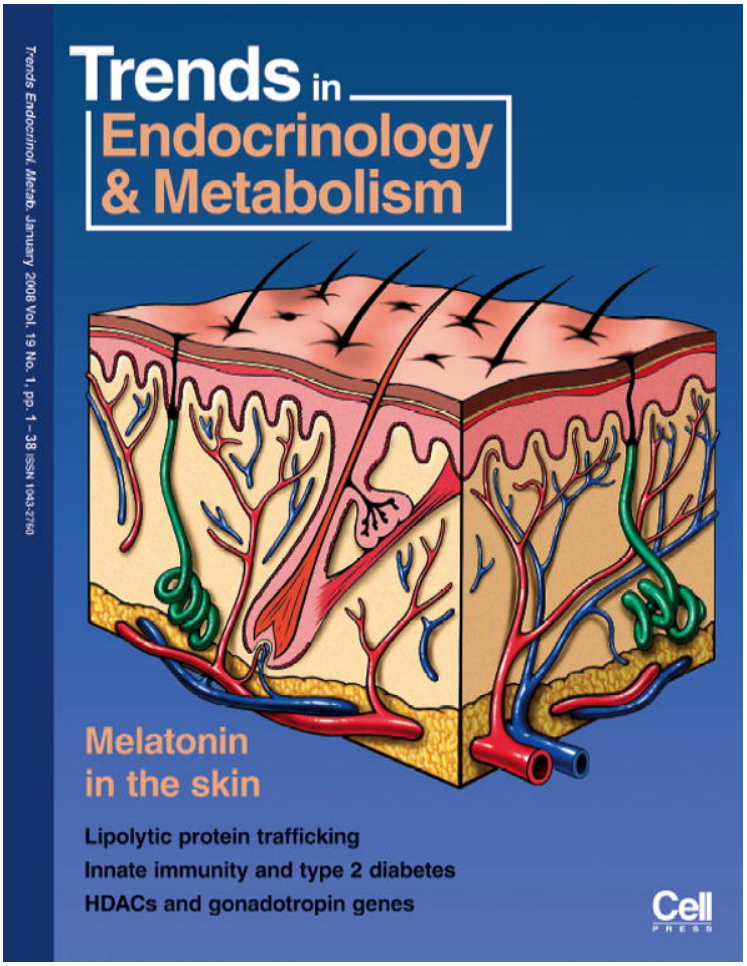

# The hypothalamic–pituitary–adrenal axis in asthmatic children

Kostas N. Priftis[1], Anastasios Papadimitriou[2], Polyxeni Nicolaidou[2] and George P. Chrousos[3]

[1] Department of Allergy-Pneumonology, Penteli Children's Hospital, Athens, Greece
[2] Third Department of Pediatrics, Attikon University Hospital, Athens University Medical School, Athens, Greece
[3] First Department of Pediatrics, Aghia Sophia Children's Hospital, Athens University Medical School, Athens, Greece

**Reduced responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis in patients with various chronic allergic inflammatory disorders and a blunted HPA axis response of poorly controlled asthmatics before long-term treatment with inhaled corticosteroids (ICS) have been reported. It seems that pro- and anti-inflammatory cytokines might be involved in the attenuation of cortisol and adrenocorticotropic hormone (ACTH) responses to stress in these patients. Although long-term ICS treatment might produce mild adrenal suppression in some asthmatic children, improvement of adrenal function has been detected in the majority of cases. We postulate that the anti-inflammatory effects of ICS result both in asthma remission and HPA axis improvement. Adrenal suppression of some asthmatic patients on maintenance ICS seems to be a separate phenomenon, possibly constitutionally or genetically determined.**

## Introduction

Since inhaled corticosteroids (ICS) were established as the cornerstone in the management of persistent asthma, many studies have been performed to investigate the safety of this treatment, especially in children [1,2]. Initial studies, which assessed adrenal reserve mainly by the standard adrenocorticotropic hormone (ACTH) (synacthen) test (SST), concluded that there was no evidence of adrenal suppression in asthmatic subjects on long-term treatment with ICS and, hence, no need for glucocorticoid coverage at stress situations [3,4]. However, when more sensitive methods of adrenal function were employed, mild, dose-dependent hypothalamic–pituitary–adrenal (HPA) axis suppression was unravelled [5,6]. Moreover, rarely, children developed glucocorticoid excess side-effects on doses of inhaled topical steroids normally considered to be entirely safe [7–9].

Recent data indicate that chronic inflammatory disorders might be linked to a hyporesponsive HPA axis, and that inflammatory mediators might inhibit ACTH-induced adrenocortical production of cortisol [10–12]. Following this line of evidence, low baseline adrenal function of certain asthmatic children before any treatment with ICS was reported in several studies, and this was attributed to the asthma state itself rather than to therapeutic interventions [6,13]. Recently, we reported that some asthmatic children who had their adrenal responsiveness tested before and during maintenance ICS, showed an improvement of HPA axis responsiveness to low dose ACTH while on ICS treatment, whereas adrenal suppression in response to ICS was evident in another smaller subgroup of patients [14].

This review examines the HPA axis function of asthmatic children before and during ICS treatment, and puts the evidence collected into the context of endocrine–immune interactions.

