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Dysregulation of the Hypothalamic-Pituitary-Adrenocortical System in Panic Disorder

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The responsiveness of the hypothalamic-pituitary-adrenocortical (HPA) system was investigated with the combined dexamethasone-corticotropin-releasing hormone (DEX-CRH) challenge test in 13 patients with "pure" panic disorder. After DEX pretreatment, this group of patients had higher CRH-induced adrenocorticotrophic hormone (ACTH) and cortisol levels than the control group, but lower levels than a reference group of depressed patients. The panic disorder patients were also in a middle position in the ratio of suppressors to nonsuppressors on the dexamethasone suppression test (DST) and in the ratio of normal to abnormal results on the DEX-CRH test. Our results using the combined DEX-CRH test, which is known to be much more sensitive than the original DST, support the hypothesis that HPA system functioning is altered in panic disorder patients and that this dysregulation is directly involved in the pathogenesis of the disorder.
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KEY WORDS: *Panic disorder; Major depression; Dexamethasone-corticotropin-releasing hormone (DEX-CRH) challenge test; ACTH; cortisol.*

Panic disorder is one of the most impressive "stress-related disorders" currently encountered in clinical settings (Holsboer et al. 1992; Roy-Byrne 1992; Bourgeois 1993). The panic attacks are unexpected, are perceived as producing severe physical discomfort, and are often accompanied by fear of going crazy or even of dying (APA 1987). The clinical picture of panic disorder parallels the response pattern of normal subjects in acute stress situations, as in an aversive life event such as maternal separation in human infants (Larson et al. 1991) and (simulated) flight accidents (Sive and Hattingh 1991). Panic results partly from the individual's inability to develop adequate coping strategies in response to an unexpected stressor; concomitantly, a significant increase in the activity of the hypothalamic-pituitary-adrenocortical (HPA) system can be observed (Breier et al. 1987).

Disease-specific physiological alterations in panic disorder have been investigated with a plethora of stimulation tests. These tests include infusion of sodium lactate, inhalation of carbon dioxide, and administration of adenosine receptor blockers (e.g., caffeine), α_2-adrenergic antagonists (e.g., yohimbine), serotoninergic agonists (e.g., mCPP, fenfluramine), inverse benzodiazepine agonists (e.g., β-carbolines), and benzodiazepine antagonists (e.g., flumazenil) or peptides such as cholecystokinin-4 (for reviews, see Cameron and Nesse 1988; Kahn and van Praag 1992; Nutt and Lawson 1992). However, most of these challenge tests induce panic attacks in only a certain percentage of the afflicted patients. In parallel, many of these panicogens fail to activate the HPA system. The lack of pituitary-adrenocortical activation during lactate-induced panic attacks, for example, may be due to a more pronounced concomitant surge of atrial natriuretic hormone (ANH) in panic disorder patients than in normal controls (Kellner et al.

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1995), taking into consideration that ANH has been demonstrated to inhibit the corticotropin-releasing hormone (CRH)-stimulated secretion of adrenocorticotrophic hormone (ACTH) and cortisol in man.

The issue becomes even more puzzling if the findings on HPA system regulation in panic disorder obtained so far with different research strategies are considered.

1. Generally, plasma cortisol and ACTH levels under baseline conditions have been found to be unaltered in panic disorder patients (cf., Cameron and Nesse 1988; Holsboer 1992), although there have been a few recent reports of increased plasma ACTH concentrations before pharmacological treatment (Brambilla et al. 1992) and of significantly enhanced plasma cortisol levels in an electrodermally differentiated subgroup of panic disorder patients (Kopp et al. 1989).
2. However, cortisol nonsuppression following dexamethasone pretreatment (dexamethasone suppression test; DST) can be found in nearly one third of panic disorder patients (Kopp et al. 1989; Coryell et al. 1991; Kuboki and Suematsu 1992).
3. Finally, a corticotropin-releasing hormone (CRH) challenge in panic disorder patients is followed by a blunted ACTH release, whereas the cortisol response remains similar to that found in normal controls (Roy-Byrne et al. 1986; Holsboer et al. 1987; Rapaport et al. 1989). This response pattern results in a significantly lowered ACTH/cortisol ratio after CRH challenge in the patients (Holsboer et al. 1987; Brambilla et al. 1992).

