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Blunted HPA axis responsiveness to stress in atopic patients is associated with the acuity and severeness of allergic inflammation

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ABSTRACT

Previously we could demonstrate attenuated responsiveness of the hypothalamus–pituitary–adrenal (HPA) axis to stress in patients with *chronic* allergic inflammatory disease (i.e., atopic dermatitis, allergic asthma).

The present study was designed to investigate HPA axis function in an *acute* manifestation of allergy. Patients with seasonal allergic rhinitis (SAR; $n = 20$) and non-atopic controls ($n = 20$) were exposed to a standardized laboratory stressor ('Trier Social Stress Test'; TSST). Cortisol responses to the TSST and cortisol awakening responses (CAR) were measured in SAR subjects while suffering from acute symptoms of SAR (pollen season), and during a non-active state of their disease (pollen-free season). To assess the acuity and severity of SAR, eosinophil and basophil numbers and SAR symptomatology were determined. Non-allergic control subjects were examined at identical times during the year. To control for possible sequence effects, a cross-over design was used. SAR patients showed significantly increased symptom severity ($t = 9.4$; $p < .001$) as well as eosinophil ($F(1, 31) = 9.8$; $p < .01$) and basophil ($F(1, 38) = 6.4$; $p < .05$) numbers during the pollen season when compared to a pollen-free period. When exposed to the TSST, significantly attenuated cortisol responses were found in SAR subjects during acute manifestation of the disease (pollen season) when compared to the pollen-free season ($F(16, 456) = 1.65$; $p < .05$). In SAR patients, there was a significant negative correlation between symptom severity and the cortisol response to the stressor ($r = .53$; $p < .05$). No significant between-group or between-condition differences with respect to the CAR could be determined (all $p > .05$). These findings support previous data of attenuated HPA axis responsiveness to stress in atopic conditions and further, suggest that HPA axis hyporesponsiveness in atopy may be linked to the severity of the allergic inflammatory process.

1. Introduction

Atopy refers to a familial or hereditary tendency to become sensitized to environmental substances, e.g., animal dander or pollen, and to develop hypersensitivity reactions characterized by an excessive production of immunoglobulin-E (IgE). The three major clinical manifestations of atopy, also called the *atopic triad*, are atopic dermatitis (AD), allergic asthma (AA) and allergic rhinitis (AR).

Atopy represents a global health issue affecting 20% of the population in the industrialized Western countries with increasing prevalence over the last decade (Gold and Kemp, 2005; EHNIS, 2007). Although often viewed as trivial, atopic disease is one of the major causes of hospitalization in children. Cost-identification analyses estimate the costs of AD from $364 million to $3.8 billion and of AR of $5.3 billion US Dollars per year (Mancini et al., 2008; Carr et al., 2008). These data emphasize the need to explore the pathophysiology of atopy and further, to identify factors triggering the onset and exacerbation of the disease. In the last decade it has become clear that immunoregulatory abnormalities, i.e., IgE hypersecretion and eosinophilia-associated inflammation underlie both AD and AA pathogenesis. Although a growing number of studies confirm the role of immunological dysfunctions in atopic disease (Akdis, 2008; Sicherer and Leung, 2008), they cannot explain the rapid increase in the prevalence of allergic conditions over the past two decades. This recent 'epidemic' increase of atopy must be caused by other, environmental influences that promote allergic sensitization and subsequent immunopathology. Following this line of reasoning, stress has been discussed to be one important triggering factor of atopic disease. A growing number of studies indicate that critical life events such as divorce or death of a family member as well as increased everyday life stress may trigger the onset and/or exacerbation of AD and AA (Wright, 2005; Buske-Kirschbaum, 2007). The mechanisms by which stress may affect atopy, however, are still unclear.

In a series of studies our group described impaired reactivity of the hypothalamus–pituitary–adrenal (HPA) axis in response to

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stress in atopic patients (Buske-Kirschbaum et al., 2002a, 2003, 2007). It is well accepted that an appropriate responsiveness of the HPA axis and a subsequent release of glucocorticoids (GC) may be essential to control immune functioning and to prevent an overshooting of the immune response (Elenkov and Chrousos, 2002). Following this hypothesis we assumed that in atopic patients the failure to mount a sufficient cortisol response, especially under stressful conditions when the immune system is activated, might trigger allergic inflammation and thus, exacerbation of the disease. In fact, we could show that increased IgE levels and eosinophil numbers are consequences of stress in atopic, but not in non-atopic subjects (Buske-Kirschbaum et al., 2002b).

