

Cortisol Circadian Rhythms and Stress Responses in Infants at Risk of Allergic Disease

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Key Words

Hypothalamic-pituitary-adrenal axis • Salivary cortisol, allergy • Birth order • Circadian rhythm • Stress

Abstract

Altered hypothalamic-pituitary-adrenal function associated with allergic disease has generally been thought to be secondary to the stress of chronic disease. However, recent studies suggest that altered cortisol circadian rhythm and cortisol stress hyper-responsiveness precede the inception of allergic disease and are possible links between preventive factors associated with the hygiene hypothesis and the development of allergies. Elevated endogenous cortisol responses to stressful stimuli could predispose susceptible hosts to atopy and allergic disease by biasing the developing immune system to a T helper 2-predominant immune response, greater total and allergen-specific serum immunoglobulin E responses, and/or inhibition of peripheral immune tolerance. Because glucocorticoid receptors are present throughout the human body and many genes contain glucocorticoid response elements, variances in endogenous cortisol concentrations could have an impact on the phenotypic plasticity of a wide range of immunologically active genes during early human immune development. Here, recent findings related to hypothalamic-pituitary-adrenal

function in infants predisposed to developing allergic disease are discussed along with speculation regarding the potential causal role of endogenous cortisol in the inception of allergic disease.

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Introduction

Epidemiologic risk factors suggest that early life is a critical window during which multiple factors interact to impact the genesis of the atopic phenotype and the development of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis. Allergies are more common in children born with a lower birth order, who did not attend day care during infancy, who were raised in an urban rather than farming environment, of male sex or with allergic parents [1–3]. The first 3 factors – birth order, day care attendance and farming environment – are presumed by some to be markers of microbial exposure and therefore support the hygiene hypothesis, which proposes that early microbial exposures prevent the subsequent development of atopy and allergies [1]. Maternal allergy has generally been found to be a greater risk factor than paternal allergy for allergic disease in children, suggesting that the intrauterine environment might add to

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Table 1. HPA function in infants with factors related to the inception of allergic disease

HPA Function during infancy	
Risk factors for allergic disease	
Parental allergy	Increased cortisol response to phlebotomy in newborns Increased cortisol response to vaccination at 6 months Lack of diurnal decline in cortisol at 6 months
Male sex	Normal
Maternal smoking	Unknown
Protective factors for allergic disease	
Increased number of siblings	Decreased cortisol response to vaccination at 6 months
Early day care attendance	Decreased cortisol response to vaccination at 6 months
Early life infections	Unknown
Farming environment	Unknown
Early exposure to farm animals or pets	Unknown

the genetic risk inherited by children from their allergic mothers [4]. These epidemiologic relationships, along with the skewing of immune responses during the first few years of life [5] and the onset of allergies during the preschool years [6], all support the contention that pre-natal and early life events are critical to the subsequent development of allergy.

Altered hypothalamic-pituitary-adrenal (HPA) function is a possible link between these risk factors and the development of allergic disease (table 1). Both intrauterine and neonatal events impact the development of HPA function, which in turn is related to allergic disease. Maternal asthma can suppress fetal HPA function during pregnancy by altering fetal estradiol production, a derivative of fetal adrenal dehydroepiandrosterone sulfate [7], and is a risk factor for the development of asthma in offspring [2]. Endotoxin exposure, a marker of microbial exposure, is associated with alterations of both basal circadian rhythm and stress responsiveness of cortisol in rats [8] and with a decreased risk of allergy in children [9].

Due to the critical role of cortisol in organ maturation, its distribution throughout body tissues, and the known impact on large numbers of genes, cytokines and other inflammatory mediators [10], altered HPA function during early development potentially could have a significant impact on the maturing immune system. Recently, using DNA microarray technology, it was found that glucocorticoids affected 20% of the expressed human leukocyte genome [11]. Varied cortisol levels due to altered HPA function during infancy and early childhood might play a critical role, through as yet undetermined molecular mechanisms, in the development of

immune responses at a time when the allergic phenotype is developing [6].

