The thyrotropin-releasing hormone test may predict recurrence of clinical depression within ten years after discharge

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Abstract

OBJECTIVES: The underlying pathogenic mechanisms and predictors of recurrence in major depressive disorder are still largely unknown. Hypothalamic-pituitary-thyroid (HPT) axis and hypothalamus-pituitary-adrenocortical (HPA) axis dysregulation are thought to be related to the development and course of depression.

DESIGN AND SETTING: Over a ten-year period, we investigated whether the results of thyrotropin-releasing hormone (TRH) testing and combined dexamethasone/corticotropin-releasing hormone (DEX/CRH) testing could be correlated with the recurrence of depression in 25 outpatients with clinically remitted major depression for at least 10 years.

MATERIALS AND METHODS: Twenty-five patients (16 women and 9 men, 48.1 years of age, SD=11.4, range 22–84) with major depressive disorder were available for evaluation during hospitalization. TRH and DEX/CRH tests were administered at admission.

RESULTS: Patients who recurred within ten years after remission exhibited significantly higher thyroid stimulating hormone (TSH) responses to TRH at the time of admission compared to those who did not recur. There was no significant correlation between recurrence and DEX/CRH levels after controlling for age, sex, and body mass index.

CONCLUSION: The findings of this study suggest that the TRH test may predict future recurrence in patients with depression.

ORIGINAL ARTICLE

INTRODUCTION

Numerous studies have linked abnormalities of the hypothalamic-pituitary-adrenal (HPA) system to major depression (Plotsky *et al.* 1998; Holsboer 2000). The combined dexamethasone (DEX)/corticotropin releasing hormone (CRH) test is known to be one of the most sensitive means of evaluating HPA system activity (Holsboer-Trachsler *et al.* 1991, Lauer *et al.* 1998; Kunugi *et al.* 2004; Ising *et al.* 2005; Erhardt *et al.* 2006; Ising *et al.* 2007; Heuser *et al.* 1994a; Heuser *et al.* 1994b; Oshima *et al.* 2000). The results of this test have been shown in some studies to represent a state-dependent

marker of depression (Kunugi *et al.* 2006) and to predict response to antidepressant treatment (Ising *et al.* 2005). However, other studies have not confirmed these associations (Rybakowski & Twardowska 1999, Oshima *et al.* 2000, Watson *et al.* 2002).

The hypothalamic-pituitary-thyroid (HPT) axis has also been linked to depression. A reduced thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) was found in depressed patients (Prange *et al.* 1972; Kastin *et al.* 1972), with approximately 25% to 30% of depressed patients displaying a blunted TSH response (Loosen & Prange 1982; Loosen 1985). Iovino *et al.* (1991) and Samuels and McDaniel (1997) have reported that glucocorticoids have a suppressive effect on the TSH response to TRH. Persistence of a blunted TSH response to TRH may also predict recurrence of depression or poor response to treatment for depression (Targum 1984). Although the feasibility of using the TSH response as a biological marker of depression has been extensively studied, the results of these studies have not been consistent. Some investigators have found a relationship between the results of this test and severity of depression supporting the use of this test as a state marker (Extein *et al.* 1982; Gregoire *et al.* 1977), while others have suggested using TRH responsiveness as a trait marker (Coppen *et al.* 1974). Still others have been unable to show that TRH responsiveness is a useful marker for predicting treatment outcome (Amsterdam *et al.* 1996; Loosen *et al.* 1982).

Most previous studies on the relationship between the HPT and HPA axes in depression have yielded inconsistent results. A few studies of the HPA axis and the HPT axis have revealed a reciprocal relationship between these two endocrine pathways in depression. Extein *et al.* (1981) reported that there was no significant association between the abnormalities of these two axes and that test of these two endocrine systems complemented each other as biological markers for active unipolar depression. Patil and Mujawar (2010) have also reported that there was a positive and significant correlation between HPT and HPA axis function in geriatric patients.

