Attenuated Free Cortisol Response to Psychosocial Stress in Children with Atopic Dermatitis

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Objective: Atopic dermatitis (AD) is an inflammatory skin disease characterized by a hyperactivity of the humoral immune system with an onset in infancy or early childhood. Although most of the research has focused on the pathophysiological role of the immune system in AD, the impact of endocrine signals in the pathology of AD has received only little attention. However, because the endocrine system may play a regulatory role in immune functioning, it might be of major interest to study endocrine reactivity in AD patients. The present two-part study investigated the relationship between adrenocortical stress response, heart rate response, and psychological parameters in children with AD. **Method and Results:** In Study 1, a protocol for induction of psychosocial stress in children aged 8 to 14 years was evaluated. Healthy children ($N = 16$) were exposed to the Trier Social Stress Test for Children (TSST-C) that mainly consists of public speaking and mental arithmetic tasks in front of an audience. Salivary cortisol was measured 35, 15, and 1 minute before as well as 1, 10, 20, and 30 minutes after the stress; heart rate was monitored continuously. Results showed that the protocol induced a highly significant increase in free cortisol response ($p<.001$) and heart rate ($p<.001$). In Study 2, the TSST-C was applied to AD children ($N = 15$) and age- and sex-matched healthy controls ($N = 15$). All patients were in remission and medication-free for at least 3 weeks. Again, the stress test induced significant increases in cortisol and heart rate. However, the AD children showed a significantly blunted cortisol response to the stressor compared with the control group ($p < .05$). Heart rate responses were similar in both experimental groups. Neither subjective stress ratings nor personality traits were related to the blunted cortisol response. **Conclusions:** These findings suggest that the adrenocortical response to stress is attenuated in atopic children. A hyporesponsive hypothalamus-pituitary-adrenal (HPA) axis might explain in part the stress-induced eruptions of AD symptoms.

Key words: atopic dermatitis, psychosocial stress, cortisol, heart rate, children.

AD = atopic dermatitis; TSST-C = Trier Social Stress Test for Children.

INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disorder that is often described as the result of an allergic response of the skin to environmental allergens such as food, inhalant, or cutaneous allergens. The disease usually begins in early infancy with initial onset during the first year of life. Main symptoms of AD are dry and lichenified eruptions of the skin, erythema, and intense pruritus with a broad distribution across the body including upper trunk, chest, face, and scalp. The underlying pathological mechanisms of AD are not fully understood; however, several factors such as genetic disposition, climate, or altered vegetative responsiveness are suggested to play a role in this complex multifactorial skin disorder (1, 2). Abnormalities in immune function might play a major role in the onset and course of AD. Thus, there is substantial evidence suggesting that allergen-specific hypersecretion of immunoglobulin E (IgE) and subsequent release of vasoactive mediators from activated mast cells, basophils, or Langerhans cells contribute to the development of AD symptoms (3, 4). More recent studies have speculated on the role of an aberrant cytokine profile released by atopy-specific helper T cells (TH-2-like cells) that induce allergic inflammation by influencing the switch from immunoglobulin M to IgE and by stimulating effector cells such as eosinophils to secrete toxic proteins (5, 6). An increasing number of reports attest to the importance of psychological factors such as personality traits or psychosocial stress in the maintenance and exacerbation of AD symptoms (7, 8). Evidence in support of

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this hypothesis comes from studies demonstrating that stressful life events often precede exacerbation of AD symptoms (9). Using a diary technique to assess daily emotional state and symptom severity, King and Wilson (10) demonstrated a significant relationship between interpersonal stress on a given day and skin condition on the day after. Other studies suggest that daily emotional stress such as AD-related problems, rigid family structure, or negative communication with significant others might predict symptom severity in children and adults with AD, respectively (11, 12). Although these data support the idea that the course of AD might be affected by stress, most of these studies suffer from several shortcomings. First, due to the correlational nature of the studies, the positive relation between psychosocial stress and skin condition is difficult to interpret. Thus, this positive relationship might be interpreted that a) psychosocial stress might exacerbate AD symptoms as a result of physiological alterations, or b) that increased symptom severity makes the person more vulnerable to be stressed by various situations, or c) the positive relationship is because of some third factor. In addition, most of the correlational studies fail to elucidate the underlying biological mechanisms of stress-related exacerbations of AD symptoms.

