0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(9):4245–4251
Copyright © 2002 by The Endocrine Society
doi: 10.1210/jc.2001-010872

Altered Responsiveness of the Hypothalamus-Pituitary-Adrenal Axis and the Sympathetic Adrenomedullary System to Stress in Patients with Atopic Dermatitis

ANGELIKA BUSKE-KIRSCHBAUM, ANDREA GEIBEN, HEIKE HÖLLIG, ELLEN MORSCHHÄUSER, AND DIRK HELLHAMMER

Center for Psychobiological and Psychosomatic Research, University of Trier, 54286 Trier, Germany

A growing number of animal data strongly suggest that a hyporeactive hypothalamus-pituitary adrenal (HPA) axis may be pathologically significant by increasing the susceptibility to chronic inflammation. Following this line of evidence, the specific goal of the present study was to investigate the HPA axis in patients with atopic dermatitis (AD), a chronic allergic inflammatory disease. In addition, the sympathetic adrenomedullary (SAM) system as a second potent immunoregulatory and anti-inflammatory stress-response system has been examined.

AD patients (n = 36) and nonatopic control subjects (n = 37) were exposed to a standardized laboratory stressor consisting of a free speech and mental arithmetic task in front of an audience. Cortisol, ACTH, and catecholamine concentrations were assessed before and after the stressor. To investigate feedback sensitivity of the HPA axis, a low dose (0.5 mg) dexamethasone suppression test was also performed. AD patients showed significantly attenuated cortisol and ACTH responses to the stressor, whereas catecholamine levels were significantly elevated in atopic patients. No difference between the experimental groups was found in basal cortisol and ACTH concentrations, whereas basal catecholamine levels were significantly elevated. Analysis of cortisol levels after dexamethasone treatment suggested an intact feedback sensitivity in AD sufferers at the pituitary level. The present findings suggest that patients with AD demonstrate a blunted HPA axis responsiveness with a concurrent overreactivity of the SAM system to psychosocial stress. Considering the important immunoregulatory role of the HPA axis and the SAM system, especially under stressful conditions, an aberrant responsiveness of these neuroendocrine systems may increase the susceptibility to (allergic) inflammation and may be one psychobiological mechanism of stress-related aggravation of the disease. (*J Clin Endocrinol Metab* 87: 4245–4251, 2002)

ATOPIC DERMATITIS (AD) is a chronically relapsing inflammatory skin disease with main symptoms such as dry and eczematous skin, erythematous papules, and severe pruritus (1, 2). In the last 30 yr, the frequency of AD has significantly increased, with a current estimated prevalence of 12%. AD symptomatology often results in significant morbidity associated with frequent hospitalization, school absenteeism, and missed work days (3). The unpredictability of the disease, the torturing pruritus, and the feeling to be disfigured further impose an immense psychological burden on AD sufferers and their families.

Numerous factors such as genetic disposition, climate, allergens, or microbial organisms are considered to play a role in AD (4). However, research of the last decade strongly suggests the importance of a complex dysregulation of the immune system in the pathogenesis of the disease. An imbalance of T-helper-1 (TH_1)-like and T-helper-2 (TH_2)-like T cell subsets with a predominant secretion of TH_2-derived cytokines, hypersecretion of IgE, and eosinophilia were found to be the central abnormalities in AD patients (5, 6).

Clinical observations and experimental findings have further emphasized the role of stress as a relevant triggering factor of AD symptomatology (7, 8). For example, using a diary technique, King and Wilson (9) could demonstrate a significant positive relationship between elevated levels of interpersonal stress and exacerbation of AD symptoms 24 h later. The relevance of stress in the maintenance and exacerbation of AD is further emphasized by the effectiveness of psychotherapeutic interventions, including stress management or relaxation trainings that have been demonstrated to successfully reduce itching and scratching leading to a significant improvement of AD symptomatology (10, 11).

Although there is general agreement on the existence of stress influences on AD, the underlying mechanisms of how stress may affect AD pathology remain to be defined. Accumulating findings of psychoneuroimmunological research suggest an intimate communication network between the central nervous system, the endocrine system, and the immune system facilitating the understanding of how psychological processes such as stress may influence the immunopathogenesis of AD (12). In this line of research, the hypothalamus-pituitary-adrenal (HPA) axis has been most frequently discussed as one of the major pathways through which the central nervous system exerts control over the immune system under stressful conditions. Data strongly suggest that an appropriate reactivity of the HPA axis to stressful stimuli may be necessary to control immunological processes and to prevent an immune response, for example an inflammatory response, from reaching a level that may be damaging for the host (13, 14). More recent animal data further suggest that the HPA axis may also play a protective role in chronic allergic inflammation (15–17).

These data lend support to the idea that a reduced HPA

Abbreviations: AD, Atopic dermatitis; DEX, dexamethasone; HPA, hypothalamus-pituitary adrenal; SAM, sympathetic adrenomedullary; TH_1, T-helper-1; TH_2, T-helper-2; TSST, Trier Social Stress Test.

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

axis (re)activity may be involved in the maintenance and exacerbation of atopy. This assumption is supported by the observation in AD patients that diurnal plasma cortisol variations are closely associated with the diurnal variation of atopy-relevant inflammatory parameters such as basophils or eosinophils as well as severity of allergic symptomatology (18, 19). The pathogenic significance of a dysfunctional HPA axis in skin atopy is further underlined by an incidental observation by Laue *et al*. (20). They reported that after treatment with the glucocorticoid receptor antagonist RU 486, healthy volunteers showed AD-like symptoms such as erythema and eczematous skin. None of the subjects had a prior history of atopy.