About 50% of patients with major depressive disorder (MDD) experience a recurrence of depression symptoms, and recurrence rates are as high as 20–37% during the continuation and maintenance phases of pharmacotherapy (Crown *et al.* 2002). Prevention of recurrence is therefore one of the most important challenges in the management of major depression. The findings described above suggest that both HPA axis (Zobel *et al.* 2001) and HPT axis (Prange *et al.* 1972) parameters may have the potential to predict future episodes of depression. To our knowledge, no previous longitudinal studies have compared HPAaxis function, as assessed by the DEX/CRH test, and HPT axis function, as assessed by the TRH test, in patients with depression.

To determine whether hormone testing can predict the prognosis of depression under the hypothesis that HPA dysfunction precedes poor outcomes and that the HPT and HPA axes may act cooperatively in depression, we prospectively performed two neuroendocrine challenge tests (the DEX/CRH test and TRH test) in individuals with depression, and compared the results between those who did and did not suffer from recurrence of depression within 10 years after discharge.

MATERIAL AND METHODS

Subjects

Twenty-five patients (16 women and 9 men, 48.1 years of age, SD=11.4, range 22–84) were available for evaluation during hospitalization. This was a prospective study performed in a natural clinical setting. We studied all patients who fulfilled all of the following inclusion criteria: (1) hospitalized at the Neuropsychiatry Clinic of the Oita University Hospital, (2) major depressive disorder without psychotic symptoms (i.e., not having bipolar disorder) as established by the Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association 2000) and (3) receipt of written informed consent. Exclusion criteria were (1) central nervous system disorders or medical disorders clearly affecting cerebral function, (2) alcoholism or drug dependence, (3) personality disorder (SCID-II), (4) presence of brain injury or disease, (5) pregnancy, (6) mental retardation, (7) age less than 18 years, (8) immediate danger of suicide, (9) treatment with lithium and/or carbamazepine, or (10) endocrine disorder of the pituitary or the adrenal glands. The study protocol was reviewed and approved by the Ethics Committee of the Oita University Faculty of Medicine, and all participants submitted written informed consent.

The severity of psychiatric disease was assessed using the 21-item version of the Hamilton Depression Scale (HAM-D; Hamilton 1967) and the Global Assessment of Functioning (GAF; APA 2000) at the time of admission.

All patients were treated with tricyclic antidepressant monotherapy. An adequate dosage (75 mg/day or more of imipraimine) was maintained as much as possible. The drug was changed if the patient did not achieve a certain standard of improvement after 4 weeks of treatment. Non-recurrent patients used either tricyclic antidepressants (clomipramine at doses of 150, or 300 mg; imipramine 175 mg; amoxapine 150 mg; nortriptyline 125 mg; dosulepine 100 mg),a tetracyclic antidepressant (mianserine 30, 60, or 150 mg), a serotonin reuptake inhibitor (SSRI; fluvoxamine 75 mg), or another drug (sulpiride 300 mg). All recurrent patients used tricyclic antidepressants (clomipramine 100, 150, or 200 mg; nortriptyline 75 or 150 mg; imipramine 150 mg; amoxapine 100 mg, trazodone 200 mg).We did not use additional benzodiazepines as hypnotics or sedatives for the DEX/CRH test.

We considered recurrence to have occurred when the subjects met the criteria for MDD again after dis-

charge and/or required hospitalization for depression. We followed-up patients every 4 weeks for recurrence after remission. We retained contact information or access to all patients' follow-up data in hospital discharge registers for use during the ten-year follow-up period.

TRH test

On the examination day (within 1 week after admission), patients were fasted starting at 0:00 and were forbidden to do anything except drink water, take medication, wash their faces, brush their teeth, urinate, and evacuate. They were also asked to rest in their beds. At 8:30, an intravenous line was started with a drip infusion of physiological saline to keep the vein open. At 9:00, blood was sampled to measure baseline TSH levels. Then, 0.5 mg of TRH was administered intravenously over about 2 min. Blood was sampled at 15, 30, 60, 90, and 120 min for TSH measurement. Measurement of TSH blood concentrations (mIU/L) was performed at the central laboratory of our hospital, and the maximum response value (MAX TSH) and ΔMAX TSH (MAX TSH minus baseline TSH) were determined.