## Stress system and allergic inflammation interactions

The HPA axis and the sympathetic nervous system are the peripheral limbs of the stress system, the function of which is to maintain basal and stress-related homeostasis. The stress system responds to many distinct signals, including humoural and neural signals from the immune and inflammatory reaction [15,16]. Allergy is a hypersensitivity reaction initiated by humoural or cell-mediated immune mechanisms [17]. Stress system–immune reaction interactions are undoubtedly complex and take place at multiple levels, whereas various immune-mediators have a crucial role in the initiation and propagation of immune responses.

Cytokines, such as interleukin (IL)-4, IL-5, IL-9 and IL-13, contribute to the induction of allergy in an enhanced T-helper type 2 (Th2) lymphocyte-driven immune response [18,19]. IL-4 is the major factor regulating immunoglobulin (Ig) E production by B cells and is required for optimal Th2-directed lymphocyte differentiation [20]. Although the exact role of tumour necrosis factor α (TNFα) in asthmatic patients is yet to be determined, TNFα is implicated because increased levels of this cytokine were detected in sputa after allergen challenge of sensitized atopic asthmatics [21]; furthermore, the TNFα gene has been recently associated with nonallergic asthma in children [22]. IL-6 was also recognized as potentially important because it is secreted by cells during the innate immune response and induces an expansion of Th2-effector cells, which are major players in the adaptive immune response [23].

Activation of the HPA axis by specific cytokines (e.g. IL-1, IL-6) increases the release of cortisol, which, in turn, feeds back and suppresses the immune reaction. However, decreased endogenous glucocorticoid production in corticotropin-releasing hormone (CRH)-knockout mice was associated with increased airway inflammation with

*Corresponding author:* Priftis, K.N. (kpriftis@otenet.gr).

www.sciencedirect.com 1043-2760/$ – see front matter  doi:10.1016/j.tem.2007.10.005

mechanical dysfunction of the lungs and with increased IL-4, IL-5 and IL-13 levels [24].

Chronic activation of the HPA axis or chronic inflammation might result in reciprocally protective adaptations. Mastorakos *et al.* demonstrated that, although acutely, IL-6 caused impressively marked and prolonged elevations of plasma ACTH and cortisol in humans, but in the longer-term it was associated with blunted ACTH and, to a lesser extent, cortisol responses [25]. However, TNFα reduced adrenal cortisol synthesis by inhibiting the stimulatory actions of ACTH on cultured human foetal adrenocortical cells and shifted the steroid secretory pattern towards androgen production [26]. This inhibitory effect of cytokines on the HPA axis explains the strong negative correlation that was observed between circulating levels of IL-6, TNFα and cortisol after stimulation with CRH in patients with sleeping sickness [27]. Furthermore, the allergy-related cytokine IL-4 dose-dependently inhibited pro-opiomelanocortin (POMC) mRNA expression in the anterior pituitary, without affecting CRH mRNA at the hypothalamic paraventricular nucleus, suggesting that this cytokine had a direct inhibitory action at the level of the pituitary gland [28].

Exogenously applied stress dramatically enhances airway reactivity in ovalbumin-sensitized and challenged mice. Furthermore, stress significantly increases allergen-induced airway inflammation [29,30]. This is in agreement with the clinical observation that there is an immediate effect of stress, evident within the first two days following a severely negative life event, increasing the risk of a new asthma attack [31].

## Blunted cortisol responses to stress in allergic children

A low HPA axis activity in allergic patients has been reported in a large number of clinical studies. Initially, the main interest of the researchers was concentrated on the HPA axis of asthmatics who were on long-term treatment with ICS; however, subsequently, a growing number of studies recognized that allergic/asthmatic patients not treated with ICS were also likely to have an attenuated activity and/or responsiveness of their HPA axis (Table 1).

Buske-Kirschbaum *et al.* demonstrated reduced cortisol levels in response to psychosocial stress in children and adults with atopic dermatitis, pointing to a dysfunction of the HPA axis in patients with this disorder [10,32]. The same group also found that children with allergic asthma showed significantly attenuated cortisol responses to psychosocial stress when compared with matched healthy controls [33]. Furthermore, reverse association between adrenal and bronchial responsiveness in asthmatic children has been reported, demonstrating that children with more severe disease might have relative adrenal insufficiency compared to the children with milder disease [34].

There are two other recent interesting reports on HPA axis function in allergic subjects. In the first, the circadian rhythm of salivary cortisol was evaluated in infants with an increased risk for allergic disease [35]. Indeed, infants of mothers with allergy or asthma, or an asthmatic father, had a flattened rhythm because of diminution of the expected morning surge of cortisol. In the second, the basal and synacthen-stimulated morning plasma cortisol concentrations of wheezing infants aged 5–9 and 9–12 months were evaluated by high-performance liquid chromatography [36]. In general, mean basal plasma cortisol concentrations were similar between the two age groups and increased to comparable levels 60 min after synacthen administration. However, they had a wider range of basal and stimulated values. It is of interest that ~14% of these infants did not reach a normal stimulated plasma cortisol concentration.