The specific goal of the present study was to investigate whether in AD patients suffering from chronic allergic inflammation of the skin, attenuated HPA axis (re)activity as indicated by reduced cortisol levels in response to stress can be demonstrated. Furthermore, it should be examined whether a potentially reduced cortisol response in this patient group can at least partly be explained by an aberrant reactivity of the HPA axis at the pituitary or suprapituitary level. Finally, the (re)activity of the sympathetic adrenomedullary (SAM) system in AD sufferers should be examined. Accumulating evidence suggests that various aspects of the inflammatory process such as leukocyte trafficking or secretion of proinflammatory cytokines are under the inhibitory control of the sympathetic nervous system which underlines the potential relevance of the sympathetic nervous system in the immunopathogenesis of AD (21).

Subjects and Methods

Subjects

Thirty-six patients (18 men and 18 women; age range, 20–33 yr; mean age, 25.0 ± 3.8 yr) with AD were recruited through advertisements in a local newspaper and by local dermatologists. All patients were clinically diagnosed with AD and fulfilled the diagnostic criteria established by Hanifin and Rajka (22). Only patients with a minimum history of AD for 5 yr were included. All patients were using topical emollients but no corticosteroids. None of the patients had been treated with steroids or antihistamines for at least 3 months before study onset. According to self-report, none of the patients had received treatment with high-potency inhalant or oral steroids in the past. If they had been treated with steroids, only topical application of steroids with low to moderate potency had been used. AD patients suffering from other chronic diseases than AD were excluded from the study. Severity of AD symptoms was determined by using the Costa score (23). Patients' mean score was 28.9 ± 16.5, indicating a moderate clinical activity of skin lesions in our AD subjects. For a control group, age- and sex-matched nonatopic subjects (n = 37; 19 men and 18 women; age range, 20–33 yr; mean age, 24.5 ± 3.4 yr) participated in the study. None of the control subjects had ever suffered from atopy or had a family history of atopy. By definition, the Costa score for the control subjects was zero. All control subjects were medication free and did not suffer from an acute or chronic illness. To control for a potential effect of sex hormones on endocrine measures, female AD patients and female control subjects were matched for menstrual cycle phase.

Upon recruitment of the participants, the subjects were told that the study was designed to investigate the effect of acute stress on disease-relevant endocrine parameters. They were further informed about the treatment of each experimental day (*i.e*. stressful stimulation on d 1 and resting conditon on d 2, number of blood samples, *etc*.). Participants received a compensation of 200 deutschmarks upon completion of the experiment.

Procedure

All subjects were studied on 2 consecutive days; experimental sessions were run between 1000 and 1200 h. On experimental d 1, a catheter (Vasofix, Braun-Melsungen, Melsungen, Germany) was inserted in an anticubital vein 40 min before the experimental treatment. To determine heart rates, a wireless signal transmission device (Polar Instruments, Grob-Gerau, Germany) was fitted to the subject's chest. After a 30-min rest period, a first blood sample was obtained at −10 min. Ten minutes thereafter, all subjects were exposed to the Trier Social Stress Test (TSST), which has been described and evaluated elsewhere (24). Briefly, the TSST is a standardized laboratory stressor that mainly consists of a free speech (job interview) and mental arithmetic tasks (serial subtraction) in a role-playing approach in front of an audience. Before the stress test, the subjects received a short introduction to the forthcoming tasks, followed by a rest period (2 min) to prepare for their speech. Subjects were then exposed 4 min to the public speaking task and 4 min to the mental arithmetic tasks, respectively. The subjects were told that the session would be video- and audiotaped for later analysis of paraverbal and nonverbal signs of stress. In the past, the TSST has been repeatedly shown to induce significant activation of the HPA axis, with 2- to 3-fold increases of free cortisol levels (25). Additional blood samples were drawn 1, 10, 20, 30, and 60 min after the stress test. Using the Salivette (Sarstedt, Rommelsdorf, Germany) device, subjects collected saliva samples 30, 20, 10, and 1 min before and 10, 20, 30, 40, 50, and 70 min after the TSST. After collection, samples were stored at −20 C before analysis. Finally, all subjects completed a 10-item 5-point visual analog scale of how stressful they experienced the free speech and the mental arithmetic tasks in front of the audience.

Experimental d 2 served as a control day. All subjects were treated as described for d 1, except that the subjects were not exposed to the TSST on this day.

To assess feedback sensitivity of the HPA axis at the pituitary level, a dexamethasone (DEX) suppression test was performed at 2300 h on d 2. In previous studies, it has been argued that the discriminative test power of the DEX suppression test can be enhanced by reducing the dose of DEX (26, 27). Following these suggestions, a reduced dose of 0.5 mg DEX (Jena-Pharm, Jena, Germany) was used. To determine suppression of cortisol concentration after DEX treatment, saliva samples were collected the next morning (d 3) after awakening and 10, 20, and 30 min later. Assessment of morning cortisol 1 d before the experiment (d 0) at identical time points (after awakening, +10, +20, and +30 min) served as a control for DEX-induced cortisol suppression. At d 0, additional saliva samples were obtained at 0800, 1400, and 2000 h to determine a short diurnal profile of the subjects. The experimental protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects before participating in the experiment.

Biochemical analyses

Cortisol. To determine free cortisol concentrations, saliva samples were collected 30, 20, 10, and 1 min before, and 10, 20, 30, 40, 50, and 70 min after the TSST and stored at −20 C. For analysis, the samples were thawed and spun at 3000 rpm 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 (28). The lower detection limit of this assay is 0.43 nmol/liter with inter- and intra-assay coefficients of variance of less than 10% across the expected range of cortisol levels (3–25 nmol/liter).

ACTH. Blood samples were obtained 10 min before and 1, 10, 20, and 60 min after stress exposure. ACTH was measured in duplicates by a two-side luminescence immunoassay according to the manufacturer's instructions (Nichols Institute, Bad Nauheim, Germany). The lower detection limit of the assay is 6 pg/ml with an intra- and interassay variation coefficient of less than 7%, respectively.

