

Personality, Brain Asymmetry, and Neuroendocrine Reactivity in Two Immune-Mediated Disorders: A Preliminary Report

J. Martin Martins,^{*,1} J. Alves,[†] Ana Trinca,[‡] Bruno Grima,[†] S. do Vale,^{*}
Teresa Vasconcelos,[†] Nuno Riso,[†] Vaz Riscado,[†]
and J. Charneco da Costa^{*}

**Endocrine Department and †Autoimmune Unit, Hospital de Curry Cabral, Lisbon, Portugal; and ‡Youth Project Association, Lisbon, Portugal*

Development of some immune-mediated disorders may depend on dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. To explore neuropsychologic mechanisms in relation to the abnormal endocrine reactivity in patients with systemic lupus erythematosus (SLE) and chronic hepatitis C (CHC) we used the corticotropin releasing hormone (CRH) test, the Minnesota Multiphasic Personality Inventory (MMPI), and the Edinburgh Inventory of Manual Preference Inventory (EIMP). Compared to controls, the adrenocorticotrophic hormone (ACTH) response to CRH was reduced in CHC, while SLE presented reduced baseline dehydroepiandrosterone sulfate levels; higher neurotic scores were found in SLE and higher behavior deviant scores in CHC. Peak ACTH levels were a significant factor for the MMPI profile variability, while the manual preference score was a significant factor for the ACTH response. Personality and manual preference contribute to neuroendocrine abnormalities. Different behavioral and neuroimmunoendocrine models emerge for these disorders. © 2001 Elsevier Science (USA)

Key Words: systemic lupus erythematosus; chronic hepatitis C; CRH test; Minnesota Multiphasic Personality Inventory; Edinburgh Manual Preference Index.

INTRODUCTION

Immunosuppressive effects of corticosteroids have long been used in clinical practice. More recently, it has been suggested that the intrinsic activity and/or reactivity of the hypothalamus-pituitary-adrenal axis (HPA) may be a relevant factor in the development of some immune-mediated disorders. Sternberg et al. (1989a, 1989b) first showed that the arthritis-susceptible Lewis rat presented a central nervous system defect of corticotrophin-releasing hormone (CRH) secretion, with minimal adrenocorticotrophic hormone (ACTH) and corticosterone response, after the intraperitoneal administration of streptococcus cell wall antigens. The development of the acute and chronic arthritis process could be prevented in that strain by prior administration of dexamethasone, while the usual resistant Fisher F344 rat could be rendered susceptible by the administration of corticosterone receptor antagonists like the experimental drug RU486. Since then, abnormal HPA axis reactivity has been shown in several animal models of immune disorders (Harbuz et al., 1999).

If an hyporeactive HPA axis is operative in the pathogenesis of immune-mediated diseases, the mechanisms for the decreased endocrine reactivity must then be sought. In animals and even more so in humans, neuropsychological factors may contribute

The first two authors contributed equally to this report.

¹ To whom correspondence and reprint requests should be addressed at Endocrine Department, Hospital de Curry Cabral, Rua da Beneficência, 8, 1069-166 Lisboa Portugal. Fax: 351-21-7969515. E-mail: rop25748@mail.telepac.pt.

to the intrinsic variability of HPA axis activity (Chrousos & Gold, 1992; Levine, 1993). Dysregulation of the HPA axis is known to occur in acute and chronic psychogenic stress (Chrousos & Gold, 1992; Levine, 1993) and has been systematically found in several psychiatric and psychosomatic disorders like major depression, anorexia nervosa, alcoholism, and chronic fatigue syndrome (Demitrack et al., 1991; Gold et al., 1986a, 1986b; Wand & Dobs, 1991). Such evidence suggests that cognitive and emotive modulation of HPA activity is relevant in human health and disease (Carlson, 1994; Evans, 1998).

Behavioral factors are being increasingly recognized as important in order to understand who gets sick and who recovers, one possible link being HPA activity (Adler & Matthews, 1994; Neveu, 1997; Potter & Zautra, 1997). In this regard, personality may be a global, integrative characteristic, suitable to explore relevant relations between behavior, neuroendocrine reactivity, and the immune system. Modern trait theories of personality consider hierarchical models beginning with specific behaviors and then proceeding at higher levels of abstraction and generalization to define habits, traits, dimensions and types that integrate the cognitive, affective, and motivational style of an individual (Digman, 1990; Zuckerman, 1991). Furthermore trait theories of personality directly support psychometric assessment which is fundamental to allow comparison between defined groups. Relevant associations may be found with neuroendocrine patterns, particularly when one considers temperament, a more basic and automatic set of behaviors, and less so with character, which may be more related to symbolic processing, learning, and culture (Zuckerman, 1991; Cloninger et al., 1993). The overall intrinsic activity and reactivity of the HPA is like personality, a constitutional parameter, with a strong genetic component and marked plasticity during critical development periods (Bertagna et al., 1994; Kirschbaum et al., 1992; Meaney et al., 1991), further reinforcing the possibility of relevant associations.