A low adrenocortical response during a pre-treatment evaluation of poorly controlled asthmatics was reported previously but was not commented upon as an important finding. Thus, Volovitz *et al.* [13] found that 60 min after ACTH administration during the standard SST, serum cortisol concentrations in four out of 15 asthmatic children were lower than 496.6 nmol/L, whereas cortisol suppression was no longer present when these children were clinically controlled by budesonide therapy. In another study by Kannisto *et al.* [6], cortisol values were obtained during the low-dose synacthen test (LDST) before the patients were started on ICS treatment. The authors recognized that, in their patients, the low limit of serum cortisol response was lower (330 nmol/L) than normally expected (i.e. 500 nmol/L). Similarly, Ozbec *et al.* [37] used the Kannisto *et al.* [6] diagnostic protocol for adrenal suppression and they also obtained lower values (389 and 438 nmol/L) for the low limit of the normal cortisol response. Finally, Bacharier *et al.* [38] reported that four out of 45 children receiving long-term treatment with nedocromil or placebo, but not ICS, demonstrated abnormally low serum cortisol levels during the ACTH stimulation test.

In line with these observations, we recently reported the results of a 12-month prospective study of a cohort of 41 pre-adolescent asthmatic children that were placed on long-term treatment with inhaled budesonide and followed by serial LDSTs. Approximately 10% of our cohort had a low adrenal reserve before starting any ICS treatment. These patients, as well as more than half of the remaining cohort, showed improved adrenal responses while receiving long-term ICS [14] (Figure 1).

These considerations support the concept that chronic allergic disease, regardless of the organ affected, might be associated with reduced activity and/or responsiveness of the HPA axis. Production of certain allergic inflammation-related cytokines might blunt the response of the HPA axis to both inflammation and acute stress, contributing to the aggravation of allergic inflammation owing to insufficient anti-inflammatory restrain. The heterogeneity in corticosteroid responsiveness might reflect the variety of mechanisms involved in HPA axis regulation and the involvement of multiple cytokines with stimulatory or inhibitory actions on the HPA axis [16,18–20].

## Adrenal suppression in asthmatic children on inhaled corticosteroids

There is a large amount of data regarding the safety profile of ICS on the HPA axis [1,2]. However, the clinical importance of HPA axis function studies lies in their ability to

**Table 1. HPA axis studies in children, adolescents and young patients with allergic disorders**

| Illness | Dynamic adrenal function test – stressor | Patients studied (N), age | Medication-free/on topical corticosteroids | Comments | Refs |
|---|---|---|---|---|---|
| Asthma (severe perennial) | SST; cut-off: 497 nmol/L | 15 children, 2–7 yrs | Placebo-controlled trial; budesonide 200 μg daily | In pre-treatment period, 4 children showed evidence of suppression; no impairment when on budesonide | [13] |
| Atopic dermatitis | TSST-C | 16 healthy, 8–14 yrs; 15 atopic dermatitis | None on topical corticosteroids | Significantly blunted cortisol response to the stressor in children with atopic dermatitis | [10] |
| Asthma | LDST; cut-off: 330 nmol/L (<2SD mean of studied patients) | 75 children, 5.5–14.7 yrs | 30 fluticasone 30 budesonide (moderate doses) 15 cromone | Pre-treatment low serum cortisol response limit was lower than normally expected (i.e. 500 nmol/L) | [6] |
| Atopic dermatitis | TSST | 37 normals; 36 atopic dermatitis, 20–33 yrs | Topical emollients, no corticosteroids | Patients showed significantly attenuated cortisol and ACTH responses to the stressor | [32] |
| Asthma | SST; cut-off: 550 nmol/L | 16 children, 8–16 yrs; BHR mild-moderate, severe | None on ICS | Reverse association between adrenal reactivity and BHR | [34] |
| Allergic asthma | TSST-C | 18 normals; 17 allergic asthma, 7–12 yrs | None on ICS | Asthmatic children showed a significantly blunted cortisol response to the TSST-C | [33] |
| Asthma | SST; cut-off: 30-min 500 nmol/L 60-min 550 nmol/L | 63 children, mild to moderate asthma, 5–12 yrs | Budesonide 400 μg/day, nedocromil 16 mg/day, placebo | 4 out of 45 on long-term treatment with nedocromil or placebo, but not ICS, demonstrated abnormally low serum cortisol levels during the ACTH stimulation test | [38] |
| Infants with allergic parents | Saliva at 8am, 2pm, 8pm on a day; stress of vaccinations | 68 infants at home; 88 in the clinic, 2–4 months | None on ICS | Analysis of the circadian rhythm of cortisol was flattened in infants with allergic parents | [35] |
| Asthma | LDST; cut-off: 495 nmol/L (<2SD mean of healthy controls) | 41 children, 5–10 yrs | Prospective longitudinal study; budesonide 400 μg daily | 10% had a low adrenal reserve before starting any ICS; those as well as more than half of the remaining, improved adrenal responses while on ICS | [14] |
| Asthma | LDST; cut-off = 389 and 438 nmol/L (<2SD mean of studied patients) | 30 children, 8–12 yrs | 15 budesonide 400 μg daily; 15 budesonide 600 μg daily | Pre-treatment low serum cortisol response limit was lower than normally expected (i.e. 500 nmol/L) | [37] |
| Wheezing infants | SST; cut-off: 500 nmol/L | 112 infants, 5–12 mo | None on ICS | 14% of the studied did not reach a normal cosyntropin-stimulated plasma cortisol concentration | [36] |

Abbreviations: BHR, bronchial hyperresponsiveness; ICS, inhaled corticosteroids; LDST, low-dose synacthen test; SST, standard ACTH (Synacthen) test; TSST-C, Trier social stress test for children.

identify which children placed on ICS therapy will not be able to properly respond to stress.