Thus panic disorder patients, unlike depressed patients, do not show any relevant alterations in their basal pituitary-adrenocortical hormone secretion pattern. However, after a CRH challenge, panic disorder patients, like depressed patients, display clear-cut signs of altered HPA activity. Consequently, panic disorder may be considered to be an illness that is characterized by only a "subthreshold" dysfunction of the HPA system.

In the present study we administered the combined dexamethasone suppression-CRH challenge (DEX-CRH) test to a group of panic disorder patients. This test combines the classical DST with a standard CRH challenge and assesses HPA disturbance with a very high sensitivity that exceeds by far that of the routine DST (Heuser et al. 1994b). Our hypothesis was that the combined DEX-CRH challenge test would unveil an otherwise "hidden" hyperfunction of the HPA system in panic disorder patients by producing a CRH-induced cortisol escape from dexamethasone suppression similar to that observed in depressed patients. To avoid possible confounding effects on the test results of a comorbidity with depression, we included only patients with "pure" panic disorders, that is, without an additional lifetime or current diagnosis of major depression.

METHODS

Subjects

Thirteen inpatients with a diagnosis of panic disorder with agoraphobia (9 women, 4 men; age: 31.0 ± 10.1 years) participated in the study. None of the patients fulfilled the diagnostic criteria for a lifetime or current diagnosis of major depression or any other psychiatric disorder.

Ten patients (8 women, 2 men; age 33.0 ± 7.0 years) with major depression but without any concomitant diagnosis of another psychiatric disorder, in particular an anxiety disorder, served as a reference group.

All patients were inpatients at the Clinical Institute of the Max Planck Institute of Psychiatry. Diagnoses were made according to DSM-III-R criteria (APA 1987) and were confirmed with the Structured Clinical Interview for DSM-III-R [SCID; German version: SKID (Wittchen et al. 1990)]. For the panic disorder patients, the severity of the anxious symptomatology was rated on the Hamilton Rating Scale for Anxiety (HAM-A; Hamilton 1976). For both groups of patients, the Hamilton Rating Scale for Depression (HAM-D; Hamilton 1968) was used to assess depressive psychopathology.

Ten paid healthy volunteers with no personal (confirmed by the SKID) or family history of psychiatric disorders (confirmed by a semistructured interview) served as control subjects (3 women, 7 men; age: 28.1 ± 3.5 years).

All study participants were screened by a thorough physical examination, including laboratory tests (e.g., electrocardiogram, blood analysis, and drug monitoring for amphetamines, barbiturates, benzodiazepines, cocaine, and opiates) and cranial computed tomography (patients only). Panic disorder and depressed patients who had been treated with psychoactive medication (e.g., benzodiazepines and/or tricyclic antidepressants) had to complete a washout period of at least 7 days before neuroendocrine testing. In any case, the duration of the washout period was at least three times the half-life of the respective drug and its active metabolite.

Patients and controls gave written informed consent after the purpose and procedure of the study had been fully explained. The study protocol was approved by the local Ethics Committee for Human Experimentation.

Procedure

The DEX-CRH test was performed as described in detail elsewhere (von Bardeleben and Holsboer 1989, 1991; Heuser et al. 1994b). Briefly, all participants received an oral dose of 1.5 mg dexamethasone at 2300 h on the night preceding the test. On the day of the test, a calorie- and electrolyte-balanced lunch was served. At 1300 h, subjects were asked to rest in a semi-recumbent position on a bed in a single room where they could be monitored by a video system. All subjects remained

