Eur Arch Psychiatry Clin Neurosci (2004) 254 : 349–355 DOI 10.1007/s00406-004-0512-3

ORIGINAL PAPER

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HPA axis activation determined by the CRH challenge test in patients with few versus multiple episodes of treatment-refractory depression

Received: 25 June 2003 / Accepted: 15 February 2004 / Published online: 12 November 2004

Abstract *Objective* In clinical guidelines, risk factors for a malignant illness course include 3 or more lifetime episodes of depression. Our aim was to investigate the activation of the hypothalamic-pituitary-adrenal hormonal axis in treatment-refractory affective disorder in pauciepisodic (one or two episodes) versus multiepisodic (three or more episodes) patients. *Methods* We evaluated the HPA axis in 37 patients with treatment-refractory affective disorder and in 27 healthy volunteers by measuring adrenocorticotropin hormone (ACTH) and cortisol responses following administration of corticotropin-releasing hormone (CRH). In retrospective life charts was recorded every previous illness episode for each patient. *Results* Seven of the patients were pauciepisodic and 30 were multiepisodic. The pauciepisodic patients had significantly larger peak and total ACTH responses to CRH compared to the multiepisodic patients as well as to the control group. Multiepisodic patients showed no difference compared to controls in ACTH secretion pre- and post-CRH. Cortisol secretion was the same in all three groups. *Conclusions* The pituitary adrenocortical responses were stronger in pauciepisodic patients than in multiepisodic patients and in volunteers. This cross-sectional study suggests that the HPA axis, in refractory multiepisodic affective disorders, might weaken its original activity as the illness recurs with more episodes.

Key words life charting · treatment-refractory depression · HPA axis · CRH stimulation test · ACTH

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Introduction

Dysactivation of the hypothalamic-pituitary-adrenal (HPA) axis in patients with major depression is one of the more robust and consistent findings in biological psychiatry (Holsboer 1987, 1995). HPA axis alterations are believed to be secondary to hypersecretion of corticotropin-releasing hormone (CRH) (Nemeroff 1996). CRH is surmised to have behavioral effects in animals that are similar to those seen in depressed patients, including alterations in activity, appetite and sleep (Owens and Nemeroff 1993). Some studies have reported elevations of CRH concentration in the CSF of depressed patients (Banki et al. 1987; Nemeroff et al. 1984). In humans as well as in nonhuman species, the HPA axis is an important component of the stress response apparatus (Aston-Jones et al. 1994; Cullinan et al. 1995) and one way to conceptualize depression is to define it as a condition of pathological stress response.

Increased production of cortisol measured by 24-hour urinary free cortisol and a failure to compress cortisol production after treatment with dexamethasone have been shown in as many as 50 percent of patients with major depression by a number of early investigations (Carroll et al. 1976; Sachar et al. 1970; Stokes et al. 1975). The finding has been explained by assuming that episodes of glucocorticoid hypersecretion occurring during severe depression result in the HPA system feedback loop becoming refractory (possibly at a supra-pituitary level) to the glucocorticoid (GC) signal. GC hypersecretion is associated with high plasma ACTH concentrations (Herevanian et al. 1983), which in turn is believed to be regulated by CRH (Nemeroff 1996).

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The CRH challenge methodology is a complementary way to study the HPA axis. Such studies have earlier reported blunted ACTH response, but levels of cortisol have been normal in response to CRH stimulation in depressed unipolar and bipolar patients (Gold et al. 1984; Holsboer et al. 1984, 1986, 1987). The findings have been interpreted as a down-regulation of pituitary CRH receptors (Gold et al. 1988; Nemeroff 1996). Adrenocortical hyperplasia may develop after prolonged depression-related hyperstimulation by ACTH, possibly mediated by adrenal growth factors (Nemeroff et al. 1992). As a result, depressives would require less ACTH to induce release of the same quantity of corticosteroids as normal controls would.