The present study was designed to further specify the role of HPA axis dysfunction to stress in atopy. In the past it has been emphasized that inflammatory processes may lead to activation of the HPA axis by the release of pro-inflammatory cytokines with a subsequent downregulation of the system under chronic conditions (Chesnokova and Melmed, 2002). Following this line of reasoning it may be speculated that hyporesponsiveness of the HPA axis as found in AD and AA patients may reflect a consequence of the chronic (allergic) inflammatory process. In the present study we thus tested whether impaired HPA axis responsiveness is linked to an ongoing allergic inflammatory process, or alternatively, whether it reflects a general feature of atopic disposition independent of the acuity or severity of the disease.

Seasonal allergic rhinitis (SAR) is an atopic condition characterized by sneezing, pruritus, rhinorrhea and congestion triggered by environmental allergens such as pollen, animal dander or mold (Salib et al., 2003). The pathophysiology of SAR is very similar to AD or AA in that allergen-induced mast cell degranulation and the release of pro-inflammatory mediators, i.e., histamine, proteases or leukotrienes, result in early phase symptoms such as sneezing and pruritus. Th_2-derived cytokines such as IL-4, IL-5, IL-9 and IL-13 lead to increased recruitment and activation of eosinophils, basophils, and mononuclear cells and stimulate these cells to infiltrate the nasal mucosa. The influx of inflammatory cells and their continued release of additional pro-inflammatory mediators initiate and sustain allergic inflammation giving rise to the classical more persistent symptoms of SAR such mucus hypersecretion, tissue edema and damage (Gelfand, 2004; Borish, 2003). However, SAR clearly differs from AA and AD in that SAR is a seasonal, intermittent atopic disease with clear-cut onsets and offsets of allergic symptoms triggered by mostly well-defined exoallergens. Thus, studying HPA axis responsiveness in SAR patients while the disease is active (pollen period), and while the disease is dormant (pollen-free period) is a good model to clarify how acute allergic inflammation impact on HPA axis responsiveness.

2. Methods

2.1. Subjects

Caucasian subjects ($n = 20$; mean age: 26.4 ± 1.0 yrs.) suffering from SAR were recruited with the understanding that the effect of stress on allergic parameters in SAR should be studied. Since it has been shown that the menstrual cycle, the use of contraceptives and smoking are relevant factors influencing HPA axis activity (Kirschbaum et al., 1999; Rohleder and Kirschbaum, 2006), only male, non-smoking SAR patients were recruited. SAR had been diagnosed by an allergologist in all participants and was documented by a so called 'allergy passport'. As indicated in this clinical document, all SAR patients had a history of allergy for more than five years and were positive to seasonal grass and/or birch pollen. SAR patients suffering from AA or AD or from other inflammatory condition were excluded from the study. According to their self-report, none of the SAR subjects had been treated with steroids at least three month before study onset. SAR patients treated with antihistamine were asked to stop medication two weeks before participating in the experiment. Only SAR patients complying abstention from antihistamines were included. Age-matched healthy, non-atopic male subjects ($n = 20$; mean age: 25.6 ± 0.8) participated in the study as a control group. The local ethics committee approved the experimental protocol and written informed consent was obtained from all subjects before participating in the study. All subjects were compensated with €100, for participation.

2.2. Experimental protocol

Subjects were investigated using the 'Trier Social Stress Test' (TSST) as a standardized psychosocial stressor on two different days, once during the pollen season (spring), and then again during a pollen-free season (autumn). A cross-over design was used in order to control for sequence and habituation effects. The SAR group and the control group were randomly divided into two subgroups ($n = 10$ in each group) with one SAR and one control subgroup first being exposed to the TSST during the pollen season (spring) and then the second time during the pollen-free season (autumn), and vice versa.

The cortisol awakening response (CAR) has been reported to reliably reflect the individual's adrenocortical reactivity (Clow et al., 2004; Fries et al., 2009). CAR in SAR and healthy subjects was assessed one day before the experiment during the pollen and pollen-free season after awakening and 10, 20, 30 and 60 min later. Additionally, cortisol levels were measured at 2 p.m. and 8 p.m., respectively.