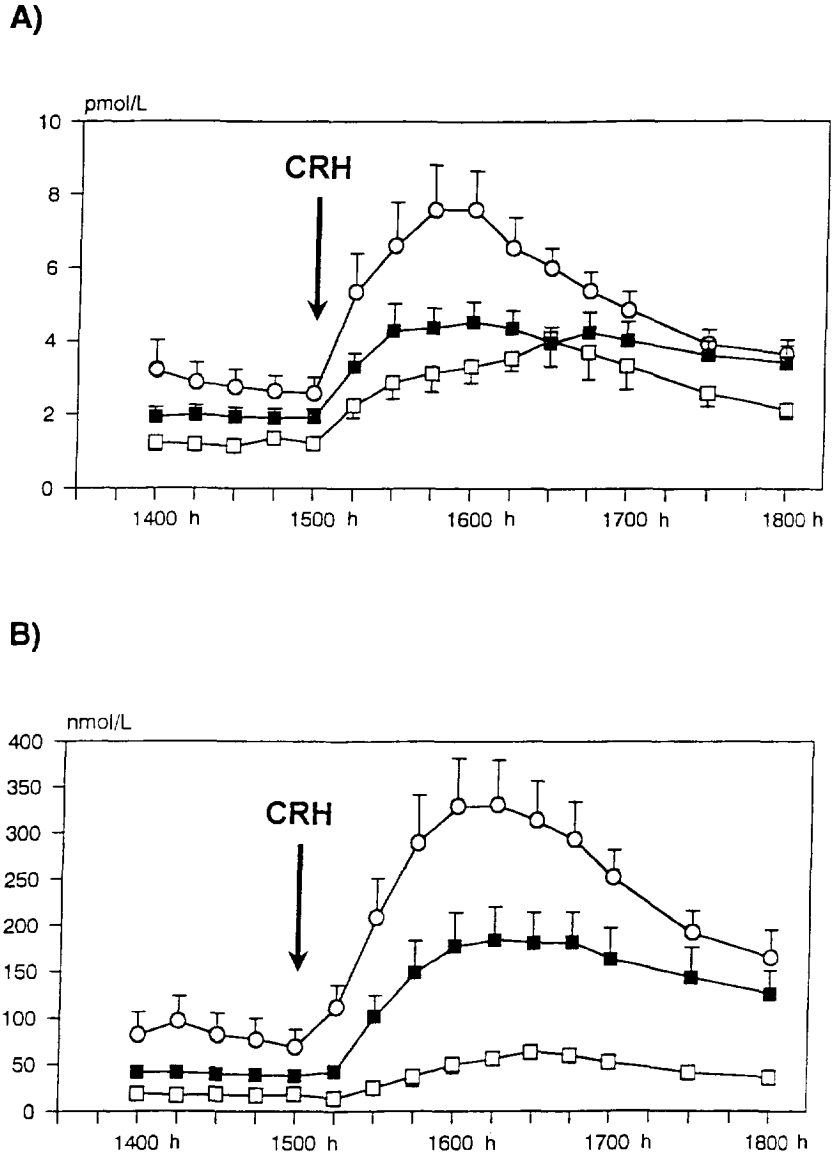

Figure 1. ACTH (**A**) and cortisol (**B**) response curves to CRH after dexamethasone pretreatment in panic disorder (*solid squares*), and major depression (*open circles*) patients and in healthy subjects (*open squares*).

seated during the whole test period. The only activity allowed was light reading. At 1330 h, a catheter was inserted into a forearm vein and connected to a long tube that ran passing through a soundproof lock into the adjacent laboratory unit. Heart rate and blood pressure were monitored automatically throughout the study. Blood samples were drawn at fixed time points (see Figure 1A and 1B) from 1400 h to 1800 h. At 1500 h, 100 μg CRH (Bissendorf Peptide, Wedemark, Germany) reconstituted in 1 ml 0.02% HCl in 0.9% saline was infused within 30 seconds.

Apart from a transient facial flush and a feeling of warmth experienced by nearly all participants, no major side effects or changes in heart rate and blood pressure were observed following the injection of CRH. Blood specimens were stabilized with EDTA (1 mg/ml blood) and aprotinin (300 KIU/ml blood) and centrifuged for 10 minutes at 4°C and 4,000 rpm immediately after sampling. After aliquoting, plasma was stored at −80°C and at −20°C before being assayed for ACTH and cortisol, respectively.

