Infusion of Epinephrine Decreases Serum Levels of Cortisol and 17-Hydroxyprogesterone in Patients with Rheumatoid Arthritis

RAINER H. STRAUB, JENS M. KITTNER, COBI HEIJNEN, MANFRED SCHEDLOWSKI, REINHOLD E. SCHMIDT, and ROLAND JACOBS

ABSTRACT. ***Objective.*** To investigate the pituitary and adrenal hormone response after an intravenous epinephrine challenge in patients with rheumatoid arthritis (RA) and controls.

Methods. Fifteen untreated female patients with RA (age 51.5 ± 3.2 yrs) and 7 healthy female controls (48.0 ± 4.3 yrs) were infused with epinephrine (0.05 µg/kg/min) for about 20 min. Plasma levels of adrenocorticotropic hormone (ACTH), and serum levels of cortisol, 17-hydroxyprogesterone (17OHP), and dehydroepiandrosterone sulfate (DHEAS) were analyzed at baseline and shortly after cessation of epinephrine infusion (20 min).

Results. At baseline and after epinephrine infusion, serum levels of cortisol ($p = 0.045$) and 17OHP ($p = 0.021$) were higher in controls compared to patients with RA. In contrast, at baseline and after epinephrine infusion, plasma levels of ACTH and serum levels of DHEAS were similar in controls and patients. After epinephrine infusion, only the patients with RA had a significant decrease of serum cortisol ($p = 0.026$) and serum 17OHP ($p = 0.026$). Plasma levels of ACTH ($p = 0.073$) and serum levels of DHEAS ($p = 0.055$) tended to decrease.

Conclusion. Serum cortisol and 17OHP (cortisol precursor) were lower in patients with RA compared to controls despite similar ACTH levels. Simulation of an adrenomedullary stress response by epinephrine infusion decreased serum cortisol and 17OHP in patients but not in controls. Such a response may play an unfavorable role during a typical stress reaction in patients with RA that may lead to a more proinflammatory situation. (J Rheumatol 2002;29:1659–64)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	CORTISOL	EPINEPHRINE INFUSION
ADRENOCORTICOTROPIC HORMONE	DHEAS	17-HYDROXYPROGESTERONE

It has been shown that major and minor psychological stress can aggravate rheumatoid arthritis (RA) and can cause disease flares[1]. Whether psychological stress can even provoke RA is unknown. In addition, for children with juvenile chronic arthritis it has been reported that psychological stress can provoke and modulate the disease[1]. At present, few mechanisms are known that link psychological stress and exacerbation of chronic inflammatory diseases in humans. Previously, we found that psychological stress such as public speaking[2] or parachute jumping[3] increases plasma levels of epinephrine and norepinephrine and increases the number of circulating natural killer cells and granulocytes via ß-adrenoceptor pathways[3]. Infusion of catecholamines into controls has corroborated these effects on leukocytosis[4]. Thus, psychological stress may aggravate a chronic disease by mobilization of additional cells that can enter arthritic joints. Another mechanism could be a stress induced increase of serum interleukin 6 because this cytokine can stimulate B lymphocytes (and thereby rheumatoid factor production) and can induce juxtaarticular osteoporosis[5-7]. Other psychoneuroendocrine immune factors that may play a role in RA pathophysiology are under intense investigation[8].

Since an alteration of the hypothalamic-pituitary-adrenal (HPA) axis has been found to be an important factor for the development of experimental arthritis[9], we focused on stress induced changes of the HPA axis in patients with RA. Changes of the HPA axis with low levels of cortisol in rela-

From the Department of Internal Medicine I, University Medical Center Regensburg, Regensburg; Department of Clinical Immunology, Hannover Medical School, Hannover; Institute of Medical Psychology, University of Essen, Essen, Germany; Department of Pediatric Immunology, Wilhelmina Children's Hospital of the University Medical Center Utrecht, Utrecht, The Netherlands.