Considerable evidence has emerged that psychosocial stress can affect a variety of immune functions via neuroendocrine processes such as activation of the hypothalamus-pituitary-adrenal (HPA) axis or the adrenergic system (13, 14). Immune functions regulated by the neuroendocrine system also include AD relevant immune processes such as antibody secretion, helper T cell function, or reactivity of macrophages or eosinophils (15–17). Thus, stress-induced alteration of the (neuro)endocrine milieu might represent an important factor in stress-related exacerbation of AD symptoms. This idea is strongly supported by recent findings suggesting that reduced activity of the HPA axis after pharmacological or psychological stimulation might be associated with disease processes characterized by a hyperreactive immune system such as experimental allergic encephalomyelitis (EAE) or adjuvans arthritis (18, 19). These studies have suggested that an adequate responsiveness of the HPA axis is necessary to prevent the immune response from reaching a level that is potentially damaging to the host. Although the pathological mechanisms of inflammatory processes in autoimmune disorders are different from allergic inflammation found in AD, it could be hypothesized that hyporesponsiveness of the HPA axis as indicated by reduced cortisol secretion during stressful stimulation might be involved in AD pathogenesis.

With this background, two studies were conducted. To induce a reliable psychological and physiological stress response in children, first, a standardized laboratory stressor (Trier Social Stress Test for Children (TSST-C)) was established and evaluated (Study 1). Furthermore, a subsequent study was designed to investigate whether AD children show reduced cortisol secretion and abnormal heart rate responses to the TSST-C (Study 2). The second study also examined whether a specific personality profile might be related to the AD diagnosis and to a potentially altered physiological stress response in AD patients.

METHODS

Study 1: Evaluation of the Trier Social Stress Test for Children

Subjects. Sixteen healthy children (9 boys and 7 girls), aged 9 to 14 years (mean age 12.4 years) were recruited through advertisements in a local newspaper and volunteered for a study "investigating the psychological and physiological effects of stress in children." The parents were informed by telephone about the goal of the study as well as the experimental protocol. They were further asked to inform their children that they would participate in a study that would include various tasks similar to a school exam. Children with known medical problems or any signs of current infection were excluded. All children participated voluntarily and written parental consent for their children's involvement in the study was obtained. Additionally, the experimental protocol was approved by the local ethics committee. After finishing the experiment each child received a voucher for a free movie in a local cinema.

Experimental Protocol. Experimental sessions were run between 3:00 PM and 4:30 PM with two subjects participating per day. After arriving, the parents of the children (mostly their mothers) completed a questionnaire including informations about sociodemographic data (ie, age, school type, number of siblings, or profession of the parents) as well as medical and psychological status of the children (ie, acute or chronic diseases, previous or current medication, behavioral problems). After having completed the questionnaire the parents left the experimental setting and the children were informed about the experimental protocol. To determine heart rates, a wireless signal transmission device (Polar Instruments, Germany; see below) was fitted to the children's chests. After 20 minutes the subjects were escorted to the experimental room and introduced to the TSST-C. This psychosocial stress protocol represents an adapted version of a standardized stress paradigm developed and evaluated in our laboratory for studies with adult subjects (20).

The TSST-C was performed as follows: In the experimental room, two persons were already sitting behind a table, and a tape recorder, a video camera, and a microphone were installed. Next, the children received the beginning of a story. They were told that after a preparation period of 5 minutes in another room, they should finish telling the story as exciting as possible in front of the committee and that they should try to perform better than all the

other children. The unfinished story used in this study was the following:

> "Yesterday my best friend Robert and I went home from school. Suddenly, we had the idea to visit Mr. Greg who lived in the big old house located in the dark forest near our town. Mr. Greg was a crazy old man and our parents didn't like the idea that we sometimes went visiting him. There was a rumor in town that there was a mystery about the old house. When we arrived at the house we were surprised that the door was open. Suddenly we heard a strange noise and cautiously, we entered the dark hall. . .".
> The unfinished story had been previously chosen from among seven other stories by a panel of children with respect to how exciting and difficult to finish the story would be.
>
> After the preparation period (5 minutes) the subjects were again escorted to the experimental room and were asked to stand at the microphone in front of the audience and to finish the story in a free speech of 5 minutes duration. Whenever children finished the story in less than 5 minutes, they were asked to continue in a friendly, supportive manner.
>
> After 5 minutes the committee asked the subjects to serially subtract the number 7 from 758 (9 to 11 years) or the number 13 from 1023 (12 to 14 years) as fast and as accurately as possible. On every failure, the subjects had to restart at 758 or 1023, respectively, with one member of the committee interfering "Stop, please start again." The mental arithmetic tasks had been graded previously by a teacher so that they were of appropriate difficulty for the children tested here.
>
> It is of methodological importance to notice that in contrast to the TSST for adults, the members of the audience of the TSST-C in Study 1 were instructed to provide the children with adequate positive feedback, either facial or verbal.
>
> The stressor was followed by a 10-minute feedback period in which the subjects completed a 10-item 5-point manipulation check of how stressful they experienced the free speech and the arithmetic tasks in front of the audience. Furthermore, the children had the opportunity to ask questions and the stressful situation was discussed. Every child was told that he or she had performed as well as the other participants and that the stern behavior of the committee was pretended in order to induce competitive conditions. At the end of the feedback period the children were freed from the heart-monitoring device. During a 20-minute rest period that followed, the children completed a personality questionnaire, Persönlichkeitsfragebogen für Kinder (PFK) (Personality Questionnaire for Children) (21) and an anxiety inventory, Angstfragebogen für Kinder (AFK) (Anxiety Inventory for Children), (22). Finally, they received the cinema voucher and were picked up by their parents.

Cortisol. Saliva samples were obtained 35, 15, and 1 minute before as well as 1, 10, 20, and 30 minutes after the stressor using the Salivette sampling device (Sarstedt, Rommelsdorf, Germany). This device mainly consists of a small cotton swab on which the subject gently chews for 0.5 to 1 minute. Thereafter, the swab is transferred into a small plastic tube. The samples were stored at −20°C before analysis. After thawing, the devices were centrifuged at 2000 rpm resulting in a clear, watery supernatant. For cortisol determination 100 μl of saliva was used for duplicate analysis with a time-resolved fluorescence immunoassay (Delfia) which is described elsewhere (23). The intra- and interassay coefficients of variance for this assay were less than 8% at a cortisol concentration of 5 nmol/l.

Heart Rate. Heart rate was monitored continuously using a wireless signal transmission device (Sport Profi, Polar Instruments, Germany). Heart rate was averaged over 5-minute intervals reflecting the different experimental periods of the study, ie, rest during Periods 1 and 2, introduction to the experimental setting, preparation, free speech, mental arithmetic, and feedback.

Psychological Measures. The PFK assesses selected personality traits, ie, emotional excitability, extraversion and activity, social withdrawal and social anxiety, ambition in school, obedience and dependency to adults, masculinity of attitudes, general anxiety, self-conviction, and submissive behavior in children. Internal consistencies vary between $\alpha = .67$ and $\alpha = .77$ (Cronbach's α). The AFS is often used to determine test anxiety and manifest anxiety in children. With internal consistencies of $\alpha = .81$ and $\alpha = .87$, these scales show good reliability.

Statistical Analysis. Analyses of variance (ANOVAs) for repeated measures were computed for heart rate and cortisol changes in response to the TSST-C with subsequent Newman-Keuls post hoc tests for single comparisons. Greenhouse-Geisser corrections were applied where appropriate. For group comparisons (eg, sex differences) the areas under the response curves (AUCs) were computed for heart rate and cortisol responses for each individual and statistical significance was computed by Mann-Whitney *U*-tests. Furthermore, Spearman rank correlations were computed for assessment of associations between age, personality traits, and the biological stress indices of heart rate and cortisol responses (AUCs).