In "naturalistic" follow-up studies of treatments of depression, three or more earlier episodes indicated a more rapid relapse rate (Keller et al. 1982). In clinical guidelines, risk factors for a malignant illness course, and consequently an increased emphasis on active maintenance-phase treatment, include 3 or more lifetime illness episodes of depression (Bauer et al. 2002; Kennedy et al. 2001; Reesal and Lam 2001). For bipolar disorder, a total of two previous episodes is the best minimum criterion for lithium prophylaxis (Grof et al. 1979). The underlying biology of this clinical distinction between more or less than 3 episodes is not clearly defined but might be understood by the concepts of *allostasis* and *allostatic load*. The term *homeostasis* captures the idea of a physiological set-point that is re-established after stress. Allostasis is a term that incorporates change in the physiological systems and the anticipation of change, resulting in a new set-point for physiological end-points. This new set-point is the result of the stress endured by the body, the allostatic load (McEwen 1995a, b). In other words, allostatic load refers to the hidden price paid when an individual is under continuing stress, and in the case of depression, the allostatic load may be the depression itself (McEwen 1995a). In a related illness–posttraumatic stress disorder (PTSD)–the biological systems of the HPA axis seem to adapt to a new level (allostasis, as opposed to homeostasis) (Yehuda et al. 1995) as a sequel of the stress response.

Our aim was to evaluate the HPA axis in patients with severe treatment refractory affective disorder by means of the CRH challenge test, and further relate this to the course of illness, as measured by more or less than 3 affective illness episodes over the entire life span. We defined the patients having had one or two illness episodes as *pauciepisodic* and those with 3 or more episodes as *multiepisodic*. Earlier studies have not addressed the question whether few versus many affective illness episodes is important for the outcome of the adrenocortical response to CRH.

Methods and materials

Life charting method

A Swedish computerized life-charting program was used, as previously described (Ehnvall and Ågren 2002), based on the original idea from Adolf Meyer (Meyer 1948) and the Post procedure (Roy-Byrne et al. 1985).

Patients

Thirty-seven consecutive patients were admitted following their informed consent over a three-year period (1994–1997) to a Treatment-Refractory Affective Disorder Program at the Sahlgrenska University Hospital at Mölndal, Sweden. All patients were characterized by refractoriness to at least two full-dose pharmacological antidepressant therapies for at least 6 weeks duration and they had been referred to the program for an extensive evaluation, frequently secondary or tertiary referrals. The research protocol was approved by the Ethics Committee of the Medical Faculty at Göteborg University.

The study sample consisted of 17 males aged 48.8 ± 14.1 years (mean ± SD), and 20 female patients aged 46.5 ± 11.3 years. All patients met DSM-IV criteria for major affective disorder (American Psychiatric Association 1994). The severity of depression was measured using the Schedule for Affective Disorders and Schizophrenia, SADS (Endicott and Spitzer 1978). From this scale, the score on the Hamilton Depression Rating Scale, HDRS was extracted (Endicott et al. 1981), comparable to the HDRS scale with 21 items. The HDRS score range for mild depression is 7–17, for moderate depression 18–24, and for severe depression > 25. Mean Hamilton score for worst week of the most recent depressive episode for the whole sample was 25.6 ± 5.4. Mean Hamilton score for past week for the whole sample was 19.3 ± 5.9. Twenty-eight patients suffered from unipolar depressions and 9 had bipolar disorders. Within the group of bipolar disorders, 3 had bipolar I, and 6 had bipolar II disorder. The great majority of the subjects were outpatients at the time of evaluation.

At the time of the investigation, all subjects had been off any antidepressant or neuroleptic medication for at least two weeks. No subject suffered from any psychotic symptoms, and individuals with substance abuse or dependence within the past 6 months were excluded. Medical history and examination indicated that all the patients were in reasonable health with no evidence of endocrine, severe cardiac, hepatic or neurological disease.

Comparisons of group means for measures on illness course in the study sample revealed that these affectively ill patients formed an especially difficult-to-treat subgroup of affectively ill individuals; see Table 1.

Twenty of the 37 patients had received lithium prophylaxis for longer or shorter periods. Seven of the patients had only had one or two illness episodes, even though these had been long lasting (mean 4.4 ± 3.7 years) and difficult to treat. We defined this patient group as pauciepisodic, and those with 3 or more episodes as multiepisodic. Fig. 1 demonstrates the results from applying different cut-offs in terms of differences in the two ACTH variables. The distinction set at < 3 *versus* ≥ 3 episodes turned out clearly significant differences in both $ACTH_{peak}$ and the $ACTH_{AUC}$, see below.