Basal state HPA axis tests are generally inferior in diagnosing HPA suppression, whereas dynamic testing has the advantage of providing an assessment of stress reserve [39,40]. Although the insulin tolerance test (ITT) and the metyrapone test have been considered by some physicians to be the gold standard of adrenal function tests, both include risks and are in limited use [41]. ITT has been linked to deaths in children, whereas metyrapone is usually unavailable. As first line alternatives, the CRH stimulation test and the SST have been proposed and are usually employed [39]. The conventional high dose of intravenous injection of 250 μg is primarily useful in determining severe and clinically important adrenocortical insufficiency. This test produces supraphysiologic ACTH levels in the circulation and results occasionally in false-negative results, even in patients with a clinically impaired adrenal reserve. A variation of the SST is the LDST (0.5–1.0 μg), which is considered more accurate in assessing physiologic cortisol secretion than the SST and more sensitive in detecting evolving or mild adrenal suppression [40,42]. The salivary low-dose ACTH test yields results that parallel the response of circulating cortisol and might provide an alternative to the blood test [43,44].

The recent GINA (global strategy for asthma management and prevention) report correctly concludes that although differences exist between the various ICSs and the inhalation devices employed, treatment with the recommended doses of an ICS is normally not associated with any clinically significant suppression of the HPA axis in children. With higher doses, small changes in adrenal function can be detected with sensitive methods [45].

We reported that 20% of asthmatic children on long-term treatment with low to moderate doses of inhaled budesonide had mild biochemical adrenal suppression (via LDST), which was not related to the ICS dosage or duration of treatment [46]. Adrenal suppression in asthmatic children on even moderate doses of ICS have also been detected (via LDST) by others [47]. A flat adrenal response in association with fluticasone propionate in 2.8% of children tested (via LDST) was also reported, whereas impaired responses were seen in 39.6% of them; all were receiving more than 1000 μg/day.

In a 12-month observational study of 35 prepubertal asthmatic children requiring at least 1000 μg/day of

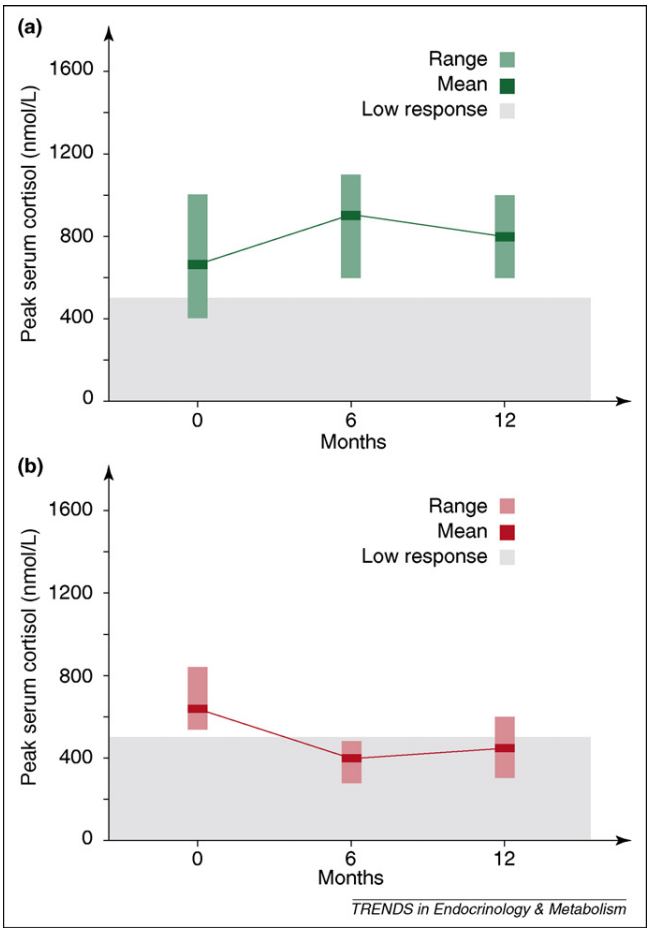


**Figure 1**. Adrenal response to LDST in asthmatic children before and on maintenance ICS treatment. Most asthmatics have an improvement over time of their HPA axis responsiveness while on conventional doses of ICS **(a)**, whereas adrenal suppression is evident in a subgroup of patients **(b)**. A low adrenal response of poorly controlled asthmatics might be observed during their pre-treatment evaluation (a), because cytokines involved in the pathophysiology of asthma seem to be inversely associated with cortisol production. The grey areas show the values of low response.

budesonide or equal potency of fluticasone propionate, 46% of the subjects had evidence of biochemical adrenal suppression at the LDST [48].

In a survey of adrenal crises associated with inhaled corticosteroids in the UK, 33 patients (28 children, five adults) met the diagnostic clinical and biochemical criteria (abnormal SST or glucagon stimulation test) for an adrenal crisis [49]. Most of these were using fluticasone metered dose inhalers with a spacer and high doses ranging between 500–2000 μg/day. Twenty-three children exhibited acute hypoglycaemia. In 65% of the patients there was no obvious precipitating cause for the hypoglycaemia; in the remainder of patients, there was evidence of a stressful event or a reduction/discontinuation of ICS.