2.3. The 'Trier Social Stress Test' (TSST)

Experimental sessions were run between 10 a.m. and 11 a.m. After completing a visual analogue scale assessing the severity of ongoing SAR symptoms (VAS-SAR), a catheter (Vasofix, Braun Melsungen, Germany) was inserted into an anticubital vein. Thirty minutes thereafter, all subjects were exposed to the TSST which has been described elsewhere (Kirschbaum et al., 1993). Briefly, the TSST is a standardized laboratory stressor consisting of a free speech (5 min) and mental arithmetics (serial substraction, 5 min) in a role-playing approach in front of an audience. The TSST has repeatedly been shown to stimulate significant activation of the HPA axis and the sympathetic adrenomedullary (SAM) system and is considered to be one of the psychological stress tests leading to the largest cortisol and ACTH changes (Dickerson and Kemeny, 2004). After the TSST the subjects completed a visual analogue scale of how stressful they experienced the stress test (subjective stress experience, SSE). Blood samples were obtained 10 min before the stress test. Additionally, saliva samples were collected 30, 10 and 1 min before and 15, 25, 35 and 45, 55 and 75 min after the TSST using a saliva sampling device (Salivette, Sarstedt, Rommelsdorf, Germany). Saliva samples were stored at −20 °C until analysis.

2.4. Cortisol analysis

Saliva samples were thawed and spun at 17,438*g* for 5 min to obtain samples with low viscosity. Clear saliva (100 µl) was removed for duplicate analysis of cortisol levels using a time resolved fluorescence immunoassay (DELFIA) that has been previously described in detail (Dressendörfer et al., 1990). The lower detection limit of the assay is 0.43 nmol/l with inter and intra-assay coefficients of variance of less than 10% across the expected range of cortisol levels (3–25 nmol/l).

2.5. Leukocyte subsets

Peripheral blood was collected in EDTA tubes 10 min before the stress test on both experimental conditions, i.e., during pollen and no-pollen season. Leukocyte cell counts (lymphocytes, eosinophils, basophils, neutrophils) were determined using a haematology analysator (Technikon H3; Bayer Diagnostics, Germany). The variation coefficients of the cell populations are <14%.

2.6. IgE

A blood sample to assess total IgE levels was obtained 10 min before the TSST on both experimental days (pollen/pollen-free season) and centrifuged at 1000*g* for 15 min. One millilitre of serum was split in aliquots and stored at −20 °C until analyses. Total serum IgE levels were quantified by a commercial enzyme immunoassay (EIA, IBL, Hamburg, Germany) according to the manufacturer's instructions.

2.7. SAR severity (VAS-SAR)

Self-ratings of SAR disease activity were evaluated using a 10-items visual analogue scale. The VAS-SAR is based on the *Allergic Rhinitis Questionnaire* (Bousquet et al., 2008) as well on a questionnaire used by allergologists to recognize and diagnose SAR in clinical practice. SAR patients were asked to rate the severity of the main clinical symptoms of SAR (rhinorrhea, tearing eyes, pruritus, nasal congestion, sneezing, eye lid swelling, increased light sensitivity, burning eyes, fatigue, irritability) from 0 (“not at all”) to 100 (“extremely”). A general disease activity score ($VAS\text{-}SAR_G$) was computed by $(symp_1 + symp_2 + symp_3 + \ldots + symp_{10})/10$.

2.8. Statistical analyses

For the endocrine (cortisol) and immune (IgE, leukocyte subpopulations) parameters with repeated measures ANOVAs were computed on the absolute hormone/immune levels to test for stress-induced changes (time effects), overall differences between SAR and controls (group effect), or different response profiles between the two groups (group × time effects). In case of significant interaction effects, Newman–Keuls post hoc tests were computed. Symptom severity ($VAS\text{-}SAR_G$) and subjective stress experience (SSE) after TSST exposure during pollen and pollen-free seasons were compared by *t*-tests for dependent variables. The area under the curve (AUC) for the cortisol stress response was computed according to the trapezoid formula as described elsewhere (Prüssner et al., 2003). Due to missing data (insufficient saliva or blood volume), analyses of eosinophil numbers and cortisol levels of the CAR were based on a reduced sample size (eosinophil numbers: SAR active: $n = 18$; SAR inactive: $n = 19$; controls active: $n = 17$; controls inactive: $n = 19$; CAR: SAR active: $n = 18$; SAR inactive: $n = 19$; controls active: $n = 16$; controls inactive: $n = 19$).