DEX/CRH test

The DEX/CRH test was performed the day following the TRH test (Figure 1). DEX 1.5 mg was orally administered at 23:00 on the day preceding the DEX/CRH test. On the test day, after urination and evacuation, an intravenous line was secured by a drip infusion of physiological saline at 13:30, and patients remained at rest in their beds. At 14:00, 14:15, and 15:00, blood was sampled to measure baseline levels of ACTH and cortisol. The baseline level was taken as the average of these three measurements. Immediately after blood sampling at 15:00, CRH (100 μg) was administered intravenously. Then, at 10, 20, 30, 60, 75, 120, and 180 min after CRH administration, blood (6 mL) was sampled for measurement of ACTH and cortisol. Each blood sample was immediately refrigerated, and plasma was separated on the same day. ACTH (pmol/L) was measured by immunoradiometric assay at the Otsuka Assay Laboratory, and cortisol (nmol/L) was measured at Lintec. The maximum response (MAX ACTH) and ΔMAX ACTH (MAX ACTH value minus baseline value) was determined. We also determined the relationship between the hormonal test results, age, body mass index (BMI), previous episodes of depression, HAMD scores and GAF scores.

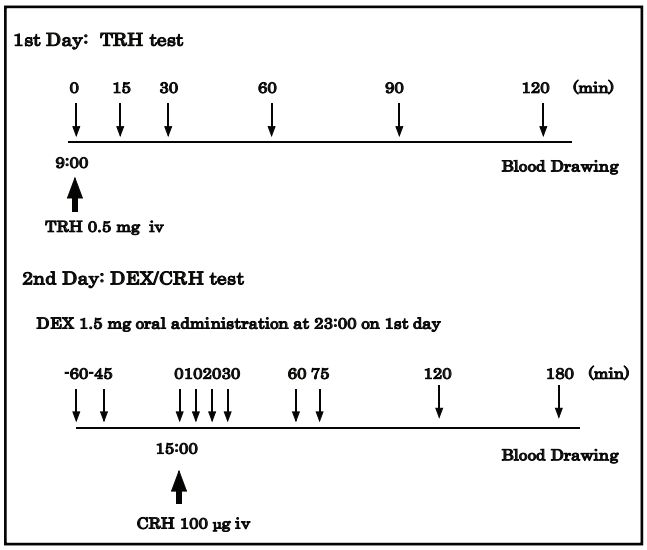

Fig. 1. Hormonal test protocol.

Statistical analysis

Demographic data, clinical features, diagnoses, and medications were compared between groups with Fischer's exact tests and t-tests.The Mann-Whitney *U* test was used for comparison of hormonal test results for assessment of differences by sex. We then went on to estimate the recurrence-free survival rates using the Kaplan-Meier method by tracking patients from their index discharge date. Differences in area under the curve (AUC)for each hormonal test between the recurrence and non-recurrence groups were compared with t-tests. Pearson correlation coefficients were computed to investigate the association between AUCs of the hormonal tests, age, BMI, previous episodes of depression, HAMD scores and GAF scores. AUC was calculated by the trapezoidal method to evaluate the degree of HPT and HPA axis function. Repeated measures analysis of variance (ANOVA) was used to assess differences in ΔACTH, Δcortisol, and ΔTSH between recurrent and non-recurrent patients. Statistical significance was set at $p<0.05$.

RESULTS

Demographic and clinical characteristics

Twenty-five patients (16 women and 9 men, 48.1 years of age, SD=11.4, range 22–84) were available for evaluation during hospitalization. In these patients, gender, age, age at MDD onset, family history, recurrence of MDD, body mass index, duration current hospitalization, HAMD and GAF scores, antidepressant dose at discharge, and comorbidities were evaluated. There was no difference in gender (%), age, age of MDD onset, duration of MDD, MDD recurrence (%), comorbidity of obsessive-compulsive disorder, or HAMD scores between recurrence and non-recurrence groups (Table 1).

There were also no significant differences in demographic or clinical factors between recurrence and non-recurrence groups. Among the 25 subjects regularly followed for 120 months, nine patients (6 women and 3 men) suffered from a recurrence of depression. One patient recurred within two months, and three patients recurred within six months after discharge. An additional four patients recurred within 12 months after discharge (Figure 2). Altogether, a total of nine patients recurred within 27 months. All of these patients were

considered to have suffered recurrence; that is, none of the subjects, including those who recurred after discharge, exhibited poor compliance or adherence to medication regimens according to information obtained from patients and their families.