Catecholamines. Plasma was collected 10 min before and 1, 10, and 60 min after the TSST. Plasma concentrations of epinephrine and norepinephrine were determined after alumina extraction and subsequent reverse-phase HPLC with electrochemical detection. Separation was achieved by a nucleosil C_{18}-column followed by postcolumn derivatization, which is described elsewhere (29).

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

Heart rates. Heart rates were monitored continuously at 1-min intervals with electrocardiogram precision using a wireless signal transmission device (Sport Profi, Polar Instruments).

Statistical analyses

For all endocrine parameters with repeated measures (cortisol, ACTH), ANOVAs were computed on the absolute hormone levels to test for stress-induced changes (time-effect), overall differences between AD patients and controls (group-effect), or different response profiles between the two groups (group by time-effects). Where significant differences between the two groups were observed (norepinephrine, epinephrine) in prestress samples, the baseline levels served as covariates in the ANOVAs. In case of significant interaction effects, Newman-Keuls *post hoc* tests were computed. For norepinephrine and epinephrine responses, the net increases (sample 2 minus sample 1) were computed and compared between AD patients and controls by *t* tests for independent samples.

Results

One specific goal of the study was to evaluate a potentially aberrant responsiveness of the HPA axis and the SAM system to psychosocial stress in AD patients. ANOVA of the cortisol data on the experimental d 1 yielded significant group, time, and group × time effects (group, $F_{(1, 70)} = 4.70$; $P < 0.05$; time, $F_{(9, 630)} = 11.88$; $P < 0.001$; group × time, $F_{(9, 630)} = 5.44$; $P < 0.001$). As illustrated in Fig. 1A, confrontation with the TSST resulted in significantly increased cortisol concentrations 20 and 30 min after stress exposure (Newman Keuls test; $P < 0.01$). However, although AD sufferers and controls did not differ in basal cortisol levels (Newman Keuls test, $P > 0.05$), a significantly blunted cortisol response to the psychosocial stressor was found in the patient group. Comparable data were found with respect to ACTH levels. After being exposed to the TSST, significant elevation of ACTH levels was found in both groups (time, $F_{(4, 268)} = 45.97$; $P < 0.01$) whereas again, AD sufferers showed significantly diminished ACTH responses to the TSST (group × time, $F_{(4, 268)} = 5.15$; $P < 0.001$; group, $F_{(1, 67)} = 4.04$; $P < 0.05$); see Fig. 1B). Analogous to the cortisol data, no difference between the groups was observed in basal ACTH levels. On the resting d 2, no differences in cortisol or ACTH levels between AD patients and controls could be determined (all $P > 0.05$; data not shown).

In contrast to the altered reactivity of the HPA axis in AD patients, no difference between the groups was found in a short circadian profile of salivary cortisol levels (0800, 1400, and 2000 h) as indicated by a nonsignificant group and a nonsignificant group × time effect (all $P > 0.5$; data not shown). Furthermore, there was no difference in morning cortisol concentrations. Awakening was followed by a significant increase of morning cortisol levels in AD sufferers as well as in control subjects (time, $F_{(3, 210)} = 45.93$; $P < 0.001$); however, no differences between the groups could be observed (group × time, $F_{(3, 210)} = 1.32$; $P > 0.05$; Fig. 2A). After treatment with DEX, a pronounced suppression of morning cortisol levels was observed in the morning of d 3 with no statistically significant difference between the AD and the nonatopic control group ($F_{(1, 67)} = 1.37$; $P > 0.05$; Fig. 2B).

Analysis of norepinephrine concentrations on d 1 yielded a significant group ($F_{(1, 71)} = 12.5$; $P < 0.001$), time ($F_{(3, 213)} = 235.7$; $P < 0.001$), and group × time effect ($F_{(2, 142)} = 6.32$; $P = 0.0023$; baseline introduced as covariate). Comparable data were found with respect to epinephrine concentrations as indicated by a signficant group ($F_{(1, 71)} = 12.13$; $P < 0.001$), time ($F_{(3, 213)} = 56.62$; $P < 0.001$), and group × time ($F_{(2, 142)} = 4.97$; $P = 0.0082$) effect. As illustrated in Fig. 3A, AD patients showed significantly elevated norepinephrine and epinephrine concentrations in response to the stressor.