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R.H. Straub, MD, Rheumatologist, Professor of Experimental Medicine, Department of Internal Medicine I, University Medical Center Regensburg; R. Jacobs, PhD, Department of Clinical Immunology; J.M. Kittner, Doctoral Student, Fellow of Rheumatology, Department of Clinical Immunology, Hannover Medical School; C. Heijnen, PhD, Professor, Head, Department of Pediatric Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht; M. Schedlowski, PhD, Professor, Head, Institute of Medical Psychology, University of Essen; R.E. Schmidt, MD, Rheumatologist, Professor, Head, Department of Clinical Immunology, Hannover Medical School.

Address reprint requests to Dr. R.H. Straub, Department of Internal Medicine I, Laboratory of Neuroendocrinoimmunology, University Medical Center, D-93042 Regensburg, Germany. E-mail: rainer.straub@klinik.uni-regensburg.de

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tion to systemic inflammation and low serum levels of adrenal androgens are typical features of RA[10]. However, it is unknown whether stress with increased blood levels of catecholamines can change secretion of adrenocorticotropic hormone (ACTH) and adrenal steroids in RA. In this study, we employed epinephrine infusion as a validated stress model to simulate a distinct stress response[4]. Levels of plasma ACTH, serum cortisol, serum 17-hydroxyprogesterone (17OHP), and serum dehydroepiandrosterone sulfate (DHEAS) were investigated in female patients with RA and female age matched controls before and after standardized epinephrine infusion.

MATERIALS AND METHODS

Patients and controls. We included 15 female Caucasian patients fulfilling the American College of Rheumatology criteria for RA[11]. The mean age of RA patients was 51.5 ± 3.2 years (median 58 yrs, range 22 to 65). No patient had received disease modifying antirheumatic drug (DMARD) therapy or oral glucocorticoids prior to the study. All patients had mild longterm disease treated by nonsteroidal antiinflammatory drugs (NSAID) or other non-DMARD (median 6.2 yrs, range 1 to 26). Disease activity was scored by means of the RADAR questionnaire[12] (mean RADAR 8.1 ± 1.7 points, median 10 points, range 0 to 20 points; maximum possible score of the RADAR: 60), and mean C-reactive protein was 5.1 ± 1.1 mg/l (median 3.0 mg/l, range 1 to 15). According to these 2 latter variables, our group of female patients with RA had mild disease activity.

For comparison, 7 healthy Caucasian women were included as controls. Their mean age was 48 ± 4.3 years (median 54 yrs, range 30 to 58; not significantly different from the RA patients). Controls with drug or alcohol abuse, medication, or infections within the last 2 weeks were excluded.

The Ethics Committee of the Hannover Medical School approved the study and patients and controls gave written consent.

Procedure. The procedure has been described in our earlier study[4]. Briefly, all experiments were conducted at the same time of the day starting at 8:00 AM in a sitting position. An IV cannula was inserted into a cubital vein 30 min before the start of infusion, and subjects were given an infusion of epinephrine (0.05 µg/kg/min) over 20 min. This time interval between insertion of the cannula and collection of baseline cortisol has been used to avoid nonspecific stress responses[4]. Blood samples were drawn before (baseline) and immediately after the end of infusion at 20 min. Because plasma levels of ACTH and serum levels of cortisol rapidly increase within 15 min after IV injection of corticotropin releasing hormone (CRH)[13], and to avoid the influence of any secondary late phenomena, we measured early responses at 20 min. According to this procedure, within 5 min, plasma epinephrine concentration increases to more than 10 times the baseline plasma level and remains stable throughout the entire infusion period. Controls and patients exhibited mild cardiovascular changes with an increased heart rate (plus 10%), an increase of the systolic (plus 5%) and a decrease of the diastolic blood pressure (minus 10%). Blood samples were immediately centrifuged at 4°C, and plasma and serum were stored at –70°C until assayed.

Laboratory variables. We used radioimmunometric assays for the quantitative determination of serum levels of cortisol (Coulter Immunotech, Marseilles, France; detection limit 10 nmol/l). Plasma levels of ACTH (IBL, Hamburg, Germany; detection limit 0.1 pmol/l), serum levels of 17OH-progesterone (IBL; detection limit 0.3 nmol/l), and serum levels of DHEAS (IBL; detection limit 130 nmol/l) were measured by means of immunometric enzyme immunoassays. Intraassay and interassay coefficients of variation were below 10% in each test.