The pauciepisodic group was exclusively composed of unipolar patients, whereas the multiepisodic group consisted of 9 bipolar and 21 unipolar patients. Analyses of variance (ANOVA), and the Scheffé post hoc test between group pairs were used for comparing CRH challenge test variables between unipolar patients in the pauci- and multiepisodic groups and the multiepisodic bipolar patients. There were no significant differences in any of the above variables between multiepisodic uni- and bipolar patients. Consequently, we labeled this group "multiepisodic".

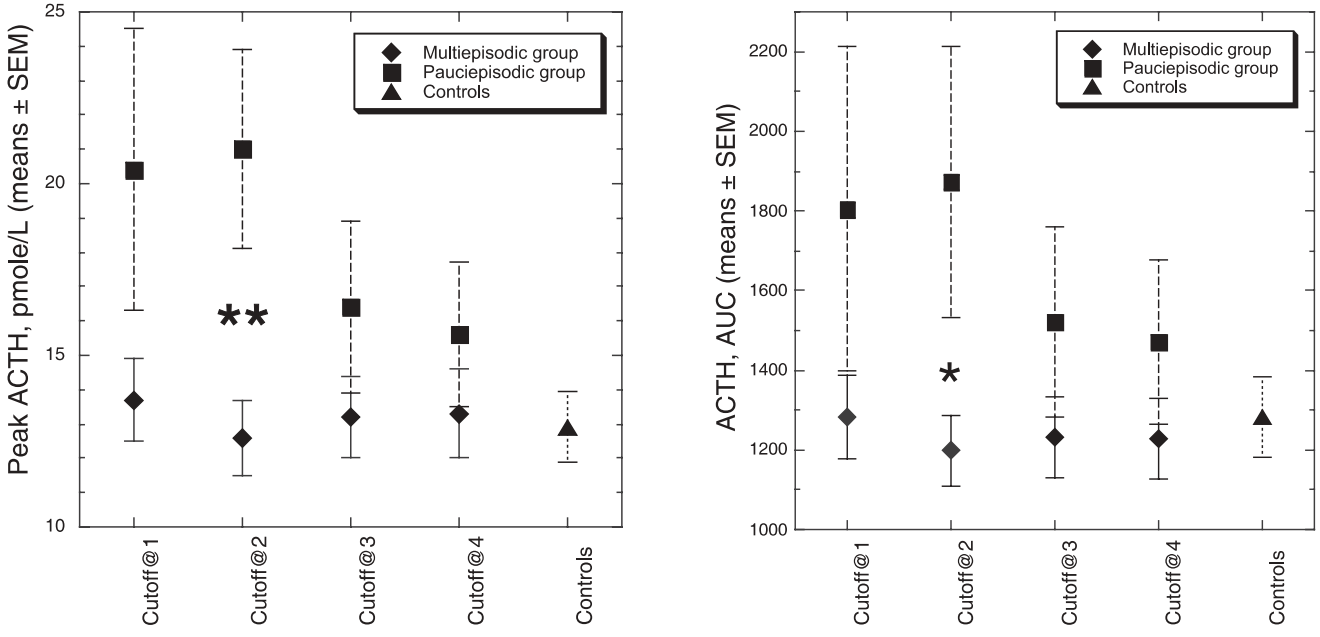
Healthy volunteers

Twenty-seven paid healthy volunteers served as control subjects: twelve males aged 38.7 ± 12.3 years (mean ± SD), and fifteen females

Table 1 Background variables from patients with treatment-refractory affective illness and healthy control subjects

	Multiepisodic Patient Group, $n = 30$ (mean ± SD) M	Pauciepisodic Patient Group, $n = 7$ (mean ± SD) P	Controls $n = 27$ (mean ± SD) C	Statistics
Females, *n*	18	2	15	χ^2, NS
Males, *n*	12	5	12	χ^2, NS
Age, years	48.8 ± 13.4	42.3 ± 6.6	37.3 ± 11.3	ANOVA – Scheffé post hoc: M = P P = C M > C, $p = 0.003$
Age at first episode (years)	30.5 ± 15.6	28.6 ± 5.3		*t* test, NS
Duration of illness (years)	18.3 ± 11.0	13.7 ± 8.5		*t* test, NS
Total time spent in illness (years)	5.9 ± 3.1	4.4 ± 3.7		*t* test, NS
Percent of life spent in illness episodes	12.5 ± 6.1	11.1 ± 10.1		*t* test, NS
Percent of life spent in illness episodes since onset	43.2 ± 27.0	46.4 ± 41.7		*t* test, NS