Neural lateralization is a general phenomenon as indicated by Geschwind and Galaburda (1985a, 1985b, 1985c) and depends on an asymmetric distribution for neurotransmitter systems and endocrine receptors (Glick et al., 1979; McEwen et al., 1979). In addition to the well-known laterality effects on cognitive functions like attention, language, and spatial and arithmetic talents, dramatically illustrated in stroke clinical syndromes, there is now experimental evidence in animals and humans for a sidedness effect on HPA reactivity (Geschwind & Galaburda, 1985a, 1985b, 1985c; Kim et al., 1999; Wittling, 1990; Wittling & Pfluger, 1990) that could be the missing link for the reported associations of autoimmune disorders and handedness (Geschwind & Galaburda, 1985a, 1985b, 1985c; Kang et al., 1991; McManus et al., 1990; Wood and Cooper, 1990). Furthermore, brain asymmetry has been related to cerebrospinal fluid CRH and serum cortisol levels and also to affective style and some immune parameters (Davidson, 1998; Davidson et al., 1999; Kalin et al., 1998, 2000). Central asymmetry may therefore be another relevant factor contributing to HPA reactivity.

To explore the mechanisms of abnormal HPA reactivity, it may be informative to compare personality, brain asymmetry, and HPA reactivity in two disorders, where different aspects of a dysfunctional immune response are key features.

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many organ systems (Hahn, 1997). Although a general activation of the immune system is considered to characterize SLE, there is evidence suggesting some inhibitory aspects of the overall immune dysfunction. In fact, antibody responses to exogenous antigens may be decreased (Hahn, 1997; Horwitz & Stohl, 1993) despite the increase

in total immunoglobulin production (Klinman et al., 1991); T-cells tend to have reduced ability to proliferate in response to mitogens (Hahn et al., 1982) and down-regulation of the activated T- and B-cell network by suppressor T cells has been described (Schifferli et al., 1989).

Infection with the hepatitis C virus is clinically silent in most cases, but its propensity to develop a chronic disease is as high as 50% (Dienstag, 1983; Goodman & Ishak, 1995). The high frequency of chronic disease seems to depend on an immunotolerance status that would allow for the persistence of the virus in blood and liver tissue. An imbalance between T cells (helper—types 1 and 2) response is considered a major factor for chronicity (Bertoletti et al., 1997). However, while most liver injury results from direct virus cytotoxicity, immune aggression reflecting immune activation may occur, presenting as cryoglobulinaemia, glomerulonephritis, or Sjörgen syndrome (Haddad et al., 1992; Misiiani et al., 1992).

The study of complex systems may require the analysis of individual components; however, a global integrated analysis is the only way to disclose relevant associations between such elements and is the logical approach in the clinical setting. The objective of this report is to characterize and contrast neuroendocrine reactivity, brain asymmetry, and personality in two disorders characterized by different immune abnormalities and to explore relevant interactions that could account for HPA variability and contribute to the formulation of specific models. Patients with SLE and CHC were studied and compared to a control group. The protocol included personality evaluation with the Minnesota Multiphasic Personality Inventory (MMPI), handedness assessment with the Edinburgh Inventory of Manual Preference (EIMP), and the ACTH/cortisol responses to CRH in addition to baseline prolactin (PRL) and dehydroepiandrosterone sulfate (DHEAS) measurements.

PATIENTS AND METHODS

Thirty consecutive subjects were included in this study. The following groups were defined, each including 10 subjects: Group A—patients with SLE using the criteria of the American College of Rheumatology (Tan et al., 1995); patients had not been treated with systemic or topic corticosteroid preparations for at least 6 months prior to the study and did not present evidence of clinically relevant hepatic or renal involvement (normal liver function tests and normal creatinine clearance). Group B—patients with CHC defined by liver histology and the isolation of HC virus mRNA using the polymerase chain reaction (Goodman & Ishak, 1995); none of the patients presented evidence of cirrhosis and all of them were in class A of the Child classification (Dienstag, 1983; Goodman & Ishak, 1995); medical treatment when appropriate was initiated only after completion of the research protocol. Group C—control subjects with simple multinodular goiter, with normal thyroid function tests [triiodothyronine (T_3), tiroxine (T_4), free thyroxine (fT_4), and thyroid stimulating hormone (TSH)] and negative values of thyroid autoantibodies (antithyroglobulin and antithyroid peroxidase); these patients were not being treated with thyroid hormone supplementation (Studer et al., 1989).