Plasma cortisol concentrations were analyzed using a commercially available radioimmunoassay kit with a coated-tube technique (ICN Biomedicals, Carson, CA). The detection limit was 0.3 ng/ml plasma; intra- and interassay coefficients of variation for 20- and 40-ng/ml levels were <7%. Immunoradiometric assays without extraction procedures were used (Nichols Institute, San Juan Capistrano, CA) for ACTH measurements. The detection limit for plasma ACTH concentrations was 3.5 pg/ml in our laboratory, and the intra- and interassay coefficients of variation at 20 pg/ml plasma were <8%.

Statistical Analysis

The mean values for the samples drawn between 1400 h to 1500 h were termed Baseline concentrations. The

maximal hormone response after CRH administration (between 1515 h to 1800 h) as termed Peak and the time period from 1515 h until the occurrence of the peak was called Peak Latency. Furthermore, the maximal post-CRH hormonal increase corrected for baseline was calculated (Delta). The ACTH and cortisol responses to CRH were calculated as the net areas under the response curved (AUC_{net}) using trapezoidal integration. Pituitary-adrenal ratios as crude estimates of adrenal responsiveness were defined as the ratio of AUC_{net} for ACTH to AUC_{net} for cortisol. In addition, the DST status was determined based on the highest plasma cortisol concentration between 1400 h to 1500 h with a cut-off value at 110 nmol/l defining DST nonsuppression.

Besides calculation of descriptive statistics (means ± SD), a multivariate analysis of variance (MANOVA) was carried out to identify possible main group effects. If there were such effects, modified least significant difference tests were computed to unveil differences among the three samples under investigation. To reveal possible differences with respect to gender distribution, DST suppressor/nonsuppressor, and normal/abnormal DEX-CRH challenge test ratios among the three groups, Pearson's chi-square testing (two-tailed) was carried out. To control for gender difference, an analysis of covariance (ANCOVA) with sex as the covariate was done. Correlational analysis was done by computing Pearson correlation coefficients.

RESULTS

The three groups of subjects, panic disorder patients, depressed patients, and healthy control subjects, were of similar age. There were differences in the ratios of women to men, but they did not reach significance. The depressed patients displayed significantly higher HAM-D scores than the panic disorder patients (Table 1).

Table 1. Characteristics of Subjects and Results of DEX-CRH Test in Patients with Panic Disorder, Patients with Major Depression, and Healthy Subjects

	Panic Disorder (n = 13)	Major Depression (n = 10)	Healthy subjects (n = 10)	MANOVA	Multiple Tests (MODLSD)		
	P	D	C	F(2,30)	P*D	P*C	D*C
Age	31.0 ± 10.1	34.2 ± 6.4	28.1 ± 3.5	1.00			
Women/Men	9/4	8/2	3/7	χ^2 = 5.90			
HAM-D	10.5 ± 5.3	28.4 ± 5.7	—	26.81***			
HAM-A	20.1 ± 6.7	—	—				
ACTH							
Baseline (1400 to 1500 h; pmol/L)	1.9 ± 0.8	2.8 ± 1.5	1.2 ± 0.4	6.13*	NS	NS	‡
Peak (max. conc. after CRH; pmol/L)	5.3 ± 2.7	8.1 ± 3.4	4.6 ± 2.6	4.02*	‡	NS	‡
Delta (peak–baseline; pmol/L)	3.3 ± 2.3	5.3 ± 3.2	3.4 ± 2.5	1.85			
AUC net (1500 to 1800 h)	313 ± 221	414.3 ± 308.3	289 ± 158	0.77			
Cortisol							
Baseline (1400 to 1500 h; nmol/L)	39.9 ± 31.6	80.8 ± 74.5	17.6 ± 6.3	3.71*	‡	NS	‡
Peak (max. conc. after CRH; nmol/L)	215.0 ± 154.0	384.6 ± 179.7	73.4 ± 37.5	10.63***	‡	‡	‡
Delta (peak–baseline; nmol/L)	175.1 ± 147.0	303.8 ± 188.0	55.8 ± 36.6	7.11**	‡	‡	‡
AUC net (1500 to 1800 h)	17709 ± 16942	26664 ± 22589	4287 ± 3060	4.43*	NS	NS	‡
DST suppressors/nonsuppressors	12/1	7/3	10/0	χ^2 = 5.11			
Response to CRH stimulation							
Normal/Abnormal[a]	4/9	0/10	8/2	χ^2 = 14.11***	‡‡[b]	‡‡[b]	‡‡[b]
Pituitary-adrenal ratios	0.11 ± 0.22	0.02 ± 0.01	0.12 ± 0.10	1.32			