Tab. 1. Demographic and clinical characteristics of patients with and without recurrence within ten years after discharge

	Recurrence (N=9)	Non-recurrence (N=16)	
DEX/CRH test			
$ACTH_{AUC}$	25.1±22.8	25.1±22.8	p=0.54
CortAUC	10.1±9.9	6.0±5.2	p=0.35
TRH test			
TSH_{AUC}	16.5±9.7	8.9±4.5	p=0.02

Tab. 2. Results of DEX/CRH and GHRH tests in the recurrence and non-recurrence groups.

	Recurrence (n=9)	Non-recurrence (n=16)	
Sex (women/men)	6/3	8/8	p=0.68
Age (years)	51.9±21.3	47.8±16.0	p=0.30
Age at onset (years)	48.2±18.3	46.1±17.0	p=0.78
Family history	0(0%)	7(43.8%)	p=0.15
Recurrent MDD (% patients)	44.4	6.3	p=0.14
Body mass index	21.8±3.4	21.3±2.3	p=0.65
Duration of this hospitalization (days)	89.0±54.1	128.2±82.1	p=0.21
HAMD-17 at admission	21.3±5.3	21.6±7.9	p=0.93
HAMD-17 at discharge	2.2±2.7	3.3±1.9	p=0.28
GAF at admission	53.9±6.0	54.1±4.2	p=0.93
GAF at discharge	73.7±10.8	71.1±8.8	p=0.53
Dose of antidepressants at discharge (equivalent to imipramine, mg/day)	172.2±79.5	142.2±53.0	p=0.27
→Obsessive-compulsive disorder	0	12.5	p=0.54

Tab. 3. Spearman's correlations between results of hormonal tests and demographic and clinical characteristics.

	Age	BMI	Previous episodes	HAMD	GAF
DEX/CRH test					
$ACTH_{AUC}$	0.015	−0.119	0.446 *	−0.354	−0.037
$Cort_{AUC}$	−0.155	−0.086	0.603 *	−0.334	−0.109
TRH test					
TSH_{AUC}	−0.100	−0.202	0.445 *	−0.319	0.069

*p<0.05

Changes in DEX/CRH and TRH tests in admission

There were no differences in $ACTH_{AUC}$ (25.1 (SD=22.8); 25.1 (SD=22.8)) or Cortisol $_{AUC}$ (10.1 (SD=9.9); 6.0 (SD=5.2)) between the recurrence and non-recurrence groups (respectively. Table 2) There were no differences in ACTH ($F_{1, 23}$=0.04, p=0.84) or cortisol ($F_{1, 23}$=0.08, p=0.98)levels after DEX/CRH tests between recurrence and non-recurrence groups (Figures 3, 4). There was also no difference in TSH_{AUC} (16.5 (SD=9.7); 8.9 (SD=4.5)) between the recurrence and non-recurrence groups (respectively, Table 2). However, there was a significant difference in TSH levels measured by the TRH test between recurrence and non-recurrence groups ($F_{1, 23}$=8.9, p<0.01), with TSH in the recurrence group being higher comparison to the non-recurrence group (Figure 5).

Relationships between hormone tests and demographic a

There was no significant correlation between age, BMI, HAMD scores, or GAF scores and hormone test results ($ACTH_{AUC}$, $Cort_{AUC}$, and TSH_{AUC}; Table 3). However, the mean number of previous episodes of major depression exhibited a significantly positive correlation with $ACTH_{AUC}$ (partial correlation coefficient 0.446, p=0.025), $Cort_{AUC}$ (partial correlation coefficient 0.603, p=0.001) and TSH_{AUC} (partial correlation coefficient 0.445, p=0.026).