Patients were assisted at the outpatient department of a public central hospital and were referred by the family physician. A detailed medical report was obtained in every case as well as a routine hematological and biochemical profile and a 12-lead ECG and thorax X ray. Additionally, in every group analytical evaluation needed for the diagnosis and further workup of the patients was obtained according to the

medical standards. In the next follow-up visit, patients were fully informed of objectives and content of the research protocol and written informed consent was obtained. The research protocol was also approved by the Hospital Ethical Committee and fully complies with the Helsinki Declaration.

On 2 different days of the following week, as convenient for the patient, a visit to the Endocrine Department was arranged. On one of those days, the CRH test was performed after an overnight fast as follows: First, the patient was again informed of the procedure, and height and weight, resting blood pressure and heart rate were recorded while the patient remained in the supine position for 10 min; an antecubital vein was obtained and the venous line was maintained patent by the slow infusion of normal saline (less than 50 ml for the entire procedure); after 15 min a venous blood sample was obtained (sampling time 0) and CRH (human CRH, CRH Ferring GmbH, Kiel, Germany) was infused over 1–2 min (1 μ g/kg body wt); at 5, 10, 15, 30, 60, and 120 min, venous blood samples were again obtained. One of the authors performed the test, was always present, and recorded any side effects. Blood samples were collected in ethylenediaminetetracetic acid (EDTA) and glass tubes, immediately refrigerated at +4°C, and sent to the Endocrine Laboratory; serum or plasma were obtained in the next 2 h and kept frozen at –70°C until the assay within the next 2 weeks. ACTH and cortisol measurements were obtained at all time sampling moments, while DHEAS and PRL were measured only at baseline.

On the second day, the MMPI and the EIMP were taken (Montenegro, 1982; Oldfield, 1971); this took place in the morning, in a private room, with no time limit and the patient was left alone and undisturbed after a brief explanatory statement by one the authors. The tests were scored according to the appropriate booklet and authors instructions respectively; regarding personality evaluation using MMPI, in addition to individual scales scores, the following conventional superordinate traits were used: neurotic triad = hypochondria + depression + hysteria; psychotic dyad = paranoia + schizophrenia; behavior deviant = psychopathic deviate + masculinity-femininity + mania (Perse, 1986; Greene, 1991).

Immunoradiometric assay (IRMA) and enzyme-linked immunoassay (ELISA) methods were used for the measurement of ACTH (IRMA, Nichols Institute, San Juan Capistrano, CA), PRL (IRMA, Diagnostic Products Corporation, Los Angeles, CA), cortisol and DHEAS (ELISA, Diagnostic Products Corporation). The intra- and interassay variation coefficients were 9 and 7% for ACTH, 7 and 5% for cortisol, 9 and 8% for DHEAS, and 8 and 5% for PRL respectively. Other tests, including thyroid function tests, thyroid autoantibodies, liver enzymes, creatinine clearance, viral load, viral genotype, and liver histology, were performed using standard methodology; since they were only used for patient characterization and were not entered further in the analysis, specific methodology is not described.

Statistical analysis was performed with the Statistical Package for the Social Sciences Program (SPSS Inc., Chicago, IL). The area under the curve (AUC) for the ACTH and cortisol responses in the CRH test was computed according to the trapezoidal rule (Rowland & Tozer, 1995). Results are expressed as a percentage or as mean \pm standard deviation as appropriate. The normal distribution of continuous variables was verified by the Kolmogorov–Smirnov goodness-of-fit test. Nonnormal distributed variables were transformed using natural logarithms (ln) prior to analysis; however, when no major differences regarding the nontransformed variables were found, these are reported for the sake of simplicity. The chi-squared (χ^2) test, Stu-

dent's *t* test, and factorial analysis of variance (ANOVA) with post hoc *t* tests with the Student–Newman–Keuls correction for multiple comparisons were used to examine differences between groups as defined. The limit for statistical significance was 0.05 (Wonnacott & Wonnacott, 1990).

RESULTS

Patients clinical characteristics are summarized in Table 1. There were significantly more male subjects in the CHC group than in either the SLE or the control groups. Patients with SLE were also significantly older than patients with CHC or the control group.

For the sake of clarity, differences between groups are first presented.