A systematic review of the literature was recently performed by Pedersen, focusing on randomized, controlled studies of 12 months or more duration, to identify studies examining each of the following three areas: growth, bone mineral density and cortisol levels [50]. Ten studies met the inclusion criteria for cortisol levels. It was found that recommended doses of ICS generally had little or no effect on plasma- or urinary-cortisol levels versus nonsteroidal therapy.

From the aforementioned studies, it is obvious that a dose-dependent adrenal suppression in asthmatic children on ICS does exist. However, adrenal suppression might be detected even when they are on small and moderate doses. We do not know whether these children would present symptomatic adrenal insufficiency if they were treated with larger doses. Sometimes the results of various studies seem contradictory. This could be owing to the fact that they might have been derived by various testing methods with different abilities to detect HPA axis impairment. For example, morning serum cortisol or urinary-free cortisol concentration is a poor discriminator of adrenal hypoactivity.

## Single nucleotide polymorphisms related to the HPA axis

Recently, research has disclosed various associations between asthma and genes related to the HPA axis (Figure 2). Thus, single nucleotide polymorphisms (SNPs)

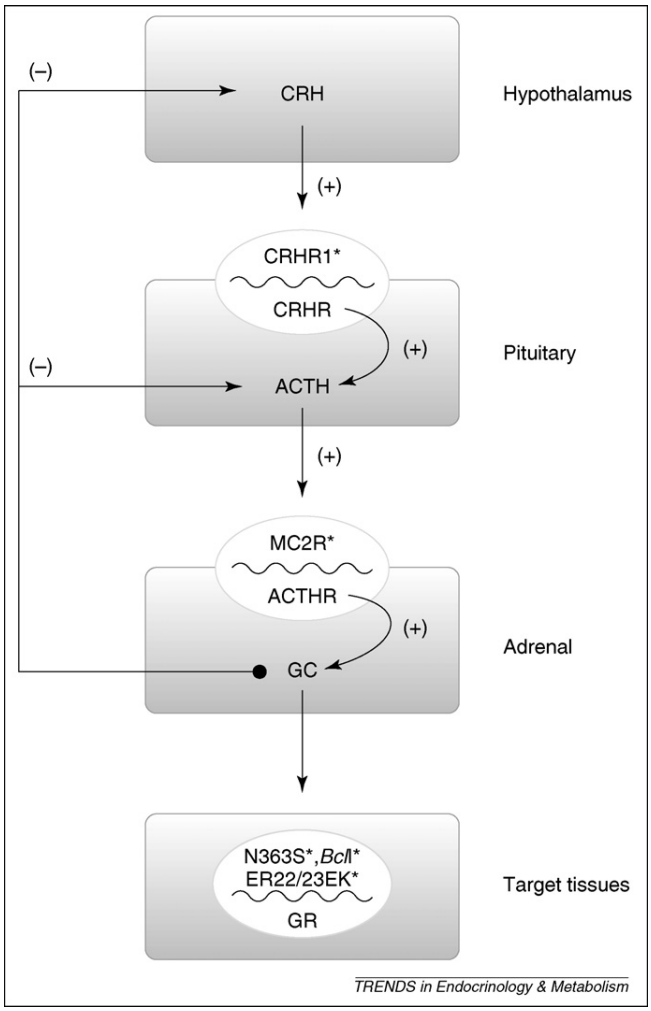


**Figure 2**. Simplified representation of HPA axis and SNPs that influence sensitivity and lung function responsiveness to ICS and response to stress. In circles are the HPA axis receptors whose genes have been reported to carry SNPs that influence sensitivity and lung function to ICS. The symbol + represents stimulation, - inhibition. Abbreviations: HPA, hypothalamic–pituitary–adrenal; SNP, single nucleotide polymorphism; ICS, inhaled corticosteroids; CRH, corticotropin-releasing hormone; CRHR, CRH receptor; ACTH, adrenocorticotropin; ACTHR, ACTH receptor; GC, glucocorticoids; GR, glucocorticoid receptor (MC2R, N363S, BclI, ER22/23EK are various types of SNPs).

of such genes determined an individual's sensitivity to glucocorticoids or resulted in a faster improvement of lung function in response to ICS therapy. Moreover, a certain polymorphism was associated with an impaired adrenal response to stress.

Hypothalamic CRH exerts its actions through binding to the CRH receptor. The predominant subtype is the CRH receptor 1 (CRHR1), which mediates the release of ACTH and the catecholaminergic response to CRH [51]. CRH does this in synergy with arginine vasopressin (AVP), which exerts its effects via its receptor V3 [52]. ACTH and the melanocortins (α-, β- and γ-melanocyte-stimulating hormone) are derived from a larger precursor molecule, the POMC. The biological effects of ACTH and the melanocortins are exerted by activation of the melanocortin receptors (MCR). To date, five melanocortin receptors have been identified (MC1R to MC5R) and they are widely distributed throughout the body; MC2R is the receptor that mediates ACTH action at the adrenal cortex [53].