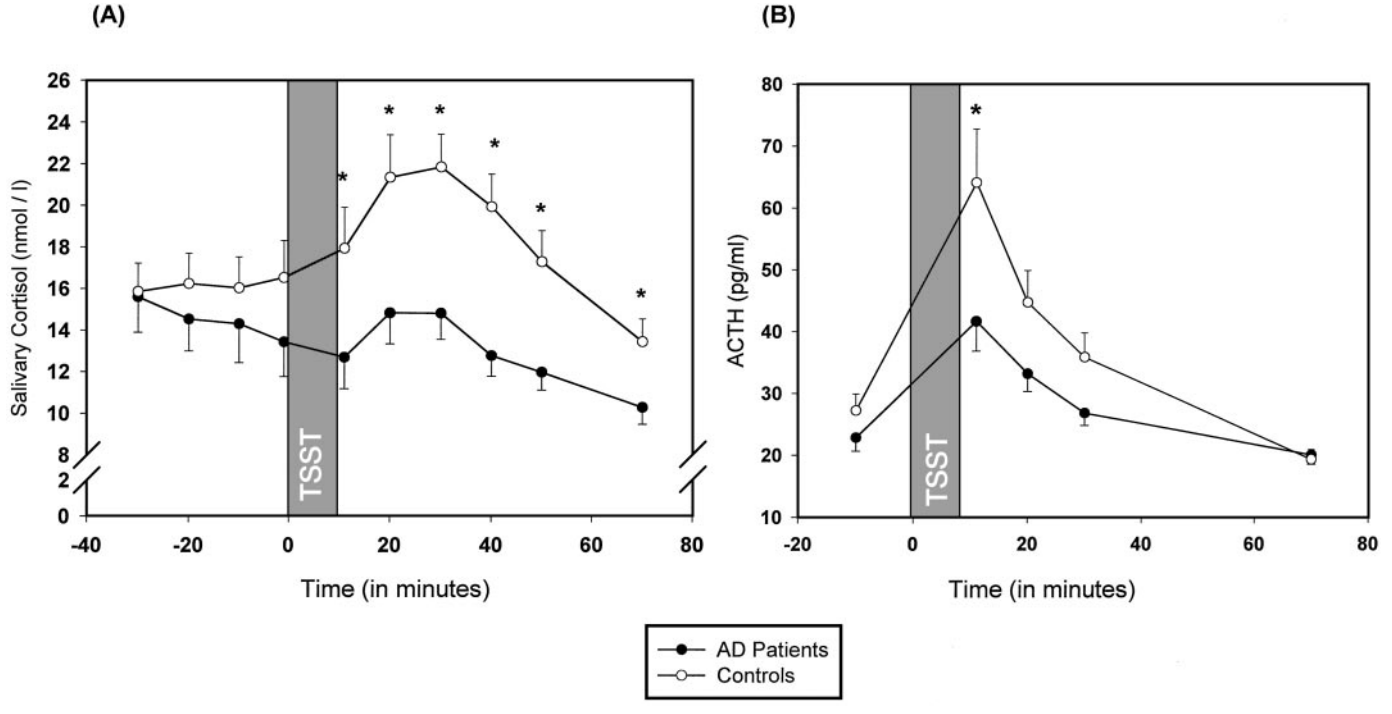

FIG. 1. Salivary cortisol (A) and ACTH (B) levels in response to psychosocial stress (TSST) in AD patients and nonatopic controls (means ± SEM). *Asterisks* indicate significant differences in cortisol levels between the two groups (Newman-Keuls tests following ANOVA).

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

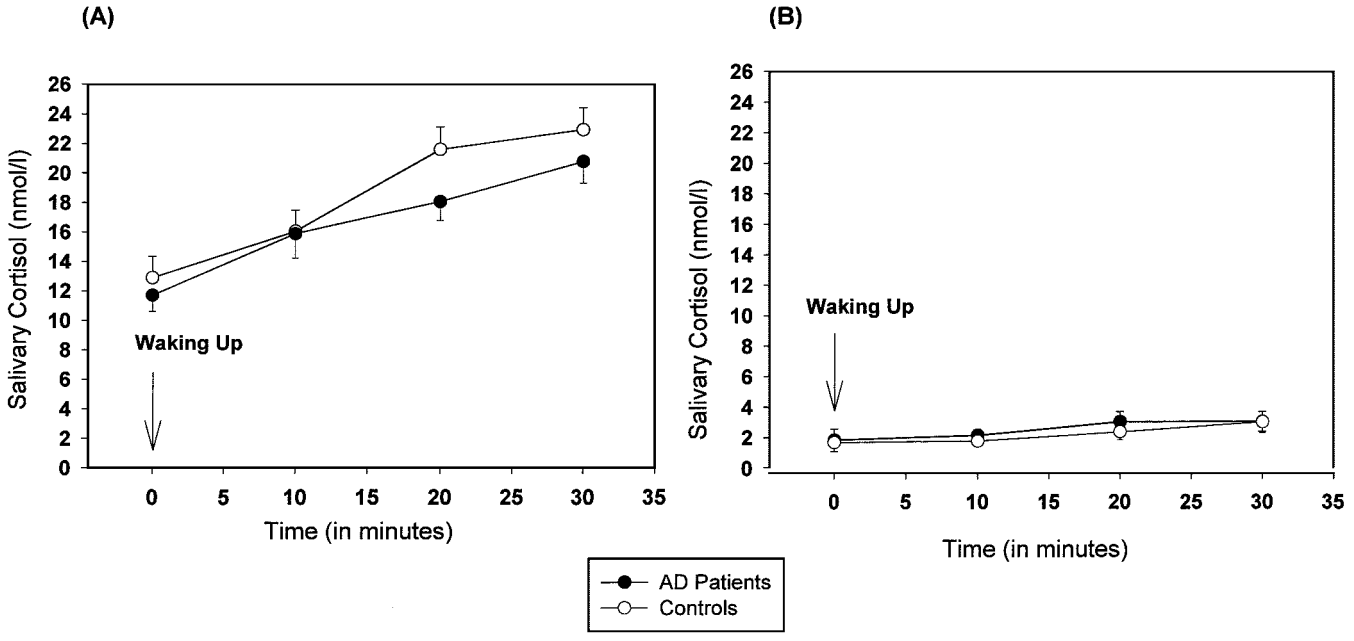

FIG. 2. Salivary cortisol in the morning (A) and after treatment with 0.5 mg DEX (B) in AD patients and nonatopic controls (means ± SEM).

Interestingly, elevated norepinephrine and epinephrine levels were also found under resting conditions in AD subjects (group effects: norepinephrine, $F_{(1, 71)} = 10.41$; $P = 0.018$; epinephrine, $F_{(1, 71)} = 6.43$; $P = 0.013$; see Fig. 3B).

Heart rates in response to the TSST are summarized in Fig. 4. As expected, heart rates peaked during the TSST (time effect, $F_{(40, 2720)} = 177.53$; $P < 0.001$). Although there was a trend toward elevated heart rate stress responses in AD patients, the difference between the groups did not reach statistical significance (group × time, $F_{(40, 2720)} = 1.31$; $P = 0.08$). It is important to note that heart rate responses were not found to be elevated under resting conditions on d 2 (data not shown).