Baseline endocrine measurements are summarized in Table 2 and Fig. 1. Baseline ACTH and cortisol levels were not significantly different between groups; there was, however, a statistical trend for lower baseline nondimensional ACTH/cortisol ratio in groups A and B combined versus group C (1.1 ± 0.8 vs 1.5 ± 0.6 , $t = 1.74$, $df = 28$, $p < .10$). DHEAS levels were significantly different by diagnostic group [$F(2, 28) = 3.688$, $p < .05$], with post hoc analysis showing significantly lower levels in SLE in relation to CHC and the control group (81 ± 100 , 200 ± 90 , and 177 ± 89 $\mu\text{g/dl}$, respectively, $t = 2.73$ $df = 28$, $p < .05$, A vs groups B and C combined).

TABLE 1
Clinical Characteristics of Subjects and Controls

	SLE	CHC	CONTROL
Sex (m/f)	2/8	7/3	2/8
Age (years)	44 ± 13	30 ± 5	25 ± 4
Years after diagnosis	6 ± 3	3 ± 3	NA
Organ involvement		NA	NA
Blood	3/10		
Vascular	2/10		
Skin	9/10		
Joints	10/10		
Kidney	1/10		
Lungs	3/10		
Ds-DNA (Ab) (+)	8/10	NA	NA
Viral Load (mEq/L)	NA	8.0 ± 8.6	NA
Viral genotype	NA		NA
1a		2/10	
1b		2/10	
3a		4/10	
4		2/10	
Liver histology ^a	NA		NA
Inflammation (0/1/2)		1/5/4	
Fibrosis (0/1/2)		1/8/1	
Medical treatment	HCQ—10/10	None	None
Contraceptive drug use	1/10	1/10	4/8
Illicit drug use	NA	9/10	NA

Results are expressed as the mean \pm standard deviation or as frequencies as appropriate. NA—non applicable; (m/f)—male/female; Ds-DNA (Ab) (+)—positive titers ($>1/40$) of double strand deoxyribonucleic acid antibodies; HCQ—hydroxychloroquine; ^a—as defined by Child (Goodman and Ishak, 1995).

TABLE 2
CRH Test—ACTH and Cortisol Responses

Min	SLE		CHC		CONTROL	
	ACTH (pg/ml)	Cortisol (µg/dl)	ACTH (pg/ml)	Cortisol (µg/dl)	ACTH (pg/ml)	Cortisol (µg/dl)
0	16 ± 10	17 ± 7	23 ± 17	20 ± 8	26 ± 27	16 ± 10
5	69 ± 88	17 ± 6	26 ± 21	18 ± 6	93 ± 134	15 ± 10
10	64 ± 102	20 ± 7	20 ± 21	19 ± 7	110 ± 140	18 ± 10
15	75 ± 75	20 ± 3	24 ± 13	21 ± 5	99 ± 113	19 ± 8
30	62 ± 50	23 ± 4	21 ± 14	22 ± 5	105 ± 116	23 ± 10
60	35 ± 17	23 ± 7	15 ± 5	24 ± 11	48 ± 50	23 ± 8
120	16 ± 13	18 ± 6	10 ± 4	18 ± 13	27 ± 31	16 ± 6
AUC*	39 ± 31	20 ± 5	16 ± 7	21 ± 8	65 ± 72	18 ± 4

Results are presented as the mean ± standard deviation; *AUC—area under the curve; for ACTH units are pg/ml.h. and for cortisol µg/dl.h

PRL baseline levels were lower in both disease groups than in the control group but the difference only reached the level of a statistical trend (7 ± 3 ng/ml vs 12 ± 9 ng/ml, $t = -1.95$, $df = 28$, $p < .10$, combining groups SLE and CHC).

ACTH responses to the CRH test are presented in Table 2 and Fig. 2. Significant responses were found both for ACTH [ANOVA of the ACTH by time of sampling $F(6, 204) = 2.522$, $p < .05$] and cortisol [ANOVA by time of sampling $F(6, 204) = 3.826$, $p < .001$]. The ACTH response was significantly different according to group diagnosis [ANOVA by group $F(2, 202) = 9.909$, $p < .001$] with no significant sampling time—diagnostic group interaction. ACTH response evaluated as the AUC was much lower in the CHC group (16 ± 7 pg/ml h) than in the SLE group ($39 \pm$