Reviews of evidence from human adults and animal models support the hypothesis that alterations of HPA function are associated with allergic disease [10, 12]. However, investigations of this relationship in human infants have been limited because of ethical and methodological challenges. The recent capability to measure cortisol concentration in small quantities of saliva now allows for the study of endogenous cortisol patterns during infancy. This review will focus on findings from human infants linking early abnormalities of HPA function with the development of atopy and allergies. Physiological adaptation to different concentrations of endogenous cortisol in the developing infant might occur within immune-related genes that exhibit phenotypic plasticity. A model integrating the present evidence with this concept of phenotypic plasticity of gene expression will be proposed as a possible mechanism by which early life alterations of HPA function might impact the subsequent development not only of allergic disorders, but also of other immune-related diseases.

Allergies and Infant Cortisol Circadian Rhythms

HPA function matures significantly during the first year of life. At birth, newborns do not exhibit a diurnal decline of cortisol. Studies, primarily measuring salivary cortisol, estimate the age of onset of the adult pattern of cortisol circadian rhythm to range from 1 to 9 months, with the peak concentration of the morning surge of sal-

ivary cortisol averaging 10–12 nM (0.36–0.44 μ g/dl) at 6 months of age [13–17].

It was proposed that the relatively wide age range of 1–9 months found in these studies is primarily the result of methodological differences in the operational definition of the circadian rhythm and/or sampling times used in the studies [18]. For example, in one study the circadian rhythm was defined as a higher value in the morning (6:00–08:00 h) than in the evening (22:00–24:00 h) with a steady decline in between these times [14], whereas in other studies a circadian rhythm was determined to be present only when the morning cortisol was either 16.5% [13] or 25% [15] higher than that obtained later in the day. The erratic sleep/wake schedules of infants add to the methodological challenges of performing studies in this age range.

Few studies have investigated possible factors associated with the onset of the circadian rhythm of cortisol as a cause for these disparate results regarding differential maturation of the HPA function among healthy term infants. One study found that 6-month-old infants of allergic mothers were more likely to lack the expected morning surge in salivary cortisol compared to infants of nonallergic mothers (fig. 1) [18]. However, it is not known if the flattened circadian rhythm of cortisol seen in these infants was due to a maturational delay in obtaining the expected diurnal decline or a fixed abnormality. This difference is important, as some individuals consistently have been observed to have a flattened circadian rhythm due to a lack of the expected morning surge of cortisol [19]. This abnormal rhythm, along with a blunted cortisol response to stress, has been referred to as hypocortisolism and has been found in both allergic and nonallergic inflammatory diseases, including asthma and rheumatoid arthritis [20].

Historically, it had been assumed that alterations in HPA function associated with inflammatory disease resulted from the chronic stress of disease and that chronic stress would be related to elevated levels of cortisol [21]. Contrary to this theory, recent studies have found that asthma was associated with a lower morning cortisol, resulting in a flattened circadian rhythm [22]. In addition, similar results in children with asthma or other allergic disorders suggest either that altered HPA function might precede the onset of adult disease or that not many years of chronic inflammatory disease during childhood are required to alter HPA function [23–25]. Therefore, the presence of this abnormal circadian rhythm in infants at risk for allergic disease by virtue of having an allergic mother and in children and adults with allergies not