3. Results

To evaluate the allergic status and severity of the allergic inflammatory process during the two experimental conditions (pollen, no-pollen), total IgE levels, eosinophil number, basophil number and symptom severity were assessed. Analyses of total IgE levels indicated significantly increased IgE levels in SAR patients when compared to the control group (group effect: $F(1, 38) = 4.8$; $p < .05$) with no significant changes of IgE concentrations between pollen and pollen-free seasons (time effect: $p > .05$; see Fig. 1B). Accordingly, eosinophil numbers were significantly elevated in SAR patients when compared to controls (group effect: $F(1, 31) = 12.29$; $p < .01$). Further, eosinophil numbers were significantly increased during the pollen season when compared to the pollen-free season while no difference between the two conditions could be detected in the healthy control group (time effect: $F(1, 31) = 7.7$; $p < 0.01$; time × group effect: $F(1, 31) = 9.8$; $p < 0.01$; see Fig. 1C). Basophil numbers showed a similar pattern with significantly increased basophil counts in SAR subjects during the pollen season when compared to the pollen-free season (time effect: $F(1, 38) = 6.4$; $p < .05$; see Fig. 2D). A significant between-condition effect was also found with respect to SAR symptoms in that SAR subjects described their symptoms as more severe during the pollen than during the pollen-free season ($t = 9.4$, $p < .001$; see Fig. 1A). No between-group and between-conditions effects could be detected with respect to lymphocyte and neutrophil cell counts (all $p > .05$; data not shown).

Analysis of the cortisol data yielded significantly increased cortisol levels in response to the TSST across both groups (time effect: $F(8, 456) = 19.9$; $p < .001$). As depicted in Fig. 2, however, SAR subjects showed significantly attenuated cortisol levels during acute manifestation of the disease (pollen season) when compared to the pollen-free season (condition × time effect: $F(16, 456) = 1.65$; $p < .05$). No significant differences of cortisol stress responses between the two experimental groups were found during the pollen-free season, i.e., during the inactive disease state ($p > .05$). Correlational analyses indicated a significant negative correlation between the cortisol secretion in response to the TSST (area under the curve) and symptom severity ($VAS\text{-}SAR_G$) in SAR patients ($r = -.53$; $p < .05$; see Fig. 3). No differences between the two groups and the two experimental conditions were found in the subjective stress ratings of the TSST (SSE; all $p > .05$; data not shown). Morning cortisol levels significantly increased after awakening in both experimental groups (time effect: $F(4, 200) = 19.34$; $p < .001$) with no significant between-group or between-condition differences (all $p > .05$; see Fig. 4).

4. Discussion

In our previous work we could demonstrate significantly attenuated HPA axis responsiveness to stress in patients with AD and AA when compared to non-atopic controls (Buske-Kirschbaum et al., 2002a, 2003). Regarding the important anti-inflammatory role of a functional HPA axis we hypothesized that the failure to mount a sufficient HPA axis response renders the organism highly susceptible to an exaggerated (allergic) inflammatory response. This idea is in line with animal and human data showing that disruption or attenuation of HPA axis function is linked to an increased risk for chronic inflammatory disease, i.e., autoimmune and allergic disease (Buske-Kirschbaum et al., 2002a,b; Elenkov and Chrousos, 2002; Eskandari and Sternberg, 2002; Heesen et al., 2007). It is, however, important to note that these data are of correlational nature. It is still unclear whether a disturbed HPA axis reflects a predisposition of the individual that may contribute to allergic sensitization and manifestation of allergy, or alternatively, if HPA axis hyporesponsiveness is a consequence of the inflammatory disease itself. The first idea would be supported by our previous work showing that newborn babies with atopic disposition show an altered HPA axis responsiveness, i.e., an increased cortisol stress response to venipuncture stress when compared to newborns without atopic disposition (Buske-Kirschbaum et al., 2004). These data have been replicated in a recent study (Ball, 2006) suggesting an altered HPA axis function in atopic individuals without manifestation of the allergic response. Alternatively, there are a number of animal data supporting the latter hypothesis of an HPA axis modulation by the chronic inflammatory process itself. In these studies activation of the HPA axis by pro-inflammatory cytokines with a