Differences in demographic and clinical characteristics and, hormone tests by sex

There were no significant differences in age, age at onset of depression, family history of mood disorders, recurrent MDD, body mass index (BMI), HAMD-17 scores at discharge, GAF scores at admission, GAF scores at discharge, or dose of antidepressants at discharge by sex

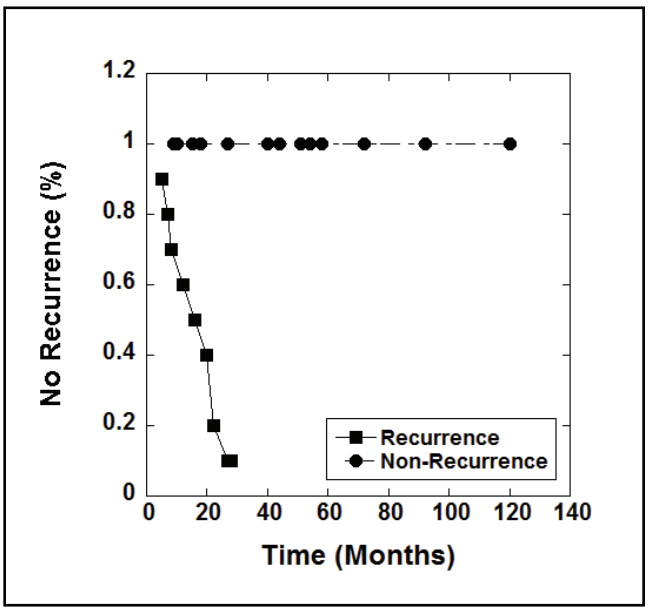

Fig. 2. Time to recurrence within 10 years of the index discharge (Kaplan Meier Survival curves estimating time until recurrence).

(Table 4). However, there were significant differences in the duration of hospitalization and HAMD-17 at admission by sex (Table 4).The duration of hospitalization in men was longer compared to women (p<0.01). Also HAMD-17 scores in women were lower compared to men (p<0.01).

There were no differences in $ACTH_{AUC}$, $ACTH_{MAX}$, $cortisol_{AUC}$ and $cortisol_{MAX}$ in the DEX/CRH test and TSH_{AUC} in the TRH test by sex (Table 5). In contrast, there was a significant difference in TSH_{MAX} in the TRH test by sex, with TSH_{MAX} in women being higher compared to men (p=0.02; Table 5)

DISCUSSION

We performed DEX/CRH and TRH tests on inpatients with depression upon admission. Nine of 25 patients being followed over time recurred within 10 years after discharge, and this relapsing group exhibited significantly higher TSH responses to the TRH test at the time

Tab. 4. Differences in demographic and clinical characteristics by sex.

	Women (n=16)	Men (n=9)	
Age (years)	51.8±18.1	45.2±14.5	p=0.18
Age at onset (years)	48.8±18.1	43.6±15.7	p=0.48
Family history	4(0.25%)	3(33.3%)	p=0.53
Recurrent MDD (% patients)	4(25%)	1(11%)	p=0.64
Body mass index (BMI)	21.1±2.2	22.7±3.3	p=0.18
Duration of this hospitalization (days)	138.8±83.3	70.1±16.0	p<0.01
HAMD-17 at admission	18.6±5.6	27.4±5.9	p<0.01
HAMD-17 at discharge	3.1±2.3	2.4±2.1	p=0.47
GAF at admission	40.0±9.9	40.6±7.3	p=0.88
GAF at discharge	71.8±9.7	72.6±9.3	p=0.84
Dose of antidepressants at discharge (equivalent to imipramine, mg/day)	164.1±72.4	133.3±41.5	p=0.26

Tab. 5. Differences in results of hormonal tests by sex.

	Women (n=16)	Men (n=9)	
DEX/CRH test			
$ACTH_{AUC}$	46.7±55.5	22.9±15.4	p=0.22
$ACTH_{MAX}$	29.3±31.6	18.7±16.7	p=0.36
$Cort_{MAX}$	7.5±6.5	5.8±5.3	p=0.51
$Cort_{AUC}$	14.9±12.8	8.9±9.1	p=0.22
TRH test			
TSH_{AUC}	13.3±8.6	7.8±5.0	p=0.1
TSh_{MAX}	10.8±6.0	5.1±3.8	p=0.02*