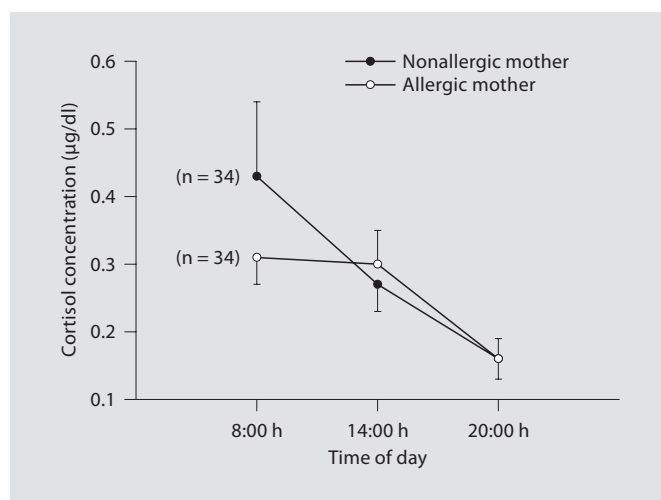


Fig. 1. Diurnal variation of cortisol by maternal allergy. $p = 0.023$; difference between diurnal variation of infants of allergic mothers compared to nonallergic mothers [18].

treated with glucocorticoids suggests that this characteristic of the cortisol circadian rhythm might be a fixed disorder associated with the allergic phenotype. However, no longitudinal study has been completed to investigate this definitively.

Allergies and the Cortisol Response to Stress

Newborn infants respond to stressful stimuli with the expected rise in cortisol. However, the degree of cortisol rise is altered during development. When salivary cortisol was measured before and after normal vaccination in healthy infants during the first year of life, the cortisol rise gradually declined at each age point, ultimately becoming insignificant [26]. Therefore, while newborns have a large rise in cortisol to stressful stimuli, the expected normal maturation of the infant is expected to be accompanied by a gradual habituation of this response.

Two studies have examined infant responses to stressful stimuli in relation to risk factors for allergic disease. Newborns at risk for the development of allergic disease by virtue of parental allergies were compared to newborns with nonatopic parents [27]. Salivary cortisol was obtained before and after the heel stick associated with routine neonatal genetic screening. Newborns with one or more allergic parents and a high cord immunoglobulin E (IgE) concentration had a greater rise in cortisol com-

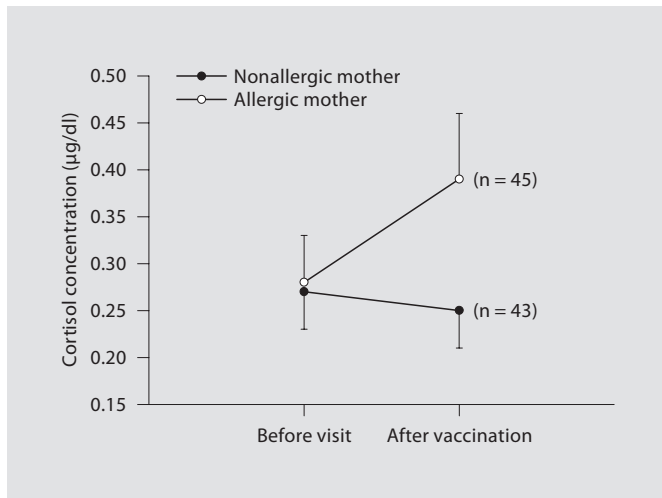


Fig. 2. Change in cortisol with examination and vaccination by maternal allergy. $p = 0.016$; difference between change in cortisol during examination and vaccination of infants of allergic mothers compared to nonallergic mothers [18].

pared to newborns with nonatopic parents and low cord IgE concentrations. In a second study, salivary cortisol was measured before and after vaccination in a group of 6-month-old infants (fig. 2) [18]. Infants with an allergic mother, but not an allergic father, had a greater rise in cortisol than infants with a nonallergic mother. In addition, protective factors for allergies, such as early day care attendance and higher birth order, were associated with a lower cortisol rise to vaccination. Both of these studies suggest that elevated cortisol responses to stress might be a risk factor for the subsequent development of allergic disease.