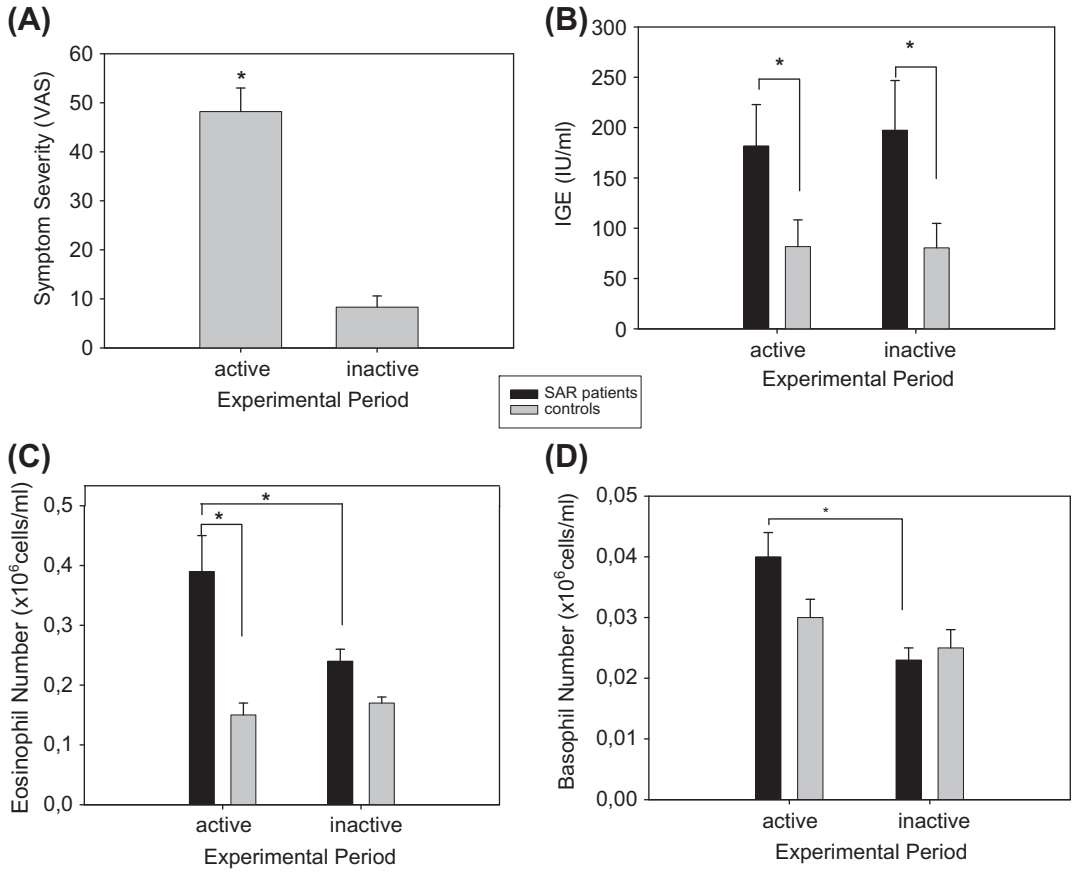

Fig. 1. Symptom severity in SAR patients during the pollen (active) and the pollen-free (inactive) seasons (A). Total IgE levels (B), eosinophil (C) and basophil (D) numbers in SAR and control subjects during the pollen (active) and the pollen-free (inactive) seasons (means ± SEM; *asterisks* indicate significant differences between the two groups).