Pauciepisodic group: < 3 episodes
Multiepisodic group: ≥ 3 episodes



Cutoff @ 1 = Pauciepisodic group ≤ 1 episodes, n = 3 and 34
Cutoff @ 2 = Pauciepisodic group ≤ 2 episodes, n = 7 and 30
Cutoff @ 3 = Pauciepisodic group ≤ 3 episodes, n = 12 and 25
Cutoff @ 4 = Pauciepisodic group ≤ 4 episodes, n = 15 and 22
Controls, n = 27

Fig. 1 The treatment-refractory affectively ill patients with a cut-off value at less than three episodes had significantly higher $ACTH_{peak}$ and $ACTH_{AUC}$ as compared to those having three or more episodes

aged 36.2 ± 10.8 years. Mean age was significantly lower than the multiepisodic group of patients described above, but not significantly different from the pauciepisodic group. The possible importance of age in various comparisons was covaried out by ANCOVAs.

The volunteers were recruited among hospital staff, medical students and staff at the Volvo Company in Gothenburg. In order to be accepted, the control subject had to deny a history of psychiatric illness in him- or herself, parents and siblings, and be physically and psychiatrically healthy. With the exception of oral contraceptives, no drugs were allowed.

The CRH challenge test

The subjects fasted for 13 h (except for water) and refrained from smoking. At 14:30 h an intravenous (IV) catheter was inserted into an antecubital vein and kept open with normal saline. Blood was drawn for the determination of ACTH and cortisol concentrations at −240 (15:00 h), −180, −120, −60, 0, + 15, + 30, + 45, + 60, + 90, + 120, + 150, and + 180 minutes, with the subjects in supine position. At 19:00 h (0 minutes), when the HPA axis is normally quiescent, a bolus of 100 μg of synthetic human CRH was injected (Ferring, Arzneimittel GmbH, Kiel, Germany). The IV was removed at 22 h. The samples were immediately placed on ice and centrifuged at 4°C and 2500 × g for 10 min within 1 h of collection. Plasma was carefully separated and stored at −20°C until assayed. No major adverse effects on heart rate, blood pressure or respiratory rate were recorded. Approximately 50 percent of the subjects experienced a transient upper body and facial flush, which disappeared after 5–15 min.

Hormone assay procedures

Serum ACTH and plasma cortisol concentrations were determined by radioimmunoassays (RIA). ACTH was analyzed with reagents from Euro-Diagnostica (Malmö, Sweden) following vendor's instruction. Cortisol was measured using rabbit antiserum raised against human cortisol in a final dilution of 1:80000. The interassay coefficient of variation was 12 percent, range 2 to 40 (Ekman et al. 1993).

Calculation of hormone variables

The stimulated plasma ACTH and cortisol elevations after the IV CRH bolus injection were reduced to two variables. The baseline ACTH, or cortisol, level was identified as the mean pre-CRH value at −60 and 0 minutes before bolus injection. First, the maximum value of ACTH or cortisol was selected from the + 15 to + 90 min values, and designed the *peak value*. Second, the Area-Under-the-Curve (AUC) of the ACTH and cortisol values after CRH injection was calculated by simple triangulations programmed into Excel functions.

Statistical analyses

All variables in focus were analyzed as for deviation from statistical normality by inspection of frequency histograms on the combined patient-and-control dataset. Normalizing transformations using square root was carried out when needed, allowing the use of standard parametric procedures. The results are only presented as non-transformed measures.

Analyses of covariance (ANCOVA), and Scheffé post hoc tests between group pairs were used for comparing CRH challenge test variables between the two patient subgroups and controls, taking age into account as a covariate. Repeated-measures ANOVA tests were performed over time to compare hormonal swings between groups. *t* tests were used to compare severity of depression between pauci- and multiepisodic patients and also for comparing background variables between the two groups. Pearson correlation analyses were used to correlate number of illness episodes and $ACTH_{AUC}$ and $cortisol_{AUC}$, respectively. χ^2 tests were used to compare the gender distribution between patients and control group.