It is important to note that the altered endocrine responses to the stressor in AD patients were not related to the subjective stress rating ($P > 0.05$). The two groups did not differ with respect to how stressful they experienced the TSST ($t = 0.75$; $P = 0.68$).

Discussion

An expanding number of findings suggest that increased levels of daily stress or exposure to acute stressors can be associated with exacerbation of AD (7). Although these findings underline the significance of stress as a potential triggering factor in AD, they raise the question of the underlying psychobiological mechanisms.

Animal and human studies strongly suggest an important immunoregulatory role of the HPA axis and the biological significance of its appropriate responsiveness. It has been found that animals that fail to generate a sufficient glucocorticoid response to pharmacological or psychological stimuli are highly vulnerable to inflammatory processes (13, 30). Supporting these observations, we show here that patients suffering from allergic inflammation have significantly attenuated cortisol responses to psychosocial stress, which is in line with previous findings from our laboratory in atopic children (31). Apparently, a dysfunction of the axis at a suprapituitary site is responsible for this response profile because the ACTH response to the TSST was also blunted in the adult AD sufferers studied in the present experiment. Similar endocrine irregularities of the HPA axis have been reported after a CRH challenge test (32). After physical exercise, however, no such response difference between AD patients and controls could be demonstrated (33). This is not surprising because the HPA response to physical stress is not necessarily highly correlated with changes of this axis after psychosocial stress (34), although in some cases a closer association has been reported (35).

Interestingly, although HPA axis responsiveness was found to be significantly reduced in AD subjects, neither basal cortisol levels (*e.g.* diurnal cortisol profiles) nor feedback sensitivity of the HPA axis after treatment with 0.5 mg DEX appear to be altered. These observations are in line with previous findings by Rupprecht *et al.* (36) reporting no differences in mean basal cortisol levels and no altered feedback response of the HPA axis after oral intake of 1 mg DEX in AD sufferers. Accordingly, an HPA axis response dysfunction in AD patients may become apparent only under stimulated conditions.

It may be argued, however, that the lowered HPA responsiveness in AD patients is simply a consequence of current or past steroid treatment. It is well documented that a prolonged inhalative or oral steroid treatment can result in a blunted HPA responsiveness (37). However, none of our patients had been treated with high-potency inhaled or oral steroids in the past. There are some data to suggest that topical steroid treatment also may lead to HPA alterations when administered in high doses in an acute phase of the disease (38, 39). In contrast, the usual treatment of AD with topical steroids with low to moderate potency was reported