Statistical analysis. To assess the statistical significance of differences between values collected at baseline versus 20 min, the nonparametric Wilcoxon test for paired data was used (SPSS/PC for Windows, V.10.0.5, SPSS Inc., Chicago, IL, USA). Responses of the 2 groups in relation to the observation time were compared by multivariate analysis (general linear model, SPSS). Values are expressed as mean ± SEM and the significance level is $p < 0.05$.

RESULTS

Comparison of response curves in relation to the observation time between patients and controls. Figure 1 shows response curves for the 2 time points with mean plasma levels of ACTH (Figure 1A), serum levels of cortisol (Figure 1B), serum levels of 17OHP (Figure 1C), and serum DHEAS (Figure 1D). It is obvious that ACTH plasma levels and DHEAS serum levels are very similar in patients and controls (Figures 1A and D). With respect to serum levels of cortisol and 17OHP, patients with RA had significantly lower levels of both hormones over the entire observation period compared to controls despite similar ACTH levels (Figures 1B and C). Further, the average serum cortisol level of RA patients decreased below the lower cutoff value of acrophase concentrations of controls (< 180 nmol/l; Figure 1B). These data indicate that plasma/serum levels of all hormones tended to decrease in patients with longstanding RA in contrast to controls.

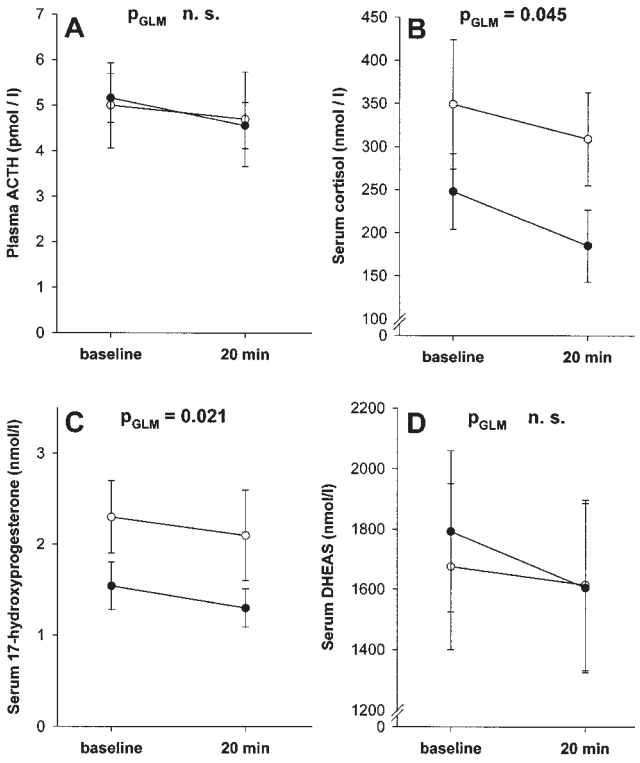

Figure 1. Epinephrine induced changes of plasma/serum levels of pituitary and adrenal hormones. The course of (A) plasma ACTH, (B) serum cortisol, (C) serum 17OHP, and (D) serum DHEAS are shown in controls (○) and in patients with RA (●). The graphs illustrate the mean hormone value ± SEM. p_{GLM} is the p value of the general linear model for the comparison of the entire curve of controls vs patients with RA in relation to the observation time.

Hormone response of individual subjects due to epinephrine infusion. Plasma levels of ACTH in patients tended to decrease after infusion of epinephrine (p = 0.073 in the Wilcoxon test for paired data; Figure 2B), whereas ACTH plasma levels remained unchanged in controls (p = 0.578; Figure 2A). Serum cortisol levels significantly decreased in patients but not in controls after infusion of epinephrine (Figures 2C and D). This is similar for serum levels of 17OHP, which decreased in patients with RA but not in controls (Figures 3A and B). There was a trend for lower serum levels of DHEAS in patients with RA after infusion of epinephrine (p = 0.055) that was not observed in controls (p = 0.219).