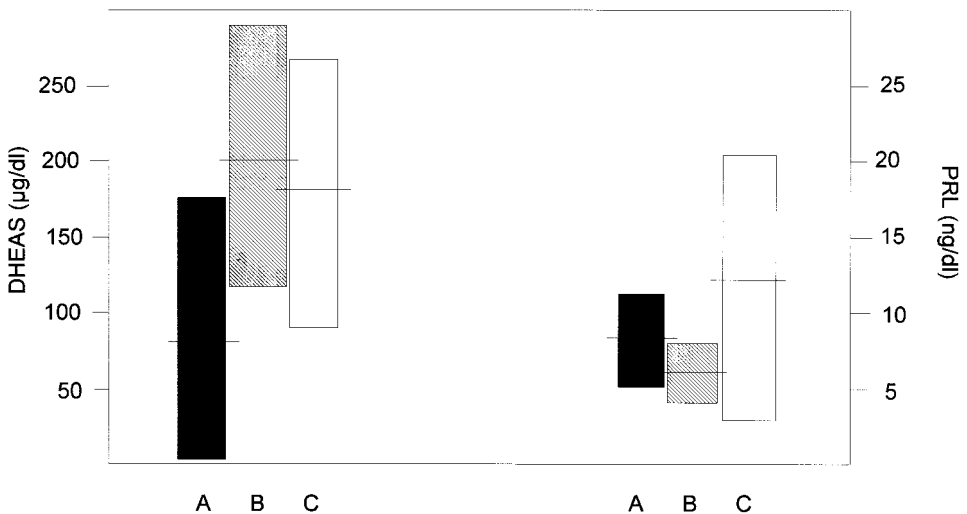


FIG. 1. Baseline measurements of DHEAS and PRL by diagnostic group. Values are indicated as the mean (horizontal line) ± standard deviation (closed box). Group A (SLE)—black; Group B (CHC)—dashed; Group C (Control)—white.

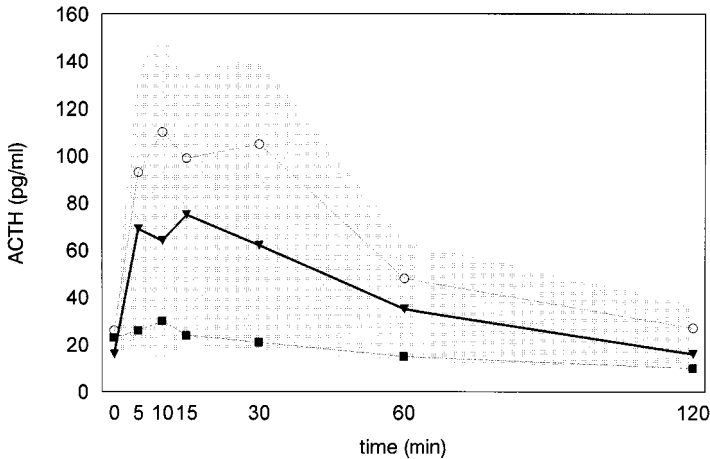


FIG. 2. ACTH response to CRH. Controls—fine line and empty circles; SLE—wide line and black triangles; CHC—fine line and black squares. The shadowed area extends from the highest mean plus the standard error of the mean to the lowest mean minus the standard error of the mean.

31 pg/ml h) or in the control group (65 ± 72 pg/ml h). For the ln-transformed AUC, a significant group effect was found [$F(2, 28) = 4.438, p < .05$] and post hoc analysis with the Student–Newman–Keuls correction showed significantly lower levels in group B in relation to either group A or C ($3.4 \pm 0.5, 4.2 \pm 0.7, \text{ and } 4.4 \pm 0.9$, respectively, for the ln-transformed values; $t = 3.37$ and $4.19, p < .05$ in both instances). For the cortisol response no significant differences were found according to group [$F(2, 202) = 0.232, ns$].

The results of the personality evaluation are indicated in Table 3; all test results

TABLE 3
Multiphase Personality Inventory (MMPI)—Standardized Results (t-score)

	SLE	CHC	CONTROL
Unanswered (?)	46 ± 3	46 ± 4	46 ± 2
Lie (L)	60 ± 13	47 ± 13	52 ± 10
Validity (F)	47 ± 6	53 ± 9	51 ± 15
Correction bias (K)	54 ± 9	52 ± 10	51 ± 9
Hypochondriasis (Hs)	$66 \pm 14^*$	50 ± 5	55 ± 14
Depression (D)	55 ± 11	56 ± 13	54 ± 8
Hysteria (Hy)	$63 \pm 8^*$	52 ± 8	54 ± 10
Psychopathic Deviate (Pd)	57 ± 9	$67 \pm 9^*$	54 ± 15
Masculinity-Femininity (Mf)	44 ± 11	54 ± 14	46 ± 11
Paranoia (Pa)	57 ± 14	60 ± 14	65 ± 13
Psychasthenia (Pt)	52 ± 7	59 ± 12	57 ± 10
Schizophrenia (Sc)	56 ± 10	62 ± 12	57 ± 15
Mania (Ma)	61 ± 10	61 ± 12	54 ± 12
Social Introversion (Si)	44 ± 8	49 ± 11	50 ± 11

Results are indicated as the mean \pm standard deviation. * $p < 0.05$ when compared to controls; since MMPI includes ten clinical scales, significance would not persist after correction for multiples comparisons.