Results

Mean heart rates during the different phases of the experiment, ie, rest (Periods 1 and 2), introduction to the stressor (Period 3), preparation (Period 4), free speech (Period 5), mental arithmetic tasks (Period 6), and feedback (Period 7) are presented in Figure 1*A*. Analysis of variance on heart rates indicated that there was a significant time effect ($F(6,72) = 10.78$; $p < .001$) but no significant effect for sex ($z = 1.75$, $p = .08$; Mann-Whitney *U*-test). Heart rate was significantly increased during the stressor (Periods 5 and 6; Newman-Keuls test; $p < .01$) returning to baseline values during the feedback period. The cortisol data parallel these findings (see Figure 1*B*). Again, ANOVA revealed a significant time effect ($F(6,78) = 8.84$; $p < .001$) and no significant effect for sex was found ($z = 0.13$, NS). Newman-Keul tests revealed a significant increase of cortisol concentration 10, 20, and 30 minutes after stressful stimulation ($p < .001$) that seems to return toward baseline values 30 minutes after the stressor. Although the cortisol rate in response to the TSST-C was comparable to the cortisol pattern observed in previous studies with healthy adults, the response magnitude seemed to be approximately 30% to 50% lower in the children (24, 25). Heart rate response magnitude did not

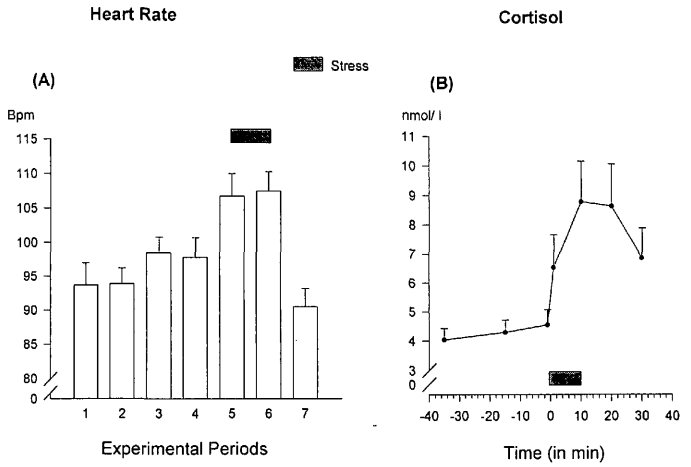

Fig. 1. *A*, Alteration of heart rates (Periods 1 and 2, rest; Period 3, anticipation; Period 4, preparation; Period 5, public speaking; Period 6, mental arithmetic; Period 7, feedback). *B*, Cortisol concentrations after psychosocial stress (TSST-C) in healthy children aged 8 to 14 years (mean ± SEM).

correlate with cortisol responses (r = .34, p<.1). Likewise, age was not correlated with heart rate or cortisol responses. Only one of 22 correlation coefficients between personality traits and stress-induced alterations of cortisol or heart rate was significant. Higher scores on the submissiveness scale was negatively correlated with the area under the response curve for heart rates (r = −.68, p = .008). Inasmuch as one of 20 comparisons yields a significant correlation at the 5% probability level by chance, this result was not considered a valid finding. No significant correlations were obtained between the biological stress indices and the subjective stress ratings.

Study 2: Endocrine and Physiological Alterations in Children with Atopic Dermatitis in Response to the TSST-C

Subjects. Fifteen children (7 boys and 8 girls) aged 9 to 14 years (mean age 11.8 ± 1.9 years) with atopic dermatitis (AD) were recruited through advertisements in a local newspaper with the understanding that "the effect of stress on psychological and physiological processes in children with atopic dermatitis should be investigated." All children were clinically diagnosed with AD by a dermatologist and met the diagnostic criteria for AD as described by Hanifin and Rajka (26). Most of the children had a history of AD dating back to infancy and only children with a minimum history of AD for 5 years were included. Care was taken that all children were in remission and were medication free for at least 3 weeks. Based on the parents' reports, none of the children were treated with steroids or antihistamines. However, some of the AD patients had a prior homeopathic medication whereas others never had any treatment.