DISCUSSION

In controls, earlier studies revealed that IV epinephrine infusion or subcutaneous injection did not change plasma levels of ACTH and serum levels of cortisol[14-18]. This was confirmed in the present study in our controls. Generally, the lack of a stimulatory effect of IV epinephrine infusion on ACTH and cortisol secretion is unexplained, because *in vitro* epinephrine stimulates ACTH and cortisol release from pituitary or adrenocortical cells or from perfused isolated organs[19,20]. The following explanations for the lack of effect of IV epinephrine on ACTH release and subsequent cortisol secretion in controls have been proposed (Figure 4, left panel): (A) Circulating catecholamines do not pass the blood-brain barrier so that stimulation of central α1-adrenoceptors of CRH neurons cannot occur[21]. (B) Epinephrine exerts its effects via α-adrenoceptors and via ß-adrenoceptors. Thus, at certain doses of epinephrine, stimulation of both adrenoceptor subtypes may lead to a balance (α and ß) that does not change intracellular cyclic AMP and subsequent ACTH secretion (ACTH stimulation via α1-adrenoceptors[21]; ACTH inhibition via ß-adrenoceptors[22]). This balance may also be relevant for the missing effect of IV epinephrine in the administered dose on the adrenal level. (C) There may be a balance between epinephrine stimulated adrenocortical cortisol secretion[20] and epinephrine mediated reflex decrease of the firing rate of sympathetic nerves to the adrenal glands[23,24], which is necessary for cortisol secretion[20]. Taken together, IV infusion of epinephrine, which increases epinephrine concentrations up to 10 times the normal value, does not change secretion of ACTH and cortisol in controls.

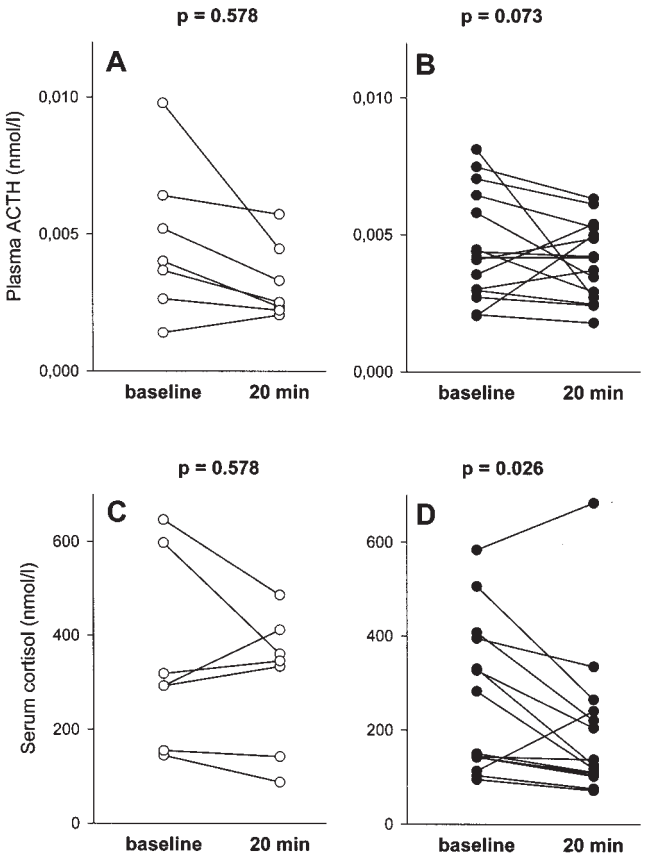

Figure 2. Plasma ACTH and serum cortisol at baseline and after epinephrine infusion in controls (A, C) and patients with RA (B, D). The p value gives the significance value for the difference of serum levels of ACTH/cortisol at baseline vs 20 min analyzed by the nonparametric Wilcoxon test for paired data.

