwood CJ, Myatt L, et al: Inflammation and pregnancy. Reprod Sci 2009;16: 206–215.
155 Donaldson K, Stone V, Seaton A, et al: Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Persp 2001; 109(suppl 4):523–527.

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