To recruit an appropriately matched control group in terms of age, sex, family history, educational background, and socioeconomic status, the AD patients were asked to bring their best same-sex friend. They were further told that it would be important that he or she and his or her friend attend the same school and spend a lot of time together. The control group included 15 healthy children aged 9 to 14 years (mean age 11.9 ± 1.8 years). None of the control subjects had suffered from AD or had a family history of atopy. Control children who had any current or chronic medical problems were excluded. There were no significant differences between groups in age, sex, educational status (school type), or family history (number of siblings, profession of the parents; all p<.05).

Comparable to Study 1, the parents of all participants completed a questionnaire including sociodemographic data as well as information about the psychological and medical status of the children (see Study 1). Puberty was recorded based on the parents' records (first menstruation, development of pubic hair). No further medical examination was assessed to determine pubertal status. All children participated voluntarily and the children's parents had been informed about the actual nature of the study and had provided written consent. Additionally, the experimental protocol was approved by the local ethics committee. As in Study 1, all children received a voucher for a free movie after finishing the experiment.

Experimental Protocol. The experimental protocol used in this study was the same as described in Study 1 except that two different groups were examined, which required some alterations of the protocol. Thus, the two subjects participating in the experiment at the same day included an AD patient and his or her

respective control. It should be noted, that the two investigators running the stress test were blinded to the diagnosis of the subject being stressed. A second alteration of the experimental protocol in Study 2 included a different feedback behavior of the audience during the stressful TSST-C procedure. Inasmuch as we had observed lower cortisol responses in the children in Study 1 compared with findings in previous studies investigating healthy adults, we suspected that the smaller endocrine response could have been because of the positive feedback behavior of the audience. It was therefore decided to treat the children similar to the adults in that no positive facial or verbal feedback would be provided by the members of the audience. Other than that, the experimental protocol was as described in Study 1. Saliva samples and heart rates were both sampled as described in Study 1. Unfortunately, heart rates were lost for one AD and one control subject because of technical failure.

Statistical Analysis. Socioeconomic status, family history, and educational background of the two groups of children were compared by χ^2 tests. All other comparisons were performed as in Study 1.

Results

As presented in Figure 2*A*, subjects with AD as well as control subjects showed increased heart rates in response to the psychosocial stressor. ANOVA indicated a significant time effect ($F(6,144) = 30.87$; $p<.01$). Heart rates were significantly increased during the stress test (Newman-Keuls test; $p<.001$) returning to baseline during the feedback period. Interestingly, the subjects already showed increased heart rate when introduced to the stressor (Period 3; $p<.001$) and while preparing the free speech (Period 4; $p<.001$) indicating that anticipation of the subsequent stressor was effective in inducing increased heart rate. No significant effects could be observed for sex ($z = 0.44$) or group ($z = 0.51$) with respect to heart rate responses.

Analysis of variance of the cortisol data also yielded a significant time effect ($F(6,156) = 23.51$; $p<.001$) and a significant time by group effect ($F(6,156) = 15.27$; $p<.05$). As can be seen in Figure 2*B*, children of both groups showed an increase of cortisol 10, 20, and 30 minutes after the stressor ($p<.001$). The magnitude of cortisol response in the children of the control group was comparable to the response seen in healthy adult nonsmokers (24, 25).

As hypothesized, a significantly blunted cortisol response was found in AD children compared with healthy controls ($z = 1.76$, $p<.05$). It is noteworthy that the attenuated cortisol response in AD children was not related to subjective stress ratings. Both groups were comparable with respect to how stressful the children rated the TSST-C (all $p<.05$). As shown in Table 1, no significant differences between AD children and the healthy control group were observed for any of the psychological variables investigated (all $p<.05$). No relationship was found between cortisol response and the developmental status (in puberty or not in puberty; $F<1$).