were valid judging by the appropriate scales [Unanswered (?); Lie (L); Infrequency (F); Correction bias (K)]. ANOVA of superordinate traits, revealed significant differences among diagnostic groups for the neurotic triad [$F(2, 28) = 3.840, p < .05$] and of the behavior deviant scores [$F(2, 28) = 4.245, p < .05$]; post hoc analysis with the Student–Newman–Keuls correction revealed that patients with SLE presented significantly higher neurotic triad scores (185 ± 27) and patients with CHC presented significantly higher behavior deviant scores (182 ± 21) than the control subjects (163 ± 26 and 154 ± 27 , respectively, $t = 2.83$ and 3.79 , respectively, $df = 18, p < .05$ in both cases).

Manual preference indexes were not significantly different between diagnostic group (group A: 76 ± 26 ; group B: 66 ± 5 ; group C: 67 ± 25). For the whole sample there was a statistical trend for more males with manual preference indexes below the median of the observed distribution (lower dexterity: 7/3 in males vs 7/13 in females, $\chi^2 = 3.28, df = 1$, Fisher exact test $p < .10$); this was significant for groups A and B combined (6/3 vs 2/9, for males and females respectively, $\chi^2 = 4.85, df = 1$, Fisher exact test $p < .05$).

Finally the association of personality, brain asymmetry, and endocrine reactivity is presented.

The ACTH peak response in the CRH test (15 min) was dichotomized around the median of the nonnormal observed distribution; this new variable was a significant factor for the MMPI profile variability in addition to scale and group [$F(1, 404) = 4.335, p < .05$]. Using superordinate traits, high responders presented significantly lower neurotic triad scores than low responders (166 ± 31 vs $187 \pm 21, t = 2.07, df = 28, p < .05$) (see Fig. 3).

The manual preference index was also dichotomized around the median of the observed distribution; this new variable further contributed to ACTH response variability in the CRH test, in addition to time of blood sampling and diagnostic group

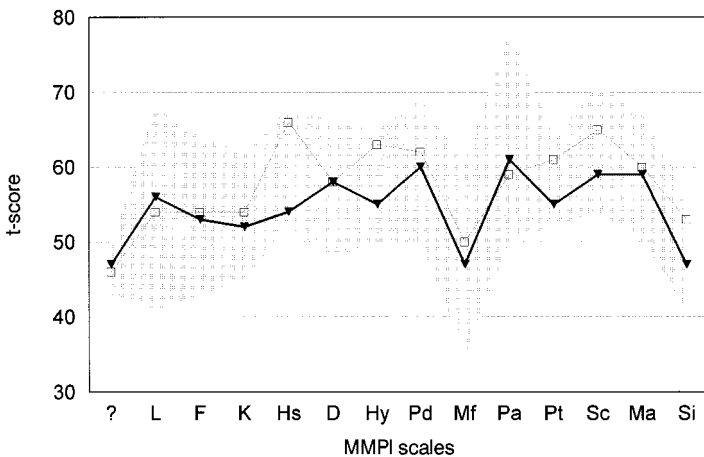


FIG. 3. Minnesota Multiphase Personality Inventory t-scores by ACTH response in the CRH test dichotomized around the median of the observed distribution. High-responders (i.e., \geq the median) are presented by the full line with full black triangles; Low-responders (i.e., $<$ the median) are presented by the dashed line with open squares. The shadowed area presents the mean \pm standard deviation of the mean for both groups.

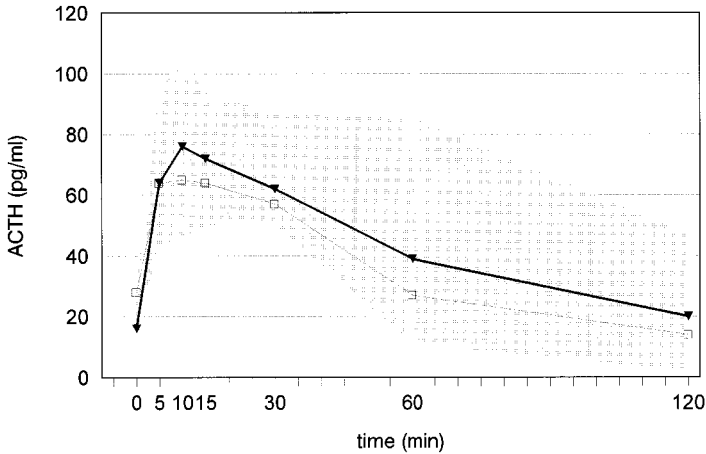


FIG. 4. ACTH response in the CRH test by the Edinburgh Manual Preference Index dichotomized around the median of the observed distribution. Higher dexterity (i.e., \geq the median) are presented by the full line with full black triangles; Lower dexterity (i.e., $<$ the median) are presented by the dashed line with open squares. The shadowed area presents the mean \pm standard error of the mean for both groups.