These findings from human infants contrast sharply with studies in children and adolescents suffering from allergic diseases such as asthma, atopic dermatitis and allergic rhinitis [23, 25, 28]. These investigations have been consistent in demonstrating that children and adolescents with allergic diseases have lower cortisol responses to stressful stimuli. It is not clear if this difference in cortisol response between healthy infants predisposed to allergic disease and older children and adolescents with allergic disease are due to age- or disease-related factors. The speculation that chronic hyperactivity of the HPA axis might ultimately lead to hypocortisolism through the downregulation of corticotropin-releasing hormone receptors in the pituitary offers one plausible explanation for these findings [20]. Alter-

natively, it is possible that an elevated cortisol response might be related to the inception of atopy, while the chronic stress of allergic disease is related to a decreased cortisol response.

Elevated Endogenous Cortisol as a Risk Factor for Allergies

It might seem counterintuitive that elevated cortisol stress responses are related to the development of atopy and allergic disease since glucocorticoids are a mainstay for the treatment of allergic inflammation. Nevertheless, at least 3 plausible mechanisms linking elevated endogenous cortisol to the development of atopy and allergic disease exist and a brief discussion of each is warranted because of the recent findings presented above. Glucocorticoids appear to bias the immune response to a T helper 2 (Th2)-type immune response and are associated with increased IgE levels, both of which are consistent with the allergic phenotype. Lastly, and more speculative, there is the possibility that glucocorticoids might inhibit cytokine expression felt to be critical to peripheral immune tolerance during infancy.

A significant body of evidence demonstrates that glucocorticoids drive the balance of Th1 and Th2 cells towards a Th2 cytokine profile [29–31]. Corticosteroids were found to inhibit production of interleukin-12 (IL-12), a critical Th1 cytokine that stimulates interferon- γ production, in human monocytes and to enhance the capacity to induce IL-4, a critical Th2 cytokine, synthesis in CD4+ T lymphocytes [29, 30]. Using a murine model, it was found that emotional stress, which was associated with elevation of serum corticosterone concentration, caused a shift of the Th1/Th2 balance towards a Th2 immune response through inhibition of interferon- γ production [32].

Allergic diseases are associated with elevated serum levels of IgE and numerous studies have suggested that glucocorticoids are associated with elevated IgE production. This apparent paradox between the efficacy of glucocorticoids for the treatment of allergic inflammation and the apparent increase in IgE with corticosteroids has been previously reviewed [33]. IL-4 and hydrocortisone are known to act synergistically to induce IgE isotype switching in human B cells [34]. Recently, this was studied in both atopic and nonatopic subjects in regard to the production of both serum total IgE and allergen-specific IgE [35]. Peripheral blood mononuclear cells from both atopic asthmatics and nonatopic subjects were studied ex

vivo. As expected, IL-4 and hydrocortisone acted synergistically to increase IgE production. However, hydrocortisone had more profound effects than IL-4 on the induction of allergen-specific IgE in sensitized subjects.

Less evidence supports the idea that elevated endogenous cortisol might be associated with decreased peripheral immune tolerance. However, much of our present understanding of the impact of glucocorticoids on peripheral immune tolerance is based on studies performed upon adult peripheral blood mononuclear cells, often at pharmacological levels of synthetic glucocorticoids. These findings might not accurately reflect the action of physiological levels of glucocorticoids on cytokine responses in infants. For example, IL-10 is a cytokine believed to be important in the induction of peripheral immune tolerance in humans. Glucocorticoids were found not to inhibit this protective cytokine in *ex vivo* studies of adult whole blood [36]. However, when the IL-10 response to stimulation of peripheral blood mononuclear cells was examined using the same *ex vivo* model in both adults and infants, IL-10 responses were not inhibited in adults, whereas significant inhibition occurred in infants [37]. An age-related difference between *ex vivo* production of IL-10 in the presence and absence of dexamethasone was also noted between adults and newborns [38]. Therefore, in infants, elevated endogenous cortisol might impair the development of peripheral immune tolerance through age-specific inhibition of cytokines such as IL-10.