Results

A clear majority of the patients had spent several years of their life in illness, and similarly, a large proportion of their lives in illness since onset of the illness (see Table 1). Only one pauciepisodic patient had spent less than a year in illness. Thus, we calculated the CRH stimulation test results for ACTH and cortisol both with and without this patient. There was no change in any significant difference after exclusion of this patient. Consequently, we present the results with this patient included (see Table 2).

Altogether, the patients had suffered 324 illness episodes. Psychopharmacological treatment had been given in 274 (85 percent) of these illness episodes (antidepressant medication for depressive episodes, and neuroleptics/lithium for manic episodes). There was no significant correlation between number of illness episodes and the $ACTH_{AUC}$ and the $cortisol_{AUC}$, respectively. No difference was found in past week extracted Hamilton scores between pauci- and multiepisodic patients (scores 20.6 ± 3.4 *versus* 19.1 ± 6.3). Due to a significant age difference between the samples (the multiepisodic patients being older than the controls, see Table 1), age was always accounted for as a covariate in doing between-group comparisons.

First, we compared the whole group of patients ($n = 37$) with the controls ($n = 27$). There were no significant differences in any of the hormonal measures (see Table 2). As noted above, the distinction set at < 3 *versus* ≥ 3 episodes elicited clearly significant differences in both peak $ACTH_{Peak}$ and $ACTH_{AUC}$ (Fig. 1). This cut-off value was therefore chosen as a categorical definer in comparing patient subsamples based on chronological principles. There was no significant difference in mean $ACTH_{Peak}$ between unipolar multiepisodic (mean ± SD; 12.0 ± 4.4 pmole/L) and bipolar multiepisodic (14.1 ± 8.8 pmole/L) patients. Thus, these two groups were pooled into one group of multiepisodic patients.

The pauciepisodic group yielded significantly higher values than the controls and the multiepisodic group on both ACTH measures, the peak as well as the AUC (Table 3). There were no significant differences between the three groups in baseline ACTH. Moreover, the baseline cortisol as well as the post-CRH values did not differ significantly between the three groups.

Fig. 2A portrays the continuous ACTH and cortisol values before and after the CRH challenge test. Analyses with repeated-measures ANOVAs taking the entire time course into account and thus adjusting for baseline dif-

Table 2 CRH stimulation test results: Serum ACTH (pmol/L) and cortisol (nmol/L) values: All patients versus normal controls

	Patient Group, $n = 37$ (mean ± SD)	Controls $n = 27$ (mean ± SD)	ANCOVAs with age covaried out Scheffé's *post hoc* test:
Baseline ACTH	3.39 ± 1.79	2.85 ± 1.35	NS
$ACTH_{Peak}$ post CRH	14.21 ± 7.06	12.92 ± 5.36	NS
$ACTH_{AUC}$ post CRH	1326 ± 627	1284 ± 525	NS
Baseline cortisol	151 ± 68	124 ± 67	NS
$Cortisol_{Peak}$ post CRH	542 ± 152	508 ± 112	NS
$Cortisol_{AUC}$ post CRH	65649 ± 23735	63587 ± 17974	NS

Table 3 CRH stimulation test results: Serum ACTH (pmol/L) and cortisol (nmol/L) values: Multiepisodic patients versus pauciepisodic patients versus normal controls

	Multiepisodic Patient Group, $n = 30$ (mean ± SD) M	Pauciepisodic Patient Group, $n = 7$ (mean ± SD) P	Controls $n = 27$ (mean ± SD) C	ANCOVAs with age covaried out Scheffé's *post hoc* test:
Baseline ACTH	3.18 ± 1.88	4.26 ± 1.10	2.85 ± 1.35	M = P = C (NS)
$ACTH_{Peak}$ post CRH	12.63 ± 5.96	21.00 ± 7.81	12.92 ± 5.36	M < P ($p = 0.005$) P > C ($p = 0.007$) M = C (NS)
$ACTH_{AUC}$ post CRH	1198 ± 482	1874 ± 899	1284 ± 525	M < P ($p = 0.014$) P > C ($p = 0.039$) M = C (NS)
Baseline cortisol	154 ± 69	135 ± 62	124 ± 67	M = P = C (NS)
$Cortisol_{Peak}$ post CRH	545 ± 158	528 ± 128	508 ± 112	M = P = C (NS)
$Cortisol_{AUC}$ post CRH	66636 ± 24615	61419 ± 20634	63587 ± 17974	M = P = C (NS)