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

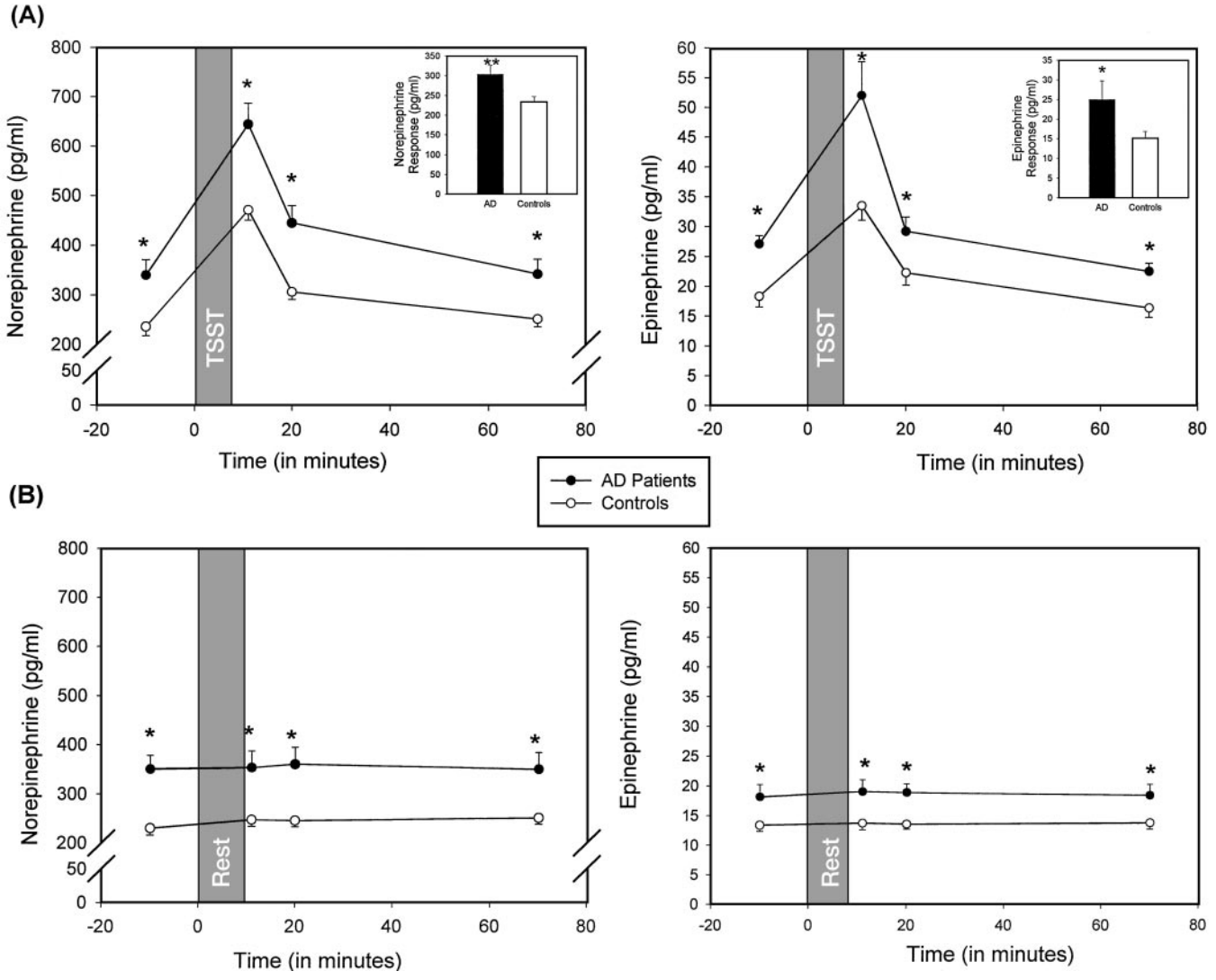

FIG. 3. Norepinephrine and epinephrine levels in response to psychosocial stress (TSST) (A) and under resting conditions (B) in AD patients and in nonatopic controls (means ± SEM). *Asterisks* indicate significant differences in catecholamine levels between the two groups (Newman-Keuls tests following ANCOVA). The *insets* show the mean net increases over baselines in both groups.

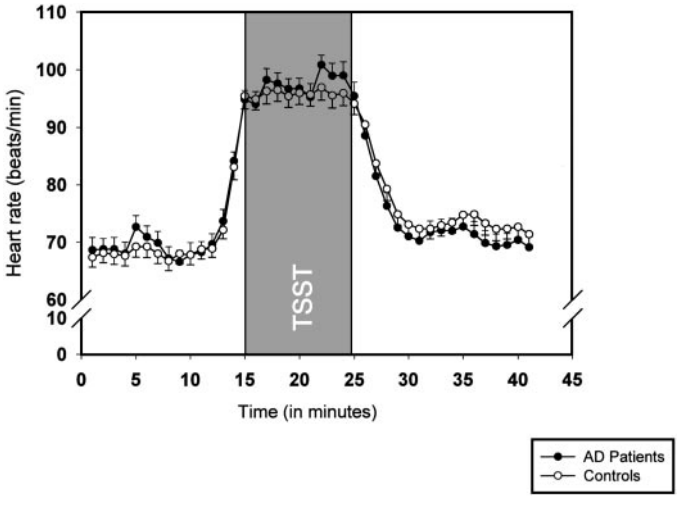

FIG. 4. Heart rates in response to psychosocial stress (TSST) in AD patients and in nonatopic controls (means ± SEM).

to have no detectable effect on HPA functioning (40–44). With these results in mind, patients were included in the present study only if they had been steroid-free for at least 3 months before study onset. Furthermore, none of the participants had received inhaled or oral steroids in the past year. Thus, it is rather unlikely that the observed reduced HPA responsiveness in AD patients was due to previous steroid treatment.

There is general agreement that beside the HPA axis, the SAM system represents another major immunoregulatory system (45). Thus, it may be assumed that an intact adrenergic signaling, especially under stressful conditions when the system is activated, may be important to ensure an appropriate and adaptive immune functioning. In this study, AD patients appear to have an overreactive SAM system to psychosocial stress. Catecholamines under resting conditions in AD subjects were found to be elevated with a concomitantly increased epinephrine and norepinephrine response to psychosocial stress, supporting similar findings of

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

response differences to standing in AD children (46). However, elevated circulating catecholamine levels do not necessarily implicate an increased adrenergic signaling, *i.e.* an overstimulation of the target cell. In a most recent study, a significantly decreased density of β-adrenergic receptors on peripheral mononuclear cells of AD patients was demonstrated (47). Furthermore, there is general agreement that AD patients show a diminished β-adrenergic responsiveness, probably due to a rapid enzymatic breakdown of cAMP by increased cAMP-phosphodiesterase activity (48, 49). This also may result in an impaired adrenergic signaling for the target cell despite a potentially strong stimulus. Thus, a more complex dysfunction of the SAM system on different regulatory levels such as catecholamine secretion pattern, receptor density of intracellular signal transduction, may be relevant in AD patients.

In sum, AD sufferers appear to show reduced responsiveness of the HPA axis and concomitantly, increased reactivity of the SAM system. Regarding the important immunoregulatory role of both systems, it may be assumed that the inability to exert an appropriate HPA axis or SAM system response and thus to generate an adequate regulatory signal for the immunological target cell may increase the risk for aberrant immune functioning, especially under stressful conditions. Of major relevance may be most recent findings specifying the role of the HPA axis and the SAM system, in that activation of both systems appears to promote TH_2 cell function and suppress TH_1 cell activity probably via suppression of IL-12 (50). AD is considered mainly a TH_2-mediated inflammatory disease, and according to these findings, (hyper)secretion of catecholamines under stressful (and basal) conditions may consolidate allergic inflammation or may even yield in exacerbation of symptomatology due to a catecholamine-induced TH_2 shift. However, trying to put our cortisol data into this model, the reader may be puzzled. If cortisol drives a TH_2 shift, attenuated cortisol levels after stress then seem more likely to prevent stress-related exacerbation of inflammation. Recently, it has been reported that AD is characterized by a biphasic response of the TH_1/TH_2 cell subsets. Sequential analyses of skin biopsies obtained from atopy patch-test sites in AD sufferers suggested that initially (acute allergic inflammation), a TH_2 response can be found, followed by a shift toward a TH_1 secretion pattern (chronification) (5, 51). On the basis of these data, reduced cortisol levels and increased catecholamine concentrations after stress in AD subjects may have different pathological significance, depending on the TH_1/TH_2 cell balance concurrently present. It should be noted, however, that in addition to the potential mechanisms described above, alternative pathways such as secretion of neuropeptides from postganglionic sympathetic nerves (*e.g.* CRH, neurotensin, substance P) may represent yet another, more direct mechanism of stress-induced aggravation of allergic inflammation (52).