[$F(1, 201) = 4.094, p < .05$], with no significant time–manual preference interaction; patients with higher indexes (higher dexterity) always presented higher ACTH levels at all time points considered (except for the baseline levels) and this was also true for each group individually considered. The ratio between peak and baseline levels was significantly higher (4.9 ± 5.7 vs $2.1 \pm 1.4, t = 1.71, df = 28, p < .05$, one-tailed t -test) (see Fig. 4).

DISCUSSION

Recent research suggests that a defect in the intrinsic reactivity of the HPA is a relevant factor in the pathogenesis of some immune-mediated disorders (Harbuz et al., 1999; Sternberg et al., 1989a, 1989b). In humans, the mechanisms for such a hypothetical dysregulation of the HPA remain to be defined. However, marked abnormalities in several psychiatric and psychosomatic disorders along with marked activation in acute and chronic psychogenic stress (Chrousos & Gold, 1992; Levine, 1993) and some evidence for a sidedness effect on endocrine reactivity (Kalin et al., 1998; Kalin et al., 2000; Kim et al., 1999; Wittling, 1990; Wittling & Pfluger, 1990) suggest the possible relevance of central neuropsychologic factors. This could help explain reported associations between stress and handedness with some immune-mediated disorders (Kang et al., 1991; Neveu, 1997; Potter & Zautra, 1997).

This report attempts an integrated approach by simultaneously considering HPA reactivity, the personality profile, and manual preference. This methodology is used to contrast two distinct immune-mediated disorders and to explore relevant associations between neuropsychologic factors and neuroendocrine reactivity. General immune hyperactivity characterizes SLE while a state of relative immunotolerance is considered to allow for hepatitis C virus persistence in blood and liver leading to chronicity (Bertoletti et al., 1997; Hahn, 1997).

The initial focus of this report is the HPA reactivity, evaluated by the CRH test.

Although there were no differences concerning ACTH and cortisol baseline levels, the ACTH response was markedly and significantly reduced in patients with CHC; in fact there was almost no response. In SLE subjects, the ACTH response was more or less half that found in the control group, but was not significantly different from that found in either the control or CHC group. No differences were found in relation to the cortisol response.

This reactivity pattern suggests an increased adrenal sensitivity (since no difference was found on the cortisol response, despite much lower ACTH levels) with a greatly decreased pituitary sensitivity (almost no response to CRH). This same pattern has been consistently reported in several psychiatric disorders such as major depression and has been interpreted as indicating chronic stress with chronically increased central CRH secretion, down-regulation of pituitary CRH receptors, and a compensatory up-regulation of adrenal ACTH receptors (Dumser et al., 1998; Gold et al., 1986a, 1986b; Krishnan et al., 1991; Raadsheer et al., 1994). This interpretation is also reinforced by the statistical trend for a lower baseline ACTH/cortisol ratio found in both disease groups.

Decreased DHEAS levels were only found in SLE subjects. The reduction of this distinctive steroid level is consistent with chronic adrenal stimulation and seem to reflect adrenal adaptation with the shut-off of adrenal sex steroid and mineralocorticoid production (Dallman, 1993; Van Den Berghe et al., 1998). Finally and incidentally the slightly decreased PRL levels in both disease groups in relation to controls might be explained by a chronic stress condition, since in this condition, in contrast to acute stress, PRL levels are generally low, although the mechanism is not completely understood (Dallman, 1993; Van Den Berghe, et al., 1998).

In short, similar but not coincidental and complex abnormalities of the HPA axis were found in both disease groups. Increased levels of CRH (Chrousos, 1995; Irwin, 1993; Martins et al., 1997), and perhaps in conjunction with increased cortisol levels, which were not specifically sought in this report, but as in other disorders with decreased ACTH response might presumptively occur and be reflected in 24-h urinary cortisol excretion (Gold et al., 1986a, 1986b; Chrousos & Gold, 1992; Dallman, 1993; Van Den Berghe et al., 1998), should favor immunosuppression; this would be more marked in CHC subjects. Immunosuppression would be further exacerbated by the decreased DHEAS and PRL levels (Alves et al., 1998; Berczi, 1997; Labrie et al., 1997); this would be more marked in SLE subjects. Endocrine evaluation therefore suggests that in both conditions there is evidence of HPA dysregulation and of endocrine changes favoring immunosuppression/tolerance, albeit for different reasons.