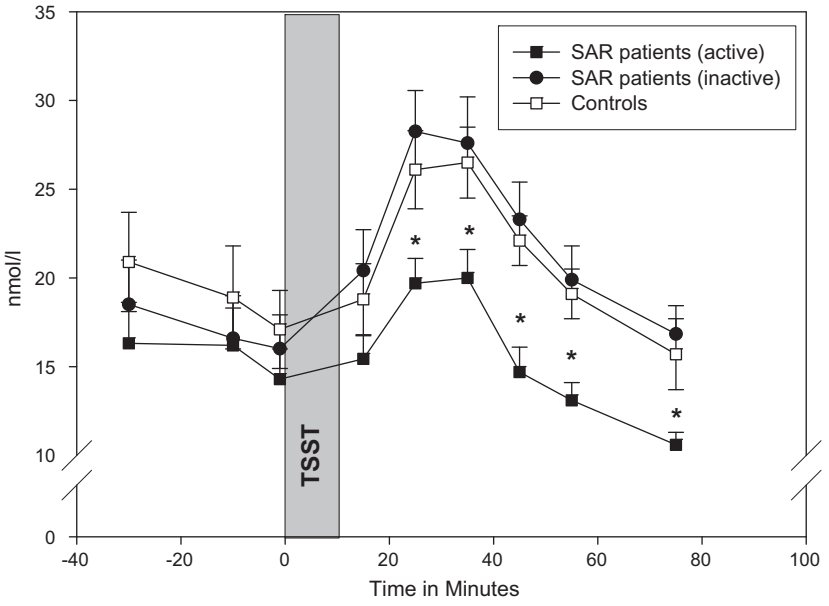

Fig. 2. Cortisol levels in response to the TSST in SAR patients ($n = 20$) and non-atopic controls ($n = 20$) during the pollen and the pollen-free seasons (means ± SEM; *asterisks* indicate significant differences (Newman–Keuls test following ANOVA).

subsequent downregulation of the system over time under chronic inflammatory conditions has been reported (Rivier, 2000; Bornstein and Rutkowski, 2002).

To further clarify the 'chicken-egg problem' of a disturbed HPA axis functioning in atopy, SAR patients were investigated. SAR is an atopic condition characterized by periods of acute allergic inflammation during times of exposure with aeroallergens (pollen season) and periods without disease expression during times without allergen contact (Salib et al., 2003). Because of the straightforward identification of the onset and offset of the inflam-

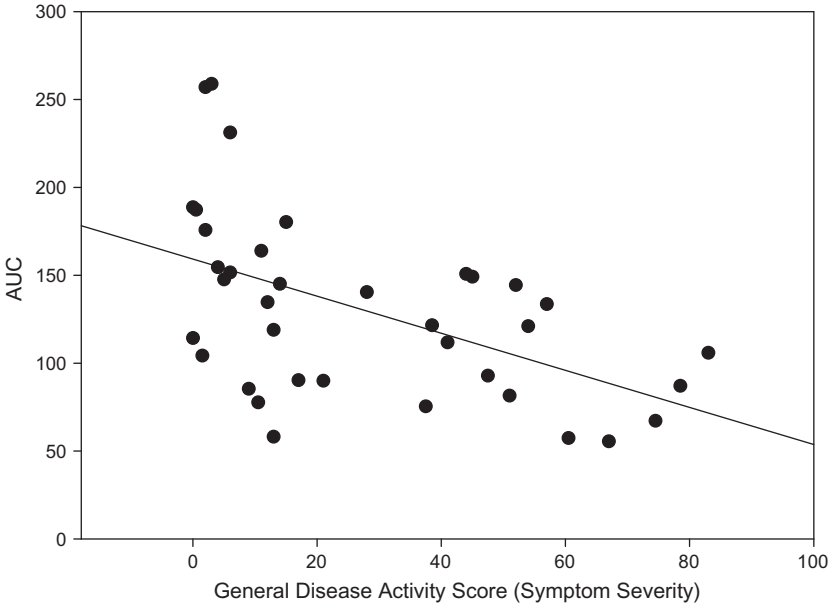

Fig. 3. Scatterplot of cortisol secretion in response to the TSST (AUC) and symptom severity (VAS-SAR$_G$) in SAR patients ($n = 20$).