Finally, it should be kept in mind that an acute stressor was used to investigate HPA axis and SAM system function in AD sufferers. However, stress is not a uniform phenomenon, and different stressors have their own biochemical set-up that might differently affect immunity (53). Investigations including chronic stressors may help to further elucidate the pathological significance of a dysfunctional HPA axis and SAM system responsiveness in the development and aggravation of AD symptomatology. Such studies may provide a better understanding of how psychological processes influence AD and may ultimately help to develop new integrative research strategies leading to a better understanding and treatment of allergic inflammation.

Acknowledgments

Received May 31, 2001. Accepted May 29, 2002.

Address all correspondence and requests for reprints to: A. Buske-Kirschbaum, Ph.D., Center for Psychobiological and Psychsomatic Research, University of Trier, 54286 Trier, Germany. E-mail: buske@uni-trier.de.

This work was supported by the Deutsche Forschungsgemeinschaft (He 1013/13-1).

References

1. **Leung DY** 2000 Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 105:860–876
2. **Boguniewicz M** 1997 Advances in the understanding and treatment of atopic dermatitis. Curr Opin Pediatr 9:577–581
3. **Van Moerbeke D** 1997 European allergy white paper. Allergic diseases as a public health problem in Europe. Brussels: UCB Institute of Allergy
4. **Thestrup-Pedersen K, Ring J** 1998 Atopic dermatitis: summary of the 1st Georg Rajka Symposium 1998 and a literature review. Acta Derm Venereol 79:257–264
5. **Grewe M, Bruijnzeel-Koomen CAFM, Schöpf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, Krutman J** 1998 A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 19:359–361
6. **Leung DY, Soter NA** 2001 Cellular and immunologic mechanisms in atopic dermatitis. J Am Acad Dermatol 44:S1–S12
7. **Buske-Kirschbaum A, Geiben A, Hellhammer D** 2001 Psychobiological aspects of atopic dermatitis. Psychother Psychosom 70:6–16
8. **Brown DG** 1972 Stress as a precipitant factor of eczema. J Psychosom Res 16:321–327
9. **King RM, Wilson GV** 1991 Use of a diary technique to investigate psychosomatic relations in atopic dermatitis. J Psychosom Res 35:697–706
10. **Ehlers A, Stangier U, Gieler U** 1995 Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. J Consult Clin Psychol 63:624–635
11. **Melin L, Frederiksen T, Noren P, Swebilius BG** 1986 Behavioral treatment of scratching in patients with atopic dermatitis. Br J Dermatol 115:467–474
12. **Ader R, Felten DL, Cohen N** 2000 Psychoneuroimmunology. San Diego: Academic Press
13. **Chroussos GP** 1995 The hypothalamus-pituitary-adrenal axis and immune mediated inflammation. N Engl J Med 332:1351–1362
14. **Sternberg EM, Hill JM, Chroussos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL** 1989 Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. Proc Natl Acad Sci USA 86:2374–2378
15. **Goujon E, Parnet P, Laye S, Combe C, Danter R** 1996 Adrenalectomy enhances pro-inflammatory cytokines gene expression in the spleen, pituitary and brain of mice in response to lipopolysaccharide. Brain Res Mol Brain Res 36:53–62
16. **Farsky SP, Saninomiya P, Garcia-Lerne J** 1995 Secreted glucocorticoids regulate leukocyte-endothelial interactions in inflammation: a direct vital microscopic study. J Leukoc Biol 57:379–386
17. **Fornhem C, Peterson CG, Scheynius A, Alving K** 1996 Influence of endogenous cortisol on eosinophil function in sensitisized pigs: direct measurements of eosinophil peroxidase. Clin Exp Allergy 26:469–478
18. **Herrscher RF, Kasper C, Sullivan TJ** 1992 Endogenous cortisol regulates immunoglobulin-E dependent late phase reactions. J Clin Invest 90:596–603
19. **Buhles N, Hölzel C, Spiteller G, Holzmann G, Altmeyer P** 1987 Disorders of steroid metabolism in inflammatory dermatoses. Z Hautk 62:1356–1363
20. **Laue L, Lotze MT, Chrousos GP, Barnes DL, Loriaux DL, Fleisher TA** 1990 Effect of chronic treatment with the glucocorticoid antagonist RU 486 in man. Toxicity, immunological and hormonal aspects. J Clin Endocrinol Metab 71: 1474–1480
21. **Chrousos GP** 2000 Stress, chronic inflammation, and emotional and physical well-being: concurrent effects and chronic sequelae. J Allergy Clin Immunol 106:S275–S291
22. **Hanifin JM, Rajka G** 1980 Diagnostic features of atopic dermatitis. Acta Derm Venereol 92:44–47