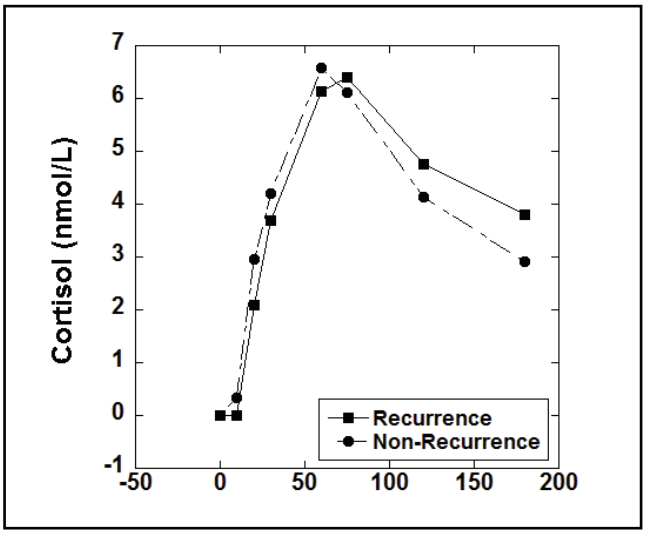

Fig. 3. Mean cortisol responses of recurrent and non-recurrent patients in DEX/CRH test.

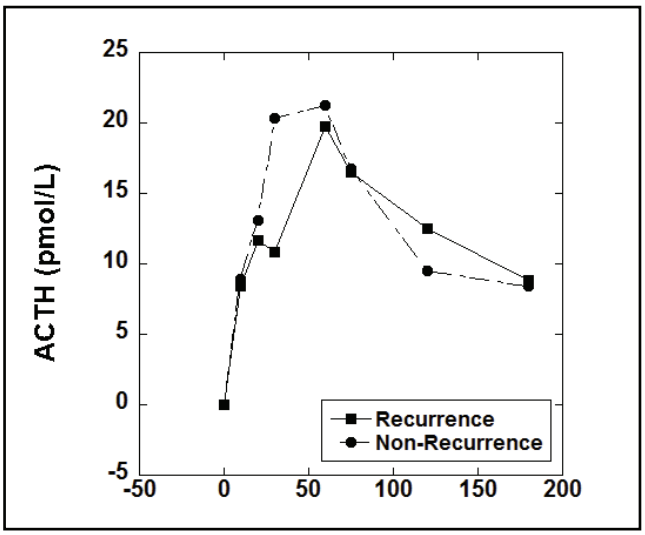

Fig. 4. Mean ACTH responses of recurrent and non-recurrent patients in DEX/CRH test.

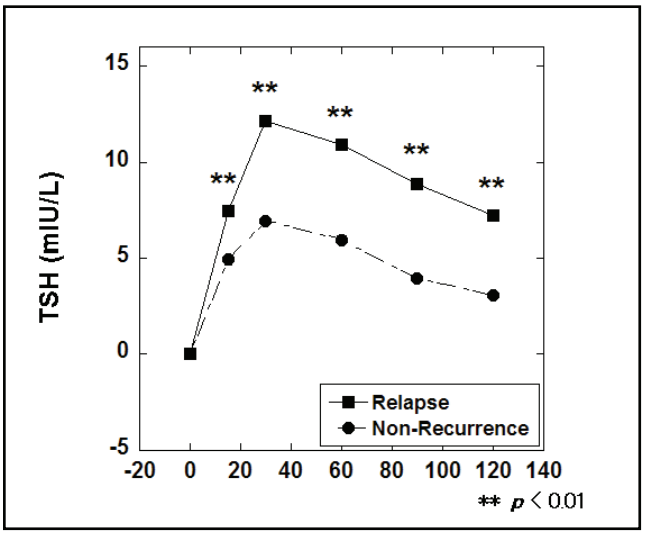

Fig. 5. Mean TSH responses of recurrent and non-recurrent patients in TRH test. The asterix indicates a significant difference in mean TSH concentration.

of admission. Recurrence and non-recurrence groups did not differ in their HAMD scores, GAF scores, or BMI at the time of admission.

Effects of demographic and clinical characteristics on hormone tests

Age: The results of our DEX/CRH and TRH tests suggest that aging is not associated with changes in HPA or HPT responses to hormone tests in depressed patients. Previous reports on the effects of age on the DEX/CRH test have been inconsistent. Kunzel *et al.* (2003) reported that there was no significant effect of age on hormonal response to the DEX/CRH test in acutely depressed inpatients. Comparatively, age effects on hormonal responses have been reported in healthy controls (Heuser *et al.* 1994a; Kudielka *et al.* 1999). However, we did not observe significant effects of age in terms of any significant correlation between age and the results of the DEX/CRH and TRH tests. The reason for this may be that the effect of age on the DEX/CRH test might not be an important factor in recurrence.