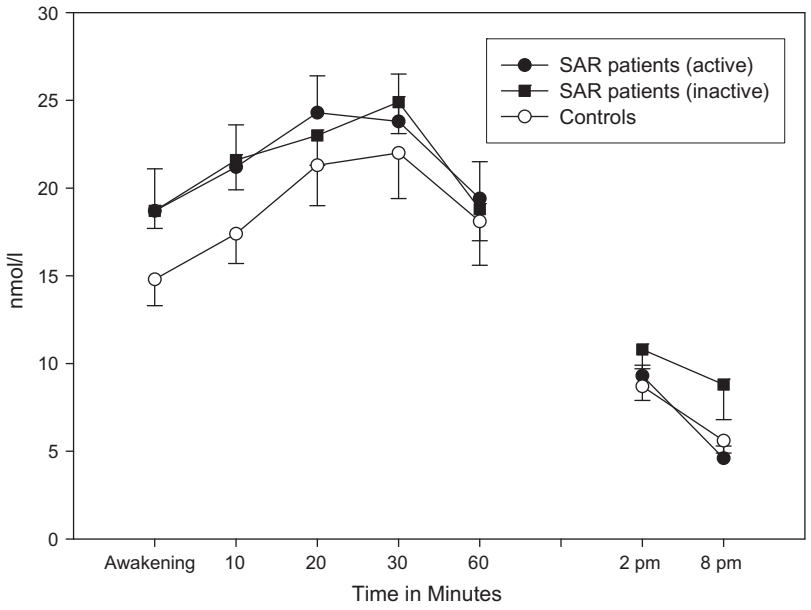

Fig. 4. Cortisol levels after awakening and 10, 20, 30, 60 min as well as at 2 p.m. and 8 p.m. in SAR patients and healthy controls during the pollen and the pollen-free seasons.

matory response in association to well-defined allergens, SAR may be an ideal model to study the impact of the allergic inflammatory status on the HPA axis.

In the present study significantly decreased cortisol responses to stress during the pollen season were observed in SAR patients. HPA axis responsiveness in SAR subjects was not different from non-atopic controls during periods without allergen exposure. These data suggest that hyporesponsiveness of the HPA axis is linked to the *acute* allergic inflammatory state rather than to the atopic disposition. This suggestion is supported by the immunological data reflecting an acute inflammatory process in our SAR subjects during the period of pollination. Thus, a significant increase of basophil and eosinophil counts were found during the pollen season when compared to the pollen-free period. There is general agreement that basophils and eosinophils are key markers of the allergic inflammatory process (Borish, 2003; Gelfand, 2004). Mobilization of eosinophils and basophils into the circulation, and subsequent accumulation into the inflammatory sites initiate the late phase response of the inflammatory reaction and is a diagnostic feature of SAR (Borish, 2003). The influx of eosinophils into the nasal mucosa correlates with the onset and progression of SAR symptomatology (Juliusson et al., 1992). Basophils are an important source of histamine secretion during the late phase reactivating many of the pro-inflammatory reactions of the early response and thus, perpetuating allergic inflammation (Naclerio et al., 1994; Rosenwasser, 2007). Additionally, SAR subjects showed significantly elevated IgE levels in both experimental conditions, i.e., during the pollen season and the pollen-free period. Increased IgE levels have been described as a useful marker of allergy and have often been used as a laboratory marker for the allergic path-

ogenesis of upper respiratory symptoms although not elevated in all patients with manifestation of SAR (Juliusson et al., 1992; Borish, 2003). The close link between HPA axis responsiveness and the acute activity of the inflammatory allergic response is further reinforced by the observation that in our SAR patients the severity of SAR symptoms during the pollen season and the cortisol stress response are significantly correlated.