HAM-D: Hamilton rating scale for depression; HAM-A: Hamilton rating scale for anxiety; AUC: area under response curve; DST: dexamethasone suppression test; P: panic disorder; D: major depression; C: healthy subjects; MANOVA: *$p < .05$; **$p < .01$; *** $p < .001$; MODLSD: Modified least significant difference test: blank fields: not tested; NS: not significant; ‡: significant group differences.

[a] According to a peak cut-off value of 110 nmol/L.

[b] Chi-square test ‡‡, $p < .05$.

In the three groups, the ratios of the DST suppressors to nonsuppressors showed a strong trend toward significant differences (Table 1).

Concerning the DEX-CRH challenge test, the time-course pattern of CRH-induced ACTH and cortisol secretion after DEX pretreatment proved to be similar in all three groups, with the panic disorder patients taking a middle position between the depressed patients and the healthy controls (Figure 1).

MANOVA results showed a significant main group effect (Wilks's lambda: 2.28, $p < .05$). The univariate F tests within MANOVA revealed that the following parameters contributed significantly to this effect (Table 1): the Baseline concentrations and the Peak values of ACTH, the Baseline concentrations of cortisol, and the Peak, Delta, and AUC_{net} values of cortisol. No effects were found regarding the ACTH Delta and AUC_{net} values or the pituitary-adrenal ratios.

Significant differences were located with the modified least significant difference tests. For ACTH, increased mean Baseline plasma levels were found only in the depressives. The PEAK values after CRH stimulation differed significantly between the panic disorder patients and the depressives and between the depressed patients and the healthy controls.

Cortisol Baseline values showed that the depressed patients had significantly elevated values compared to both the panic disorder patients and the healthy controls; although the panic disorder patients displayed Baseline cortisol concentrations that on average were more than twice as high as in the healthy control group, this difference did not reach significance. Significant differences between all groups under investigation could be observed for Peak and Delta values. For AUC_{net} values, there was a significant difference only between depressed patients and healthy controls (Table 1, Figure 2).

An abnormal DEX-CRH test result, defined as a CRH-induced cortisol response above a cut-off value of 110 nmol/l, was found in 9 (69%) panic disorder patients and in 10 (100%) depressed patients, but only in 2 (20%) healthy subjects. These differences proved to be highly significant. Subsequent group-by-group comparisons (Pearson's chi-square test) showed that all groups differed significantly from each other (Table 1).

Because there was a strong tendency to differing frequencies of women and men in the three samples ($p = .052$), we did an additional ANCOVA with sex as the covariate. However, this did not lead to any substantial changes in the results already presented. Significant sex effects were observed in the Delta values and the Peak values of cortisol [$F(1) = 4.24$, $p < .05$; $F(1) = 6.19$, $p < .05$], as well as in the PAR values [$F(1) = 9.76$, $p < .01$)]. The remaining variables under investigation were not significantly influenced by the patients' gender.

Finally, by means of correlational analyses, a significant influence of age, current psychopathology (HAM-A and HAM-D), and duration of disease on the degree of HPA system responsiveness could be ruled out in the panic disorder patients.