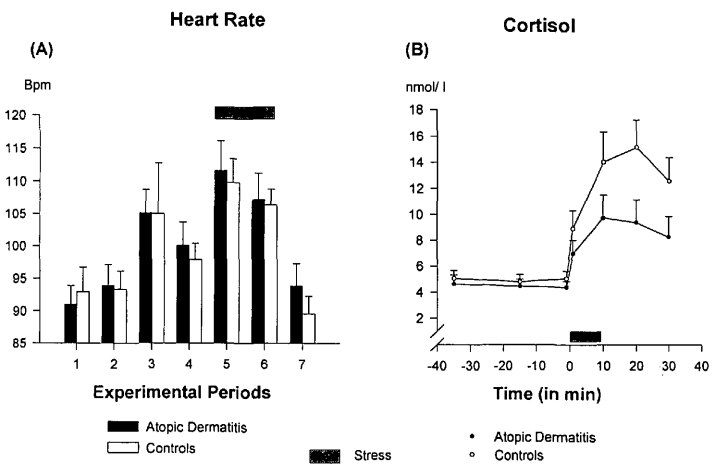

Fig. 2. *A*, Alteration of heart rates (Periods 1 and 2, rest; Period 3, anticipation; Period 4, preparation; Period 5, public speaking; Period 6, mental arithmetic; Period 7, feedback). *B*, Cortisol concentrations after psychosocial stress (TSST-C) in children with atopic dermatitis and in healthy control children (mean ± SEM).

TABLE 1. Psychometric Tests and Manipulation Check

Variable	Atopic Dermatitis		Controls		t	p
	Mean	SD	Mean	SD		
Emotional Excitability[a]	54.5	6.28	52.9	8.66	−0.96	.34
Extraversion/Activity[a]	49.7	11.34	48.2	9.1	0.39	.7
Social Withdrawal/Social Anxiety[a]	50.9	8.11	50.0	8.36	0.31	.75
Ambition in School[a]	50.8	11.91	49.0	10.89	0.43	.66
Obedience/Dependency to adults[a]	50.0	14.51	45.1	10.19	1.1	.29
Masculinity of Attitudes[a]	44.6	7.87	46.9	10.55	−0.69	.49
General Anxiety[a]	52.3	9.94	50.1	6.37	0.7	.48
Self-Conviction[a]	51.9	10.35	49.5	8.56	0.67	.51
Submissive Behavior[a]	52.3	11.75	51.8	11.49	0.12	.9
Test Anxiety[b]	48.33	8.72	51.8	11.84	−0.91	.37
Manifest Anxiety[b]	56.0	10.49	55.47	11.25	0.13	.89
Perceived Stress (TSST-C)[c]	2.73	1.0	3.13	1.24	−0.96	.35

[a] Personality questionnaire (Persönlichkeitsfragebogen für Kinder; PFK).
[b] Anxiety inventory (Angstfragebogen für Kinder; AFK).
[c] Manipulation check (stressfulness of the Trier Social Stress Test for Children; TSST-C).

DISCUSSION

The specific goal of the present study was to investigate whether children with AD show attenuated cortisol response and altered heart rate responses to a standardized psychosocial stressor. However, to examine physiological and psychological stress responses in AD children, an adequate stressor that causes a significant and reliable increase in cortisol levels and heart rate had to be developed and evaluated first. There are some reports demonstrating increased heart rate in response to school-related tasks under competitive conditions (27) or increased cortisol levels after stressful experiences such as social conflicts in the classroom, maltreatment, maternal separation, inoculation, or venipuncture (28–30). It should be noted, however, that most of these data are based on studies that have investigated mainly younger children, ie, newborn or 1- to 12-month-old babies, or have used stressors difficult to assess such as maltreatment or social conflicts. Furthermore, there are only a few reports demonstrating stress-induced modulation of more than one biological parameter, for example, cortisol response and heart rate.

The data of Study 1 suggest that the psychosocial stress test, TSST-C, which includes public speaking and mental arithmetic in front of an audience, results in significant increases of cortisol levels and heart rates in children aged 9 to 14 years. These findings are comparable with previous data of our group showing stress-induced alteration of cortisol concentration and heart rate in healthy adults using a comparable laboratory stressor (20). With this background, the TSST-C was considered to be an adequate experimental protocol to induce significant and reliable alteration of heart rates and cortisol levels in children of this age group and was therefore used as a stressor in Study 2.