Circulating serum glucocorticoids (i.e. cortisol in man and corticosterone in rodents) are secreted by the adrenals and influence, among many other important functions throughout the body, the activity of the immune system. Serum cortisol also exerts a negative feedback effect on the hypothalamus and pituitary gland. Glucocorticoids, as lipids, readily cross the plasma membrane into the cytoplasm, where they bind to the cytoplasmic/nuclear glucocorticoid receptor (GR). GR has two transcripts, resulting from alternative splicing, which code for the active isoform GRα and a nonligand-binding isoform GRβ, which does not bind glucocorticoids but acts as a dominant negative inhibitor of human GRα on glucocorticoid-responsive promoters. GRβ is expressed in virtually all human tissues, suggesting that it participates in determining glucocorticoid sensitivity [54–56].

Tantisira and colleagues [57] suggested a relation between the response to ICSs and a polymorphism of CRHR1. The hypothesis of the study was that a genetically determined decrease in the expression or function of CRHR1 could result in diminished capacity of the adrenals to secrete cortisol in response to inflammation, owing to decreased ACTH release. Therefore, a more favourable response to exogenous corticosteroids would be anticipated in asthmatics with alterations in this gene. Indeed, polymorphisms in CRHR1 were positively associated with significantly improved lung function in adult and paediatric populations, manifested by a doubling to quadrupling of the longitudinal forced expiratory volume at 1 s ($FEV_1$) response to corticosteroids after eight weeks of ICS therapy. No connection between asthma and AVP receptor subtype 3 polymorphisms have been reported as yet, but this should be considered a candidate gene for study.

Slawik *et al.* [58] characterized an ACTH receptor (MC2R) polymorphism that results in decreased adrenal responsiveness to ACTH. They identified a polymorphism within the ACTH receptor promoter (CCC) that is present at a significant frequency (1/125) in the normal male population in Germany and results in lower stimulated promoter activity *in vitro*. The presence of the polymorphism does not affect baseline hormonal characteristics; however, subjects with the polymorphism have a lower cortisol response to CRH or ACTH stimulation. It is uncertain whether, during major stress, the reduced ACTH sensitivity of the adrenal cortex could become clinically relevant.

The efficacy of treatment with glucocorticoids is influenced by an individual variation in sensitivity to these hormones. Several SNPs in the GR gene have been reported to be associated with glucocorticoid sensitivity [59,60]. Recently, Stevens *et al.* [61] performed haplotype analysis of the GR gene. They found a three-point haplotype, within intron B, which includes a SNP that alters a *Bcl*I site that is associated with enhanced sensitivity to glucocorticosteroids. The *Bcl*I polymorphism has also been associated with essential hypertension [62], increased body fat and an increased atherogenic profile in obesity [63,64].

Taken together, these data suggest that genetics is used in predetermining variation in the clinical response to glucocorticoid therapy and also susceptibility to the adverse effects of these hormones.

## Concluding comments

Researchers studying the adrenal function of asthmatic children were initially almost exclusively interested in the evaluation of the HPA axis of asthmatic patients treated with ICS. Thus, an extended literature on the safety of long-term treatment with ICS in asthmatic children has accumulated. Recent guidelines on asthma management [45] correctly note that asthma treatment with the recommended doses of ICS is normally not associated with any significant suppression of the HPA axis in children.

A more recent growing body of evidence shows that asthmatic subjects not treated with ICS are likely to have an attenuated activity and/or responsiveness of their HPA axis. The concept of this being a result of stress–immune system interactions has not only experimental but also clinical support. Pro- or anti-inflammatory cytokines involved in the pathophysiology of allergic disease, regardless of the target organ affected, seem to be inversely associated with cortisol production. In line with this concept, ICS as anti-inflammatory agents might have favourable effects in asthmatics with subnormal adrenal responses at baseline, improving adrenal function during successful long-term treatment. Indeed, most asthmatics present an improvement of their HPA axis responsiveness on conventional doses of ICS, as their airway inflammation subsides. But, some patients might experience further deterioration of adrenal function, a phenomenon which might be genetically determined. However, when ICS are administered at higher than conventional doses, secondary adrenal insufficiency, owing to excessive amount of exogenous corticosteroids, certainly becomes a probability.

## References

1 Skoner, D.P. (2002) Balancing safety and efficacy in pediatric asthma management. *Pediatrics* 109 (2 Suppl), 381–392
2 Allen, D.B. *et al.* (2003) Inhaled corticosteroids past lessons and future issues. *J. Allergy Clin. Immunol.* 112 (3 Suppl), S1–S40
3 Goldstein, D.E. and Konig, P. (1983) Effect of inhaled beclomethasone dipropionate on hypothalamic-pituitary-adrenal axis function in children with asthma. *Pediatrics* 72, 60–64
4 Katsunuma, T. *et al.* (1992) Adrenal function of children with bronchial asthma treated with beclomethasone dipropionate. *Ann. Allergy* 69, 529–532

5 Nicolaizik, W.H. *et al.* (1994) Endocrine and lung function in asthmatic children on inhaled corticosteroids. *Am. J. Respir. Crit. Care Med.* 150, 624–628

6 Kannisto, S. *et al.* (2000) Adrenal suppression, evaluated by a low-dose ACTH-test, and growth in asthmatic children treated with inhaled steroids. *J. Clin. Endocrinol. Metab.* 85, 652–657