DISCUSSION

In the present study, plasma ACTH and cortisol responses to CRH after DEX pretreatment were measured in panic disorder patients and compared with the respective values for depressed patients and healthy controls. In panic disorder patients, the responsiveness of

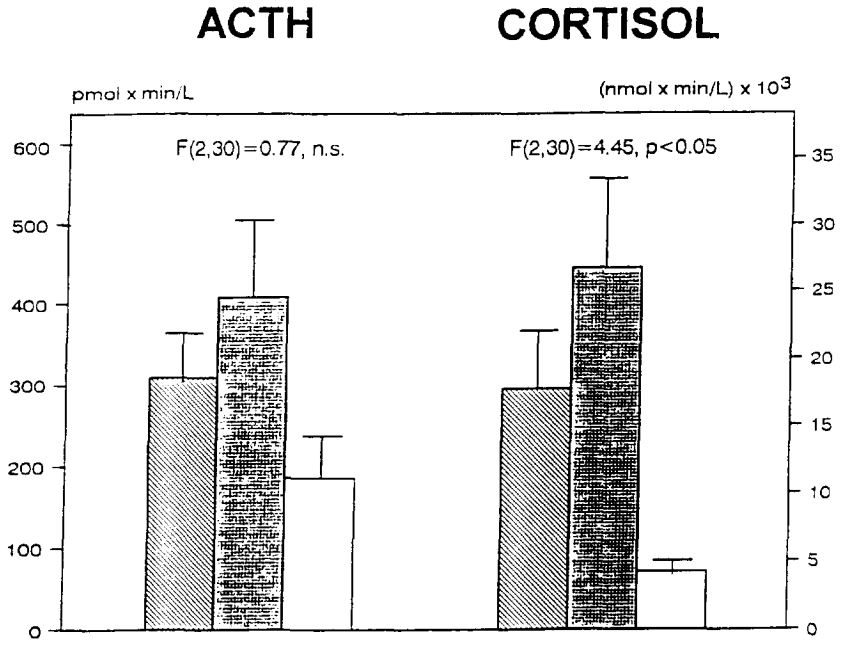

Figure 2. Net areas under the ACTH and cortisol response curves to CRH (1500 h to 1800 h, means ± SEM) after dexamethasone pretreatment in panic disorder (*grey bars*) and major depression (*dark bars*) patients and in healthy subjects (*white bars*).

the HPA system to a combined DEX-CRH challenge test was found to be higher than in healthy controls, but lower than in depressed patients. This middle position of the panic disorder patients is further reflected by the respective DST suppressor/nonsuppressor and the normal/abnormal DEX-CRH test ratios.

The ratio of panic disorder patients displaying cortisol nonsuppression in the DST was fairly low (1:12) considering the 1:3 ratio generally reported in the literature (Kopp et al. 1989; Coryell et al. 1991; Kuboki and Suematsu 1992). In contrast to these studies, however, we excluded all panic disorder patients with a current and/or lifetime diagnosis of a major depression, ensuring a "pure" diagnostic sample. The reason for this strategy was that the coexistence of a manifest depressive disorder presumably represents a confounding and amplifying factor in HPA system dysregulation (Kathol et al. 1989; Coryell et al. 1991; Blouin et al. 1992). We also found a somewhat lower-than-expected ratio of cortisol nonsuppressors to suppressors in our depressed patients. This might best be explained by the relatively mean young age in this study sample because alterations of the HPA hormone regulation are known to increase in frequency with age (Dahl et al. 1989; von Bardeleben and Holsboer 1991; Heuser et al. 1994a). Nevertheless, a higher frequency of DST nonsuppression in our depressed patients would not have changed the present finding that panic disorder patients, as a diagnostic entity, take a clear middle position in the HPA system dysregulation between depressed and healthy controls.

Given the fact that overactive CRH neurons may cause the manifold neuroendocrine and behavioral alterations commonly observed in depression (Holsboer 1992, 1995), the presence of altered HPA system responsiveness in panic disorder brings up two major points of interest, (1) the presumed etiological role of CRH in the pathogenesis of panic disorder, and (2) the discrepancy between HPA system dysregulation in panic disorder and depression.