Effects of sex: There were significant differences in the duration of hospitalization and HAMD-17 scores at admission by sex. Duration of hospitalization in women was significantly longer than that in men, while HAMD-17 scores at admission in women were significantly lower compared to men. Many previous studies have reported sex differences in hormonal responses to the DEX/CRH test (Kunugi *et al.* 2006, Kunzel *et al.* 2003; Heuser *et al.* 1994a). However, there was no difference between women and men in the DEX/CRH test. We found that peak hormonal secretion was significantly higher in women than in men on the TRH test. There might also be a relationship between duration of hospitalization and HPT axis dysregulation according to TRH test. Our results thus suggest that HPT axis activity in depression might be influenced by sex, but provide no evidence of sex differences in HPA axis activity in depression.

Effects of BMI: There was no correlation between BMI and DEX/CRH or TRH test results. The results of the present study suggest that BMI does not factor into DEX/CRH or TRH test results in depressed patients.

Relationship between severity of depression and hormonal test results

The DEX/CRH tests in the present study revealed no correlation between HAMD scores, GAF scores and either $ACTH_{AUC}$ or $Cort_{AUC}$. This may have been due to the narrow between-subject variance in HAMD scores in our sample. These results suggest that DEX/CRH test results should not be considered a state marker, in contrast with the findings of previous studies (Rybakowski & Twardowska 1999; Kunzel *et al.* 2003; Isogawa *et al.* 2005; Kunugi *et al.* 2006) that monitored HPA axis abnormalities in patients with depression during treatment. Recently, Carpenter *et al.* (2009) reported that an elevated cortisol response to the DEX/CRH test does not represents a marker for major depressive episodes. Further studies are needed to study the relationship between depressive state and DEX/CRH testing.

In the present study, DEX/CRH test results were not correlated with recurrence of depression within ten years after discharge, suggesting that HPA axis parameters might not predict prognosis following hospital treatment for depression. Previous studies employing the DEX/CRH test as a predictor of recovery from depression have yielded conflicting results. Some studies have reported that higher cortisol or ACTH responses to CRH in the DEX/CRH test are associated with recurrence risk (Zobel *et al.* 2001, Hatzinger *et al.* 2002). Ising *et al.* (2005) suggested that a second DEX/CRH test is required for optimal prediction of a lack of response to antidepressant treatment. Another study reported that cortisol responses did not differ significantly between patients who went into remission from bipolar disorder and those who did not (Watson *et al.* 2004).

In contrast, patients who recurred within ten years after discharge exhibited significantly higher TSH responses to TRH at the time of discharge versus those who did not recur. The TRH test is generally considered to be one of the most sensitive measures of HPT axis function. Some reports are indicative of a dysregulation of the HPT axis in depression. Elevated CSF TRH concentrations have been reported in depressed patients (Banki *et al.* 1988; Kirkegaard *et al.* 1979). In addition, a decrease of the mean and peak amplitude of the 24-hour TSH secretion cycle in depressed patients suggested the presence of a chronological dysfunctional within the HPT axis (Duval *et al.* 1990, 1996). All large number of studies have reported that TRH testing in depressed patients with normal thyroid function have consistently revealed a blunted TSH response (Prange *et al.* 1972; Kastin *et al.* 1972; Loosen & Prange 1982; Loosen 1985), suggesting a downreguation of pituitary TRH receptors in response to hypersecretion of hypothalamic TRH. Alternatively, thyroid hormones may not be effectively transferred to the CNS in patients with depression. Decreased CSF concentrations of transthyretin, which is essential for the transport of thyroid hormone across the blood-brain barrier, have been reported in patients with depression (Hatterere *et al.* 1993; Sullivan *et al.* 1999). Thyroid hormone supplementation, primarily with T3, is an effective augmentation treatment strategy in refractory depression (Aronson *et al.* 1996; Iosifescu *et al.* 2005). Recently, T3 augmentation of sertraline treatment of depression demonstrated the efficacy of this augmentation strategy (Cooper-Kazaz *et al.* 2007). One interesting observation that suggests a role for HPT system dysfunction in major depression comes from the antidepressant action of TRH itself. TRH has been shown to have antidepressant action in patients with treatment-refractory depression (Callahan *et al.* 1997;

Marangell *et al.* 1997). The non-relapsing group in our study showed a blunted TSH response to the TRH test. One possible explanation for this is that increased secretion of TRH into the hypophyseal-portal circulation may induce a down-regulation of TRH receptors in the pituitary.