Age and sex differences between groups do not seem to be able to account for endocrine abnormalities previously reported; despite age differences, all subjects were non-old adults, and gender is a minor influence on HPA reactivity at the clinical level (Born et al., 1995). In particular, decreased DHEAS levels are known to occur in old age and in severe chronic diseases and to have prognostic significance (Labrie et al., 1997; Orentreich et al., 1992); however, it is difficult to consider age to account for such differences since the progressive decline only occurs after the age of 45 and is slow, around 3% per year (Orentreich et al., 1992). Clinical status, considered in addition to the specific underlying condition, also does not seem to readily explain these differences. Both patient groups were without major active systemic manifestations as indicated by the absence of steroid therapy in SLE patients and inclusion in class A of the Child system for CHC subjects. Although hydroxychloroquine was

being used in SLE subjects, to our knowledge no previous reports have described any influence of this drug on DHEAS levels.

Results from this psychometric evaluation raise important new points that may help in interpreting previous neuroendocrine findings.

Personality evaluation, using a time-proven method like the MMPI, revealed significant differences between groups, despite the small number of subjects in each one. In addition to its importance in the psychiatric setting, the MMPI has also been validated in the general population, and its interpretation can be made along classic personality dimensions (Costa et al., 1986); its use in the present report is further justified given the available data regarding the CRH test in several psychiatric and psychosomatic disorders (Chrousos & Gold, 1992; Demitrack et al., 1991; Gold et al., 1986a, 1986b; Wand & Dobs, 1991). It should be noted that the original MMPI version was used instead of the revised form, the MMPI-2, since no standardized translation exists yet for the Portuguese language and also because the present report is part of a continuing project that has been using that version. Since the MMPI includes 10 clinical scales to avoid multiple comparisons, conventional superordinate traits were used instead.

Patients with CHC presented a distinctive deviant superordinate behavior trait (Perse, 1986; Greene, 1991), significantly different from what was found in the control group or in SLE subjects. This profile is generally associated with marked impulsivity, risk taking, and sensation-seeking behavior and may be casually related to the illicit drug use found in 9 of 10 subjects in that group (Greene, 1991; Zuckerman, 1984). Interestingly enough, chronic alcoholism has been associated with a decreased ACTH response with a normal cortisol response in the CRH test (Wand & Dobs, 1991), such as the one found in this study, and this may be considered a similar condition as drug addiction (Koob et al., 1998).

Significantly higher neurotic scores were found in SLE subjects and no simple explanation seems available, although this is supported by other reports (Liang et al., 1984); a simple illness reaction does not seem probable since the other subjects were also clinical groups. As noted a distinctive association between personality and the ACTH response was found in this report such that subjects with high ACTH responses in the CRH test presented lower neurotic scores; therefore high neurotic scores found in SLE subjects may contribute to the nonsignificant reduction in the ACTH response.

A final remark is relevant regarding manual preference. Although as expected males more frequently presented lower manual preference indexes, indicating relative sinistrality, we could not confirm the more common sinistrality described in several autoimmune disorders like myasthenia gravis or Hashimoto's thyroiditis, for instance (Annett, 1970; Geschwind & Galaburda, 1985a, 1985b, 1985c; McManus et al., 1991; Wood & Cooper, 1990); however, the sample size is small to begin with and furthermore hand preference is only a component of the more general asymmetry of cortical functions, which may not completely reflect that pattern (Annett, 1970; Geschwind & Galaburda 1985a, 1985b, 1985c).

However, a significant association was again found between manual preference and the ACTH response to CRH such that patients with higher scores, i.e., more marked dextrality, presented higher incremental responses; this was also true, although not significant when each group was considered individually. The fact that this is a minor effect is not surprising, since psychoneuroendocrine relations and

constraints are by nature soft ones. Present results agree with the pioneering work of other groups (Wittling, 1990; Wittling & Pfluger, 1990). This may be relevant, since if left-handedness is indeed more common in some immune-mediated disorders, then this may be a factor contributing to an hyporeactive HPA axis in those conditions that, as indicated, may contribute to the pathogenesis of those disorders.

In conclusion, an integrated psychoneuroendocrine approach to two disorders with different immune abnormalities reveals common and contrasting findings. Reduced ACTH response to CRH is found in CHC patients and much less markedly and not significantly so in SLE. Significantly decreased DHEAS levels are found only in SLE. Both groups present slightly reduced PRL levels. Both present endocrine changes favoring immunosuppression, albeit for different reasons. In both SLE and CHC personality factors and neural asymmetry are relevant factors for HPA reactivity in addition to the specific pathologic condition. Despite the significant differences and associations now reported, the small number of subjects in each group is a significant drawback, even if it argues for the magnitude of the effects; these conclusions must therefore be substantiated by other larger scale studies.

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