Pauciepisodic group: < 3 episodes
Multiepisodic group: ≥ 3 episodes

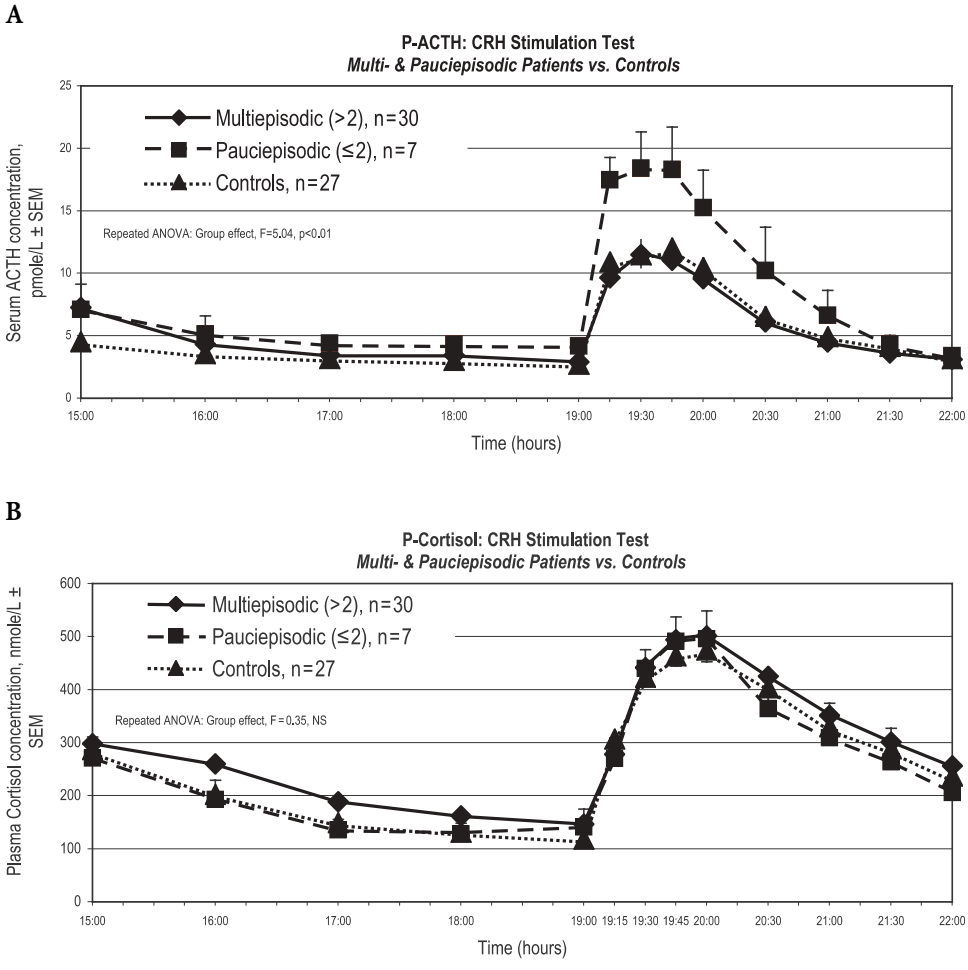


Fig. 2 **A** The pauciepisodic group with less than three episodes showed a significantly increased plasma ACTH response to CRH stimulation as compared with both the multiepisodic group and the control subjects. **B** There were no significant differences in plasma cortisol response to CRH stimulation between the pauciepisodic, multiepisodic, and control groups

ferences, demonstrated, again, that the pauciepisodic patients had a significantly higher CRH-stimulated ACTH increase than multi-episodic patients or controls (between-groups $F = 5.04$, $p < 0.01$). The cortisol increases did not differ significantly between the groups (Fig. 2B).

Discussion

A principal finding reported in this cross-sectional study is that a patient with severe treatment-refractory affective illness suffering from his/her first or second ill-

ness episode (i. e., being pauciepisodic) can be expected to have a hyperactive ACTH response on the CRH challenge test, as compared to a similar patient suffering from his/her third or later episode (i. e., being multiepisodic). Due to the small number of pauciepisodic patients, we can only discuss the findings in a preliminary fashion, and replication in a longitudinal study is obviously necessary.