In Study 2, again a significant increase in heart rate in response to the TSST-C was observed. Interestingly, and in contrast to the author's expectation, there was no significant difference for either resting heart rate or heart rate reactivity between AD children and healthy controls. This observation is in contrast to data from Faulstich et al. (31) showing significantly higher heart rates during experimentally induced stress in AD patients compared with healthy controls. It should be noted, however, that in this study adult AD patients and different laboratory stressors, including a quiz, stressful imagery, and a cold pressure test, were used.

The exposure to the TSST-C also resulted in increased cortisol levels in AD and control children. However, in children suffering from AD a significantly blunted cortisol level was found. At least two reasons could have accounted for this response difference. From a psychological viewpoint, it could be assumed that AD patients tend to interpret the confrontation with a potentially threatening situation in a different way than healthy subjects do. Alternatively, it could be suspected that AD children have a personality type that might be associated with an altered psychological and biological stress response. The latter hypothesis has been explored by several investigators demonstrating that AD patients show higher levels of anxiety, excitability and depression, problems in dealing with anger and hostility, and inadequate stress coping (7, 8). In the present study

we did not find a difference between AD children and nonatopic controls with respect to specific personality traits such as emotional excitability, extraversion, social or general anxiety, ambition in school, or self-conviction. It should be noted, however, that in using only the PFK and the AFK, we determined only some aspects of personality. With respect to these limited personality data, it cannot be excluded that AD children show an atopy-specific personality profile that might have influenced the psychological and biological stress response. It is noteworthy, however, that AD children did not seem to perceive the TSST-C as more stressful than normals, suggesting that the attenuated cortisol response in AD patients cannot be explained by a potentially atopy-specific appraisal of stressful situations.

With regard to these considerations the question arises whether reduced cortisol levels after stressful stimulation reflect a potential biological characteristic of AD patients that might play a role in the inflammatory process of AD and more specifically in stress-induced exacerbation of AD symptoms. This idea is strongly supported by recent findings of Sternberg et al. (32, 33) suggesting that attenuated HPA responsiveness might be associated with an increased susceptibility to inflammatory diseases. Lewis rats, which are highly susceptible to inflammatory disorders such as EAE or adjuvans arthritis, show reduced ACTH and cortisol responses to CRH or stressful stimulation (32, 33). More interestingly, treatment of HPA-hyperresponsive F344 rats with the glucocorticoid receptor antagonist RU 486 increased the susceptibility to inflammatory processes in these usually more resistant animals (34). These data indicate that adequate responsiveness of the HPA axis to pharmacological and psychological stimuli might be a relevant protective factor against disease processes caused by a dysregulated or hyperactive immune system. Although inflammatory processes involved in autoimmune disorders are different from allergic inflammation, it can be assumed that a defective HPA axis may represent an important pathological factor in the development and clinical course of AD. Evidence in support of this hypothesis comes from studies indicating that patients with AD show significantly impaired cortisol and ACTH response to CRH challenge (35). Moreover, an increased number of glucocorticoid binding sites on peripheral lymphocytes was observed in AD patients lending support to the idea of a potentially compensatory upregulation of glucocorticoid receptors due to a reduced action of endogenous cortisol in AD patients (36). Finally, the hypothesis that HPA axis deficiency might be a relevant pathological factor in AD is strongly underlined by the unexpected observation by Laue et al. (37) indicating that 8 of 11 healthy volunteers treated with the glucocorticoid receptor antagonist RU 486 for 7 to 14 days showed AD-like symptoms such as erythema or eruptions of the skin. None of the subjects had a prior history of atopy.

To summarize, the present findings suggest that children suffering from AD show reduced cortisol levels in response to a standardized psychosocial stressor. This observation provides additional evidence that a dysregulated HPA axis might play a role in AD. Whether this attenuated response is because of a reduced secretion of ACTH or vasopressin, an altered sensitivity of glucocorticoid receptors, or a dysfunctional feedback regulation on either an innate or acquired basis remains to be determined. Further studies are needed to evaluate the potential role of a dysfunctional HPA axis in stress-induced modulation of AD relevant immune functions and, finally, in stress-induced eruptions of AD symptoms. This might provide new insights in the pathogenesis of atopic diseases.

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