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022

23. **Costa C, Rilliet A, Nicolet M, Saurat JH** 1989 Scoring atopic dermatitis: the simpler the better? Acta Derm Venereol 69:41–45
24. **Kirschbaum C, Pirke KM, Hellhammer DH** 1993 The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28:76–81
25. **Kirschbaum C, Hellhammer DH** 1994 Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19:313–333
26. **Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW** 1993 Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 150:83–86
27. **Yehuda R, Boisenau D, Lowy MT, Giller EL** 1995 Dose-response changes in plasma cortisol and glucocorticoid receptors following dexamethsone administration in combat veterans with and without postraumatic stress disorder. Arch Gen Psychiatry 52:583–593
28. **Dressendörfer RA, Kirschbaum C, Rohde W, Stahl F, Strasburger CJ** 1990 Synthesis of a cortisol-biotin conjugate and evaluation as tracer in an immunoassay for salivary cortisol measurement. J Steroid Biochem Mol Biol 43: 683–692
29. **Kringe KP, Neidhard B, Lippmann CM** 1982 Practical aspects of the routine determination by HPLC of free noradrenaline and adrenaline in urine and plasma. In: Mohnar I, ed. Practical aspects of modern HPLC. New York: De Gryter
30. **Sternberg EM** 1995 Neuroendocrine factors in susceptibility to inflammatory disease: focus on the hypothalamic-pituitary-adrenal axis. Horm Res 43: 159–161
31. **Buske-Kirschbaum A, Jobst S, Wustmans A, Kirschbaum C, Rauh W, Hellhammer DH** 1997 Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom Med 59:419–426
32. **Rupprecht M, Hornstein OP, Schluter D, Schafers HJ, Koch HU, Beck G, Rupprecht R** 1995 Cortisol, corticotropin, and β-endorphin responses to corticotropin-releasing hormone in patients with atopic eczema. Psychoneuroendocrinology 20:543–551
33. **Rupprecht M, Salzer B, Raum B, Hornstein OP, Koch HU, Riederer P, Sofic E, Rupprecht R** 1997 Physical stress-induced secretion of adrenal and pituitary hormones in patients with atopic eczema compared with normal controls. Exp Clin Endocrinol Diabetes 105:39–45
34. **Kirschbaum C, Wüst S, Faig HG, Hellhammer DH** 1992 Heritability of cortisol responses to h-CRH, ergometry, and psychological stress in humans. J Clin Endocrinol Metab 75:1526–1530
35. **Singh A, Petrides JS, Gold PW, Chrousos GP, Deuste PA** 1999 Differential hypothalamus-pituitary-adrenal axis reactivity to psychological and physical stress. J Clin Endocrinol Metab 84:1944–1948
36. **Rupprecht M, Rupprecht R, Koch HU, Haack D, Müller OA, Hornstein OP** 1990 Multihormonal response to dexamethasone: a study in atopic dermatitis and normal controls. Acta Derm Venereol 71:214–218
37. **Clark DJ, Lipworth BJ** 1997 Evaluation of corticotropin-releasing factor stimulation and basal markers of hypothalamic-pituitary-adrenal axis suppression in asthmatic patients. Chest 112:1248–1252
38. **Turpeinen M, Mashkilleyson N, Bjorksten F, Salo OP** 1988 Percutaneous absorption of hydrocortisone during exacerbation and remission of atopic dermatitis in adults. Acta Derm Verereol 68:331–335
39. **Matsuda K, Katsunuma T, Iikura Y, Kato H, Saito H, Akasawa A** 2000 Adrenocortical function in patients with severe atopic dermatitis. Ann Allergy Asthma Immunol 85:35–39
40. **Ellison JA, Patel L, Ray DW, David TJ, Clayton PE** 2000 Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. Pediatrics 105:794–799
41. **Lucky AW, Grote GD, Williams JL, Tuley MR, Czernielewski JM, Dolak TM, Herndon JH, Baker MD** 1997 Effect of desonide ointment, 005%, on the hypothalamic-pituitary-adrenal axis of children with atopic dermatitis. Cutis 59:151–153
42. **Patel L, Clayton PE, Addison GM, Price DA, David TJ** 1995 Adrenal function following topical steroid treatment in children with atopic dermatitis. Br J Dermatol 132:950–955
43. **Barth J, Lehr KH, Derendorf H, Mollmann HW, Hohler T, Hochhaus G** 1993 Studies on the pharmacokinetics and metabolism of prednicarbate after cutaneous and oral administration. Skin Pharmacol 6:179–186
44. **Boner AL, Richelli C, De Stefano G, Valletta EA, Ferrari S, Mengoni M** 1985 Hypothalamic-pituitary-adrenal function in children with atopic dermatitis treated with clobetasone butyrate and its clinical evaluation. Int J Clin Pharmacol Ther Toxicol 23:118–120
45. **Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES** 2000 The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev 52:595–638
46. **Crespi H, Armando I, Tumilasci O, Levin G, Massimo J, Barontini M, Perec C** 1982 Catecholamines levels and parotid secretion in children with chronic atopic dermatitis. J Invest Dermatol 78:493–497
47. **Niemeier V, Gieler U, Baerwald C, Kupfer J, Schill WB, Happle R** 1996 Decreased density of β-adrenergic receptors on peripheral blood mononuclear cells in patients with atopic dermatitis. Eur J Dermatol 6:377–380
48. **Sawai T, Ikai K, Uehara M** 1995 Elevated cyclic adenosine monophosphate phosphodiesterase activity in peripheral blood mononuclear leukocytes from children with atopic dermatitis. Br J Dermatol 132:22–24
49. **Salpietro DC, Naccari F, Polimeni I, Pellegrino C** 1998 Reduced plasma cAMP levels in children with atopic dermatitis. Pediatr Allergy Immunol 9:130–132
50. **Elenkov IJ, Chrousos GP** 1999 Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab 10:359–368
51. **Thepen T, Langeveld-Wildschut EG, Bihari IC, van Wichen DF, van Reijsen FC, Mudde GC, Bruijnzeel-Koomen CAFM** 1996 Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial TH2 response to a TH1 response in situ: an immunocytochemical study. J Allergy Clin Immunol 97:828–837
52. **Theoharies TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, Chrousos G** 1998 Corticotropin-releasing hormone induces skin mast cell degranulation and increases vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology 139:403–413
53. **Pacak K, Palkovits M, Yadid G, Kvetnansky R, Kopin KJ, Goldstein DS** 1998 Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. Am J Physiol 275:R1247–R1255

Downloaded from https://academic.oup.com/jcem/article/87/9/4245/2846731 by guest on 20 August 2022