The CRH challenge responses of these pauciepisodic affective patients are consistent with the HPA axis changes reported in animal studies on the effects of chronic stress (Kaufman et al. 1997; Marti et al. 1994; Uehara et al. 1989). These animal studies have repeatedly shown that initial exposure to a stressor is associated with a marked rise in cortisol and ACTH secretion. With ongoing exposure to the stressor, animals adapt and cortisol and ACTH levels return to baseline; however, with exposure to a novel stressor or in response to exogenous CRH administration, chronically stressed animals have a significantly *augmented* ACTH response. Cortisol responses under these conditions have been found to be either normal or somewhat elevated. In other words, the rise in ACTH response seen in the subgroup of depressed individuals can perhaps be explained by this group being exposed to previous chronic stress, i. e. the episode of depression itself, and thus have a significantly augmented ACTH response. These findings could presumably reflect the initial response to stress in affective disorder, seen early in the illness course.

The second main finding is that the initial ACTH response seems to shift to a new biological set-point as the individual experiences three or more illness episodes. Earlier studies have reported higher mean basal cortisol values as well as a blunted ACTH response, but a normal cortisol response to CRH stimulation in depressed unipolar and bipolar patients (Gold et al. 1984, 1988; Holsboer et al. 1986, 1987; Nemeroff 1996).

In the group of multiepisodic patients there were no significant patient-control differences in CRH-stimulated ACTH or cortisol responses. Neither were there any differences in basal plasma cortisol values. One possible reason for this difference could be that our patients form an especially difficult-to-treat subgroup of affectively ill individuals, and the "wear and tear" of their illness may have affected their HPA axis to a shift from homeostasis to an allostatic state. Alternatively, this subgroup of affectively disordered patients may have an altered HPA axis function to start with, being more reactive in the early, as opposed to the late illness course. Few studies have related biological findings to illness course. In one former study on chronic depression (Watson et al. 2002) no significant differences were found in HPA axis activity between patients and controls. Our group have previously reported this very group of difficult-to-treat affectively disordered patients to be marked by an increased activation of brain catecholamine turnover, positively correlated with increasing lifetime burden of mood swings (Ehnvall et al. 2003), as well as displaying a pattern of kindling over the illness course (Ehnvall and Ågren 2002). Thus, there are indications that several neurobiological systems are altered in patients suffering from refractory affective disorders.

We failed to demonstrate any significant differences between our multiepisodic group and controls with respect to both basal and stimulated plasma ACTH and cortisol. A similar non-difference has been reported in chronic schizophrenia, another illness with a distinctly multiepisodic course (Chappel et al. 1986; Roy et al. 1986). Our observations in multiepisodic affective disorder as well as those in chronic schizophrenia could suggest that the HPA axis actually functions normally, similar to healthy control subjects. This is a hypothetical explanation offered for schizophrenia (Banki et al. 1987). However, it might also reflect the HPA axis functioning in a "normal-like" state with altered regulatory mechanisms when compared to healthy controls. A tentative hypothesis would be that the chronicity as well as the allostatic load of the illness itself would help explain why two clinically quite different states of illness such as advanced affective disorder and schizophrenia might demonstrate similar findings on the CRH challenge test. This might also offer a neurobiological understanding of clinical experienced knowledge that has led to guidelines stating that clinicians should emphasize active treatment in multiepisodic patients (Bauer et al. 2002; Kennedy et al. 2001; Reesal and Lam 2001).

It is important to design future prospective studies in order to address the question of long-term effects on the HPA axis in severe treatment refractory affective disorder. The possible shift from homeostasis to allostasis occurring after transgressing a certain number of depressive episodes needs to be explored in depth.

Limitations

The retrospective and cross-sectional nature of the study is an obvious limitation, as we allow the different patients to represent the illness course of one single patient. Also, the number of subjects in the study is relatively small.

Acknowledgements We wish to thank Ms Ewa Ericson and the nursing staff for expert help in handling patients and test results at Mölndal Hospital. We also wish to thank the staff at the Research and Development Unit, Varberg Hospital, for their kind cooperation, and the staff at the Varberg Hospital Library for their excellent assistance. AE was supported by the Gothenburg Medical Association and Stockholm City Council Research and Development Unit. HÅ was supported by the Swedish Medical Research Council and funds from the Karolinska Institutet.

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