Gorman and coworkers (1989) postulate an altered noradrenergic activity within the locus coeruleus (LC) as the starting point of their neuroanatomical model of panic disorder, which connects the three components of the disease (the acute panic attack, anticipatory anxiety, and phobic avoidance) to three specific sites in the central nervous system, (i.e., the brainstem, the limbic system, and the prefrontal cortex). If this model proves true, hypothalamic CRH neurons can be supposed both to stimulate and modulate this noradrenergic activity (Holsboer 1992; van Gool et al. 1992; Nisticò and Nappi 1993). This assumption is based on an array of recent neuroanatomical and neurophysiological findings. For instance, within the LC itself, CRH-containing neurons are located in close proximity to noradrenergic neurons in rats (Swanson et al. 1983). A variety of acute and chronic stressors has been demonstrated to increase CRH levels in the LC (Chappel et al. 1986). Locally available CRH by itself has been shown to enhance LC firing rates in animal models (Butler et al. 1990; Valentino et al. 1983) as well as to mediate a stress-induced increase in the LC neuronal firing rate (Valentino 1989; Valentino et al. 1991). Conversely, norepinephrine is known to stimulate CRH release in the hypothalamus (Gold 1990).

The functional significance of HPA system activation during the development of panic disorder is further supported by a variety of primate and nonprimate animal studies that have demonstrated that CRH acts as an anxiogenic agent (for reviews, see Dunn and Berridge 1990; Holsboer et al. 1992). Intracerebral CRH administration was demonstrated to increase the behavioral effects of novelty (Britton et al. 1982) as well as to augment a conditioned fear response (Cole and Koob 1988), the responsiveness to acoustic startle (Swerdlow et al. 1986) and anxiety-related behavior, for example, in the social interaction test (Dunn and File 1987) and after maternal separation (Kalin et al. 1989). These studies, which were based on effects induced by administration of pharmacological dosages of CRH have recently been confirmed by Skutella et al. (1994), who administered a CRH antisense oligodeoxynucleotide intracerebroventricularly to rats and observed anxiolysis and HPA deactivation.

If CRH hyperactivity is of pathogenetic relevance in both panic disorder and depression, the question arises as to how the discrepancy in HPA system responsiveness between panic disorder and depressed patients observed in our study can be explained. Concerning nosographic features, neither the duration of the disease nor the psychometric assessment of either anxiety or depression were significantly correlated with the degree of HPA system dysregulation in our study samples. Recently, Charney and coworkers (1993) investigated another anxiety disorder, posttraumatic stress disorder, focusing on the significance of subsequent stressors for the sensitization of different stress response systems such as the HPA system. Applied to panic disorder, their findings would suggest a close association between the frequency of panic attacks and a progressive adrenocortical dysregulation. However, because of methodological restrictions (i.e., the impossibility of recalling the exact number of panic attacks over a period often lasting many years), we did not consider the role of the frequency of panic attacks in our analysis. Only controlled, prospective studies would be helpful in the search for remedial measures. One could speculate, however, that the great variance in ACTH and cortisol responses to CRH after DEX pretreatment that we observed in our sample reflects such a variable sensitization; similar fluctuations in pituitary-adrenocortical responsivity to CRH but without DEX pretreatment were reported, for instance, by Rapaport et al. (1989). Such a kindlinglike

process could account for an interindividual variability, resulting in our findings that HPA dysregulation in panic disorder seems to be less extreme and less frequent than in depression.

Another explanation for the differences observed involves the possibility of a divergent vasopressin activity in major depression and panic disorder. In depression, the exaggerated pituitary-adrenocortical response to the DEX-CRH challenge led to the hypothesis of an increased release not only of CRH but also of vasopressin secondary to reduced glucocorticoid receptor capacity (von Bardeleben and Holsboer 1989). This hypothesis has recently been confirmed by Raadsheer et al. (1994), who found vasopressin to be overexpressed in parvocellular CRH neurons in the hypothalamus. In anxiety disorders, however, vasopressin activity seems to be unaltered. For example, using the social defeat stress paradigm as an animal model for anxiety, Pich et al. (1993) were able to demonstrate that the activation of the HPA system is mediated by hypophysiotrophic CRH but not by vasopressin. Thus, such overexpression of vasopressin is related to chronic (depression) rather than to episodic (panic) stress; the lower degree of HPA alteration in panic might therefore be attributed to the lack of excessive vasopressin, which is known to synergize the effect of CRH at corticotrophs.