Relationship between the HPA and HPT axes in depression

Contrary to our initial hypothesis, our lack of findings on a relationship between the HPA axis and HPT axis in depression support the report of Lesch *et al.* (1989), who found no correlation between these systems. However, our methods differ from theirs in that our subjects were pretreated with DEX before hormone testing (Lesch *et al.* 1989). It has been suggested that corticosteroid-serotonin (5-HT) interactions are also central to the pathophysiology of depression. The 5-HT system and HPA axis appear to have a complex interrelationship, although no clear conclusions have been reached regarding the relationship between the HPA axis and 5-HT function in depression (Porter *et al.* 2004). It is conceivable that a 5-HT-mediated relationship exists between the HPA and HPT axes, since both appear to be related to the 5-HT system.

A few clinical studies have assessed potential interactions between CNS monoaminergic systems and HPT axis function. In a recent study of healthy people, CSF 5-HIAA and HVA levels were negatively correlated with plasma TSH and T3 (Strawn *et al.* 2004), indicating that CNS monoamine-thyroid interactions are of physiological significance in euthyroid subjects. In a study of male violent offenders, a positive correlation between CSF HVA and the peripheral T3/T4 ratio was reported, indicating that increased dopaminergic activity is associated with increased peripheral thyroid hormone activity (Yhede *et al.* 2003).

Limitations

Some limitations of this study must be mentioned. First, this study was limited by its small sample size, which may have given rise to type II errors. For example, although there was no significant difference in antidepressant dosing at the time of discharge between the relapsing and non-relapsing groups, the possibility remains that insufficient antidepressant dose led to recurrence in some patients, but the sample size may have been too small to detect significant differences between antidepressant doses. In addition, plasma DEX concentration was not measured prior to CRH injection in the DEX/CRH test, although subjects were confirmed to have received DEX by the medical staff during hospitalization. There were also differences among patients in both intervals between hormonal tests and in the order that these tests were given, since the two hormone tests were repeated. However, since hospitalization itself can be a markedly stressful event for patients, we avoided performing hormone tests on the first or second day after admission. To avoid the effects of prior hormone testing, we arranged for an interval greater than three-day between the two tests. Since some maximum values in neuroendocrine tests were collected from the last point of measurement, it is unclear whether they represent true peak levels in neuroendocrine response to hormone stimulation. Determination of compliance/adherence to medication regimens was based on information supplied by the patients and their families and/or partners, and serum concentrations of antidepressants were not measured. A lot is made of the relationship between various factors such as age and sex on DEX/CRH findings. However, our study is not powerful enough to show such effects and other institutes such as the Max Plank team have much larger samples to answer these questions (Heuser 1994b). Finally, medications taken by subjects might have affected the results of the hormone tests, although we excluded subjects receiving carbamazepine, and no significant relationships were found between test results and antidepressant type in this study, or in previous reports (Heuser *et al.* 1996, Correa *et al.* 2001, Kunzel *et al.* 2003 and Kunugi *et al.* 2006). Moreover, Watson *et al.* (2004) reported that neither DEX levels nor changes in cortisol levels differed in patients taking CYP3A4-inhibiting drugs, lithium, or selective serotonin reuptake inhibitors versus patients not taking these drugs.

CONCLUSION

In conclusion, this study demonstrates that the DEX/CRH test is likely to be a state marker for depression, and that TRH testing at the time of discharge was found to predict recurrence within ten years after discharge in subjects with depression. Given the low R-squared values in this study, presumably due to the small sample size, further investigation is required to draw definitive conclusions regarding the relationship between HPT function and depression outcomes. This study suggests that the TRH test may be a predictor of future recurrence in patients with depression.

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