7 Hollman, G.A. and Allen, D.B. (1988) Overt glucocorticoid excess due to inhaled corticosteroid therapy. *Pediatrics* 81, 452–455

8 Priftis, K. *et al.* (1991) Unexpected side effects of inhaled steroids. *Eur. J. Pediatr.* 150, 448–449

9 Wong, J.Y. *et al.* (2002) Growth and adrenal suppression in asthmatic children on moderate to high doses of fluticasone propionate. *J. Paediatr. Child Health* 38, 59–62

10 Buske-Kirschbaum, A. *et al.* (1997) Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom. Med.* 59, 419–426

11 Wamboldt, M.Z. *et al.* (2003) Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress. *J. Allergy Clin. Immunol.* 111, 509–514

12 Richards, H.L. *et al.* (2005) Response of the hypothalamic-pituitary-adrenal axis to psychological stress in patients with psoriasis. *Br. J. Dermatol.* 153, 1114–1120

13 Volovitz, B. *et al.* (1993) Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N. Engl. J. Med.* 329, 1703–1708

14 Priftis, K.N. *et al.* (2006) Adrenal function improves in asthmatic children on inhaled steroids: a longitudinal study. *Neuroimmunomodulation* 13, 56–62

15 Chrousos, G.P. (2000) Stress, chronic inflammation, and emotional and physical well-being: concurrent effects and chronic sequelae. *J. Allergy Clin. Immunol.* 106 (5 Suppl), S275–S291

16 Elenkov, I.J. and Chrousos, G.P. (2000) Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends Endocrinol. Metab.* 10, 359–368

17 Johansson, S.G. *et al.* (2001) A revised nomenclature for allergy. 2001 An EAACI position statement from the EAACI nomenclature task force. *Allergy* 56, 813–824

18 Nakajima, H. and Takatsu, K. (2007) Role of cytokines in allergic airway inflammation. *Int. Arch. Allergy Immunol.* 142, 265–273

19 Calcagni, E. and Elenkov, I. (2006) Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. *Ann. N. Y. Acad. Sci.* 1069, 62–76

20 Renauld, J.C. (2001) New insights into the role of cytokines in asthma. *J. Clin. Pathol.* 54, 577–589

21 Keatings, V.M. *et al.* (1997) Late response to allergen is associated with increased concentrations of tumor necrosis factor-alpha and IL-5 in induced sputum. *J. Allergy Clin. Immunol.* 99, 693–698

22 Munthe-Kaas, M.C. *et al.* (2007) HLA Dr-Dq haplotypes and the TNFA-308 polymorphism: associations with asthma and allergy. *Allergy* 62, 991–998

23 Doganci, A. *et al.* (2005) Pathological role of IL-6 in the experimental allergic bronchial asthma in mice. *Clin. Rev. Allergy Immunol.* 28, 257–270

24 Silverman, E.S. *et al.* (2004) Corticotropin-releasing hormone deficiency increases allergen-induced airway inflammation in a mouse model of asthma. *J. Allergy Clin. Immunol.* 114, 747–754

25 Mastorakos, G. *et al.* (1993) Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J. Clin. Endocrinol. Metab.* 77, 1690–1694

26 Jaattela, M. (1991) Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. *Endocrinology* 128, 623–629

27 Reincke, M. *et al.* (1994) Impairment of adrenocortical function associated with increased plasma tumor necrosis factor-alpha and interleukin-6 concentrations in African trypanosomiasis. *Neuroimmunomodulation* 1, 14–22

28 Harbuz, M.S. *et al.* (1992) Action of interleukin-2 and interleukin-4 on CRF mRNA in the hypothalamus and POMC mRNA in the anterior pituitary. *Brain Behav. Immun.* 6, 214–222

29 Joachim, R.A. *et al.* (2003) Stress enhances airway reactivity and airway inflammation in an animal model of allergic bronchial asthma. *Psychosom. Med.* 65, 811–815

30 Joachim, R.A. *et al.* (2006) Upregulation of tumor necrosis factor-alpha by stress and substance p in a murine model of allergic airway inflammation. *Neuroimmunomodulation* 13, 43–50

31 Sandberg, S. *et al.* (2004) Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 59, 1046–1051

32 Buske-Kirschbaum, A. *et al.* (2002) Altered responsiveness of the hypothalamus-pituitary-adrenal axis and the sympathetic adrenomedullary system to stress in patients with atopic dermatitis. *J. Clin. Endocrinol. Metab.* 87, 4245–4251

33 Buske-Kirschbaum, A. *et al.* (2003) Blunted cortisol responses to psychosocial stress in asthmatic children: a general feature of atopic disease? *Psychosom. Med.* 65, 806–810

34 Barr, J. *et al.* (2002) The relation between adrenal function and the severity of bronchial hyperresponsiveness in children as measured by the methacholine provocation test. *J. Pediatr. Endocrinol. Metab.* 19, 307–312

35 Ball, T.M. (2006) Cortisol circadian rhythms and stress responses in infants at risk of allergic disease. *J. Allergy Clin. Immunol.* 117, 306–311

36 Chrousos, G.P. (2007) Basal and cosyntropin-stimulated plasma cortisol concentrations, as measured by high-performance liquid chromatography, in children aged 5 months to <6 years. *J. Clin. Endocrinol. Metab.* 92, 2125–2129