If sensitization by repetitive panic attacks indeed results in progressive HPA system dysregulation, one would expect that treatment strategies known to be effective in panic disorder would also normalize altered pituitary-adrenocortical activity. To date, four types of medication have been shown to be efficacious in the treatment of panic disorders: tricyclic antidepressants, monoamine-oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines (for reviews, see Evans 1989; Bronisch 1990; Humble and Wistedt 1992; Kahn and van Praag 1992; Roy-Byrne 1992).

A growing body of evidence is now available indicating that benzodiazepines are effective in decreasing hyperactivity of the HPA system in panic disorder, as assessed by measurement of urinary-free cortisol (Lopez et al. 1990) or plasma levels of ACTH and cortisol (Roy-Byrne et al. 1991). Attenuation of hypothalamic CRH secretion through enhancement of gamma-aminobutyric acid ($GABA_A$)–gated chloride conductance seems to be a major mode of benzodiazepine-mediated action on HPA system activity. Owens et al. (1989) first showed that alprazolam and adinazolam increased hypothalamic CRH content, but lowered ACTH concentrations. Both triazolobenzodiazepines reduced CRH in the LC and amygdala. In case of alprazolam it is of further interest that it may inhibit platelet-activating factor, which stimulates CRH (for review, see van Gool et al. 1992). It can be speculated that alprazolam may act as an antipanic drug also by suppressing CRH through inhibiting platelet-activating factor synthesis.

Two preliminary treatment studies investigating the effects of selective SSRIs on HPA system dysregulation in anxiety disorders yielded contradictory results: fluvoxamine had no effect on plasma cortisol (Den Boer and Westenberg 1990), and chronic fluoxetine treatment in obsessive-compulsive disorder patients caused an attenuation of the plasma ACTH/cortisol response to the $5\text{-}HT_{1A}$ receptor agonist ipsapirone (Lesch 1991). These effects may be mediated in part by an increase of central somatostatin concentrations. Central administration of somatostatin leads to an inhibition of CRH-stimulated ACTH secretion; correspondingly, there is growing evidence for an association between decreased (CSF) somatostatin cerebrospinal fluid levels and overactivity of the HPA system as observed in depression (for an overview, see Plotsky et al. 1995). In line with these findings, Rubinow et al. (1985) were able to demonstrate a significant increase of CSF somatostatin levels in depressed patients after administering the SSRI zimelidine, known to be effective both in depression and anxiety disorders. On the other hand, to date there has been only one study by Vecsei and Widerlöv (1988) investigating CSF somatostatin levels in panic disorder patients, which were found to be unaltered. Final conclusions concerning the influence of an impaired somatostatinergic neurotransmission on panic disorder–related HPA system dysregulation must, therefore, be considered as premature.

At last, in rat studies chronic treatment with the tricyclic antidepressant amitriptyline or the reversible MAO-A inhibitor moclobemide resulted in a decrease in circulating ACTH and cortisol as well as in adrenal size and a reduced HPA activation in response to a stressor (Reul et al. 1993; Holsboer 1995). Therefore it has been suggested that antidepressants may act through central corticosteroid receptors by normalizing HPA activation in response to stress (Barden et al. 1995).

In conclusion, the results of the combined DEX-CRH test indicate that a substantial portion of panic disorder patients have a disturbed HPA system regulation. If sensitization by repetitive panic attacks is indeed responsible for progressive HPA dysregulation, and if progressive HPA dysregulation is indeed of decisive importance for the pathogenesis of panic disorder, then therapeutic strategies capable of dampening the hyperactivity of the HPA-LC "alarm system" are indicated. Thus, apart from its scientific relevance, the DEX-CRH challenge test may also be of clinical value by sensitively monitoring HPA function and predicting a patient's response to the treatment procedure used.

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