To our knowledge this is the first study showing that in patients suffering from inflammatory disease, HPA axis dysfunction is exclusively found during the acute inflammatory state while in the same subjects, no altered HPA axis responsiveness is evident during the non-inflammatory state. The underlying mechanisms of reduced HPA axis function during active allergic inflammation and accordingly, the regeneration of HPA axis function during asymptomatic periods when the inflammation has subsided, are unclear. As described earlier, animal studies show activation of the HPA axis by pro-inflammatory cytokines with subsequent downregulation of the system under chronic inflammatory conditions (Chesnokova and Melmed, 2002). Comparable data have been reported in humans. Clinical studies using cytokines such as IL-1, TNF-α, IFN-γ or IFN-β as therapeutic strategies in cancer or multiple sclerosis (MS) patients could demonstrate that increased levels of cytokines lead to activation of the HPA axis with the development of tolerance of the system when they are administered over a long period (Nolten et al., 1993; Goebel et al., 2005). Thus, it may be hypothesized that in our SAR subjects allergic inflammation and concomitantly, the release of pro-inflammatory cytokines during pollination may decrease HPA axis responsiveness by analogous mechanisms. However, it should be kept in mind that during immunotherapy in cancer or MS patients, cytokines are given in pharmacological, rather than in physiological doses which may have different effects on HPA axis reactivity. Furthermore, in SAR patients a predominantly TH2-mediated immune response with a secretion of anti-inflammatory cytokines such as IL-4, IL-5 or IL-10 has been reported. While there is a growing body of literature showing CNS effects of pro-inflammatory cytokines, the impact of these anti-inflammatory cytokines on HPA axis function, is little studied. IL-10 has been found to act on pituitary cells to induce CRH and ACTH production and further, induces CRH release in the hypothalamic median eminence (Stefano et al., 1998; Hughes et al., 1994). Further, IL-10 affects sleep behaviour regulating sleep pattern such as nonrapid eye movement (REM) sleep (Opp et al., 1995; Smith et al., 1999). These data suggest that anti-inflammatory cytokines such as IL-10 may be a relevant endogenous regulator of HPA axis function. Future research is however needed to further study potential CNS effects of the 'classical' anti-inflammatory cytokines such as IL-4 and IL-5. Finally, in these studies cytokine treatment has been applied for long periods such as several months or a year. In our SAR subjects, allergen exposure inducing cytokine release was limited to 8–10 weeks. On the other hand, little is known about the temporal kinetics of cytokine-induced HPA axis disturbances. Impairment of HPA axis reactivity may even be possible after a short period of exacerbated cytokine release especially in a 'sensitized' individual. For instance, Kalogeromitros and his group (Kalogeromitros et al., 2007) reported activation of the HPA axis as indicated by increased cortisol levels in SAR patients 40 min after nasal provocation with *Parietaria* pollen. In SAR patients the phenomenon of 'priming' has been reported whereby over the pollen season progressively lower allergen concentrations are required to trigger the allergic response. Priming in SAR subjects has been explained by increased numbers of IgE receptors on mast cells as well as enhancement of signal transduction (Pipkorn et al., 1988; Wang and Clement, 2000). It may be tempting to speculate that in parallel to the immunological priming, reduced cytokine concentrations may be required over the course of an allergy season to alter (neuro) endocrine function in these patients.

Additional support for a close inflammatory-brain-interaction involving structures of the HPA axis comes from clinical observations. Besides the 'classic' allergic symptoms, SAR patients complain about symptoms such as lethargy, fatigue, malaise, sleep disturbances, anxiety and neurocognitive deficits (Blaiss, 2008; Borres, 2009). For example, Hartgerink-Lutgens et al. (2009) reported reduced cognitive performance in SAR sufferers after nasal provocation with allergen solution suggesting that even a short, experimentally induced allergic reaction alters cognitive functioning. Despite the mechanism by which SAR may contribute to these mental and behavioural problems are still obscure, it has been proposed that pro-inflammatory cytokines mainly released from activated T-cells and mast cells may directly pass the blood brain barrier, or indirectly, affect CNS structures by activation of vagal afferent nerves (Yarlagadda et al., 2009). Once the cytokine signal reaches the brain it has potent effects, for example, on hypothalamic cells resulting in symptoms such as malaise or fatigue (Dantzer and Kelley, 2007; Yarlagadda et al., 2009). In view of these findings it appears not too speculative to assume that an allergic inflammatory process with concomitantly increased levels of pro-inflammatory cytokines over several weeks may impact neuroendocrine functioning, i.e., HPA axis response.

In sum, the present study suggests that disturbance of HPA axis function in atopic patients is linked to the acute inflammatory process rather than to the atopic disposition. Further studies are warranted to further clarify the pathological significance of HPA axis suppression during acute inflammation. Overall, it seems clear that HPA axis activation during inflammation is an important defence mechanism limiting the immune-mediated inflammatory damage. In this way, even if HPA axis disturbance may be a side effect of an inflammatory scenario, HPA axis aberration may become of pathological relevance during the course of the disease. This may lead to a *circulus vitiosus* with HPA axis impairment initially being a symptom of the inflammatory process but when sustained for a critical period of time, it may prevent remission or even trigger exacerbation of the inflammatory response. Finally, in light of data indicating that allergic reactions impact on relevant mental and behavioural functions future studies are needed to better define the role of inflammation-related disruption of the HPA axis in these immune-neural-interactions. Besides its heuristic value, such knowledge will help to delineate new approaches for treating the allergic patient instead of treating the allergic symptom.

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