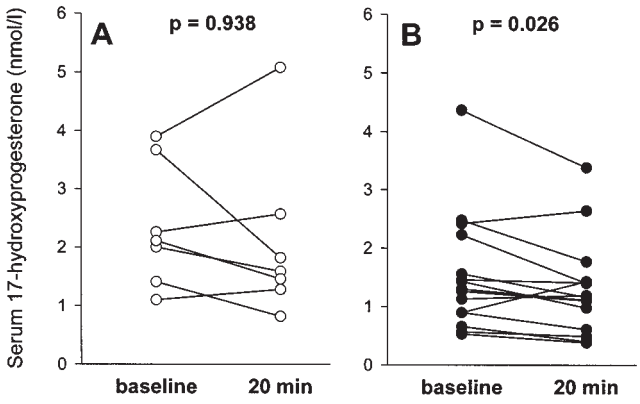

Figure 3. Serum 17-hydroxyprogesterone at baseline and after epinephrine infusion in controls (A) and patients with RA (B). The p value gives the significance value for the difference of serum levels of 17-hydroxyprogesterone at baseline vs 20 min analyzed by the nonparametric Wilcoxon test for paired data.

Epinephrine infusion rapidly decreased serum levels of cortisol and 17OHP in patients with RA. The exact site of action for the fast response after IV epinephrine is not known. Probably, such acute effects are due to modulation of the fast conversion from cholesterol to pregnenolone that occurs within minutes[25]. Further, in our RA patients, there was a trend for decreased plasma levels of ACTH and serum levels of DHEAS. This indicates that patients with RA had an overall reduction of the HPA axis activity after short term IV epinephrine infusion. This seems to be most obvious in patients with elevated levels of plasma ACTH, serum cortisol, and serum 17OHP. Thus, during epinephrine infusion, it seems that an activated HPA axis is more markedly