37 Ozbek, O.Y. *et al.* (2006) Evaluation of hypothalamic-pituitary-adrenal axis (HPA) suppression by low-dose (0.5 μg) and standard-dose (250 μg) adrenocorticotropic hormone (ACTH) tests in asthmatic children treated with inhaled corticosteroid. *J. Pediatr. Endocrinol. Metab.* 19, 1015–1023

38 Bacharier, L.B. *et al.* (2004) Long-term effect of budesonide on hypothalamic-pituitary-adrenal axis function in children with mild to moderate asthma. *Pediatrics* 113, 1693–1699

39 Zollner, E.W. (2007) Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids: part 1. Which test should be used? *Pediatr. Allergy Immunol.* 18, 401–409

40 Bernstein, D.I. and Allen, D.B. (2007) Evaluation of tests of hypothalamic-pituitary-adrenal axis function used to measure effects of inhaled corticosteroids. *Ann. Allergy Asthma Immunol.* 98, 118–127

41 Zollner, E.W. (2007) Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2) – the risk as determined by gold standard adrenal function tests: a systematic review. Which test should be used? *Pediatr. Allergy Immunol.* 18, 469–474

42 Hindmarsh, P. (2002) Commentary: exogenous glucocorticoids influence adrenal function, but assessment can be difficult. *BMJ* 324, 1083

43 Marcus-Perlman, Y. *et al.* (2006) Low-dose ACTH (1 microg) salivary test: a potential alternative to the classical blood test. *Clin. Endocrinol. (Oxf.)* 64, 215–218

44 Silva, M.L. (2007) Salivary cortisol to assess the hypothalamic-pituitary-adrenal axis in healthy children under 3 years old. *J. Pediatr. (Rio J.)* 83, 121–126

45 Global Strategy for Asthma Management and Prevention 2006. http://www.who.int/respiratory/asthma/GINA_WR_2006_copyright%5b1%5d.pdf

46 Priftis, K.N. *et al.* (2006) The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children. *Eur. Respir. J.* 27, 316–320

47 Dunlop, K.A. *et al.* (2004) Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression. *Arch. Dis. Child.* 89, 713–716

48 Paton, J. *et al.* (2006) Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch. Dis. Child.* 91, 808–813

49 Todd, G.R.G. *et al.* (2002) Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch. Dis. Child.* 87, 457–461

50 Pedersen, S. (2006) Clinical safety of inhaled corticosteroids for asthma in children: an update of long-term trials. *Drug Saf.* 29, 599–612

51 Dautzenberg, F.M. and Hauger, R.L. (2002) The CRF peptide family and their receptors: yet more partners discovered. *Trends Pharmacol. Sci.* 23, 71–77

52 Kyrou, I. *et al.* (2006) Stress, visceral obesity, and metabolic complications. *Ann. N. Y. Acad. Sci.* 1083, 77–110
53 Gantz, I. and Fong, T.M. (2003) The melanocortin system. *Am. J. Physiol. Endocrinol. Metab.* 284, E468–E474
54 Bamberger, C.M. *et al.* (1995) Glucocorticoid receptor β, a potential endogenous inhibitor of glucocorticoid action in humans. *J. Clin. Invest.* 95, 2431–2445
55 Oakley, R.H. *et al.* (1999) The dominant negative activity of the human glucocorticoid receptor β isoform. Specificity and mechanisms of action. *J. Biol. Chem.* 274, 27857–27866
56 Chrousos, G.P. and Kino, T. (2007) Glucocorticoid action networks and complex psychiatric and/or somatic disorders. *Stress* 10, 213–219
57 Tantisira, K.G. *et al.* (2004) Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. *Hum. Mol. Genet.* 13, 1353–1359
58 Slawik, M. *et al.* (2004) Characterization of an adrenocorticotropin (ACTH) receptor promoter polymorphism leading to decreased adrenal responsiveness to ACTH. *J. Clin. Endocrinol. Metab.* 89, 3131–3137
59 Huizenga, N.A. *et al.* (1998) A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids *in vivo*. *J. Clin. Endocrinol. Metab.* 83, 144–151
60 Van Rossum, E.F. *et al.* (2002) A polymorphism in the glucocorticoid receptor gene, which decreases sensitivity to glucocorticoids *in vivo*, is associated with low insulin and cholesterol levels. *Diabetes* 51, 3128–3134
61 Stevens, A. *et al.* (2004) Glucocorticoid sensitivity is determined by a specific glucocorticoid receptor haplotype. *J. Clin. Endocrinol. Metab.* 89, 892–897
62 Watt, G.C. *et al.* (1992) Abnormalities of glucocorticoid metabolism and the renin-angiotensin system: a four-corners approach to the identification of genetic determinants of blood pressure. *J. Hypertens.* 10, 473–482
63 Buemann, B. *et al.* (1997) Abdominal visceral fat is associated with a BclI restriction fragment length polymorphism at the glucocorticoid receptor gene locus. *Obes. Res.* 5, 186–192
64 Ukkola, O. *et al.* (2001) Glucocorticoid receptor Bcl I variant is associated with an increased atherogenic profile in response to long-term overfeeding. *Atherosclerosis* 157, 221–224