Connecting the Dots

The ethical and logistical barriers to performing the ideal study of the effects of HPA development during fetal and early postnatal life on the subsequent development of immune-related diseases, such as allergies, are daunting. However, within the constraints of our present ignorance I would like to speculate on how our present knowledge might be interpreted to form a coherent vision of the potential role of cortisol in the phenotypic plasticity of the human genome.

Although numerous genes have been associated with allergic disease, few genetic associations have been replicated in subsequent studies [39]. One explanation for these inconsistent findings is that both gene-gene and gene-environment interactions may play roles in the genetic determinants of allergic disease. Endogenous cortisol is a critical component and determinant of the genome's environment and would be expected to alter not

only the expression of individual genes, but also interactions between genes. For example, variation in the IL-13 gene has been associated with asthma or allergies in multiple studies and is felt to represent a true asthma or atopy susceptibility gene important for disease modification [39]. However, recent functional analyses found that the susceptible polymorphism of IL-13 was only related to IgE production when studied in the presence of hydrocortisone [40].

Two concepts, the first from systems biology and the second from evolutionary biology, are important to realizing the potential impact of early life variations in endogenous cortisol concentration of the genome's environment. A glucocorticoid action network has been described, with a critical element being that while the HPA senses and, therefore determines, the circulating concentration of cortisol, the cells of the rest of the target tissues must function within this cortisol concentration, passively accepting the actions of the circulating glucocorticoids [41]. This raises the likelihood of a discordance between HPA axis feedback regulation and peripheral target tissue glucocorticoid sensitivity occurring in some individuals. The second concept is that of phenotypic plasticity of a gene, which may be quantified by a norm of reaction. A norm of reaction is an array of phenotypes that will be determined by a genotype over an array of environments [42]. Hence, the ultimate range of phenotypes associated with a gene would be related not only to the actual genotype, but also to the degree of plasticity of the gene in relation to cortisol. Greater phenotypic plasticity of a gene in relation to glucocorticoids could explain the lack of reproducibility of genetic association studies found for allergies and asthma.

Although the quantification of a reaction norm of an immune-related gene to varying cortisol concentrations is conceptually quite simple, it would be challenging to do so in human infants where it is unethical to control their environment. Nevertheless, this concept that phenotypic plasticity exists for many genes, and that the phenotypic outcomes of some genes are, in part, determined by the environment, raises the possibility that endogenous cortisol exerts an 'environmental' influence on the phenotype outcome of some genes. For example, cytokine production was examined in peripheral blood mononuclear cells of infants stimulated in the absence and presence of physiological level of hydrocortisone [43]. Correlations between critical cytokines, such as IL-10, TGF- β , TNF- α , IL-5 and interferon- γ , varied significantly by cortisol concentration, suggesting that differing endogenous cortisol concentrations possibly play a criti-

cal role in determining the phenotype of the immune response during infancy.

This review has focused on the role of endogenous cortisol in the inception of allergies. However, the stress response consists not only of cortisol release, but also of neurotransmitter release. Recently, it was shown that mice produced less IgE when they were depleted of nor-epinephrine before the administration of antigen [44]. Consistent with this finding, salbutamol and fenoterol were found to potentiate the IL-4-induced IgE production by human peripheral blood mononuclear cells [45]. Since neurotransmitter release was not measured in the previously mentioned investigations of the cortisol re-

sponses in infants predisposed to atopy, it is impossible to disregard their possible role in the association between abnormal stress responses and the inception of allergic disease.

Regardless of the underlying mechanism, variations in endogenous cortisol could interact with genes critical to the development of allergies, possibly through pervasive transcriptional or posttranscriptional effects on the expression of cytokines and other inflammatory mediators. It remains to be determined if these findings are due to dysregulation within the integrated system of immune signaling and HPA function that begins in utero and continues to develop early in life.

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