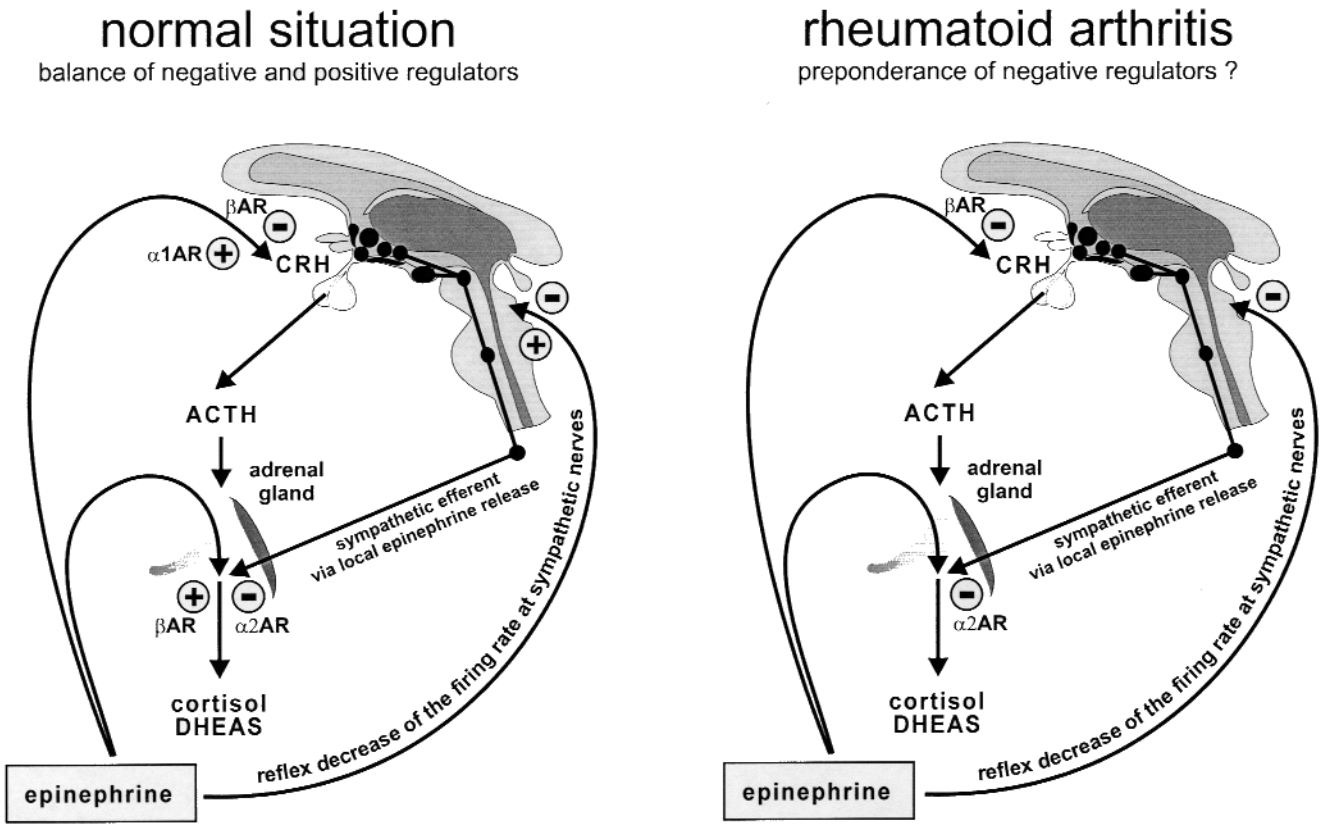

Figure 4. Influence of epinephrine on hypothalamus-pituitary-adrenal axis activity in controls and patients with RA. Left panel: In controls, epinephrine infusion does not change ACTH and cortisol secretion, which reflects a balance between negative and positive regulators. Right panel: In RA, there seems to be a preponderance of negative regulators of cortisol secretion leading to inhibition of cortisol secretion. However, the exact mechanisms and the site of action remain to be established. ACTH: adrenocorticotropic hormone; AR: adrenoceptor; CRH: corticotropin releasing hormone; DHEAS: dehydroepiandrosterone sulfate. Plus sign indicates a stimulatory effect, and minus sign indicates an inhibitory effect.

inhibited compared to a nonactivated HPA axis. The reasons for this response are not presently known. One may assume that the above mechanisms are unbalanced in patients (Figure 4, right panel): (A) For example, a preponderance of adrenergic signaling via α-adrenoceptors instead of ß-adrenoceptors may be present under inflammatory conditions[26-28], which may lead to inhibition of pituitary ACTH secretion[22]. In contrast, with respect to the adrenal gland, such a switch to ß-adrenergic signaling would increase cortisol secretion[29,30]. (B) Since in patients with RA or juvenile chronic arthritis elevated blood levels of catecholamines or an increased sympathetic tone were described[31-33], adrenoceptor expression may be changed in the tissue. Indeed, it has been demonstrated that ß-adrenoceptor expression on peripheral blood mononuclear cells was decreased[34]. This could lead to subsequent impairment of epinephrine effects due to receptor desensitization.

It is also unclear whether similar strong acute stimulation of the sympathetic nervous system by other clinical situations will also lead to decreased ACTH or cortisol secretion in patients with RA. Indeed, a recent study in patients with RA has shown that different types of psychological stress in the morning led to a stronger decrease of serum cortisol in RA patients compared to controls (not significant for ACTH). This effect did not depend on mean baseline cortisol serum concentration[35]. Another study showed that there is subtle dysfunction of steroid secretion after insulin hypoglycemia, which is a strong stimulus of the sympathetic nervous system[36]. Another longterm model could be stimulation of the sympathetic nervous system by major surgery. One study described a defective ACTH response in patients with RA 48 h after the stress of major surgery[37]. However, this has not been confirmed by other investigators[38]. In rats with adjuvant arthritis, an acute stressor (noise) does not activate the HPA axis[39]. This may depend on a decreased responsivity of the HPA axis due to downregulation of CRH production[40]. However, in general, it is difficult to compare these acute stressors in an *in vivo* situation with the investigated epinephrine infusion since other types of stimuli may induce different response patterns of the HPA axis.

In conclusion, upon epinephrine infusion, patients with RA had acutely decreased serum levels of cortisol and 17OHP and tended to have lower levels of ACTH and DHEAS, which was not observed in healthy controls.

Alterations of the stress response systems (HPA axis and sympathetic nervous system) in chronic inflammatory diseases may be responsible for the observed changes. However, in patients with RA, the underlying mechanisms remain unknown. Nevertheless, our study suggests that in RA patients, some situations may arise in which psychological stress with similar conditions comparable to epinephrine infusion may lead to an unfavorable response of the HPA axis. Downregulation of serum cortisol in such a situation may be a relevant factor for exacerbation of RA.

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