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Preliminary Communication

Combined dexamethasone suppression–corticotrophin-releasing hormone stimulation test in medication-free major depression and healthy volunteers

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ABSTRACT

Background: The hypothalamic–pituitary–adrenal (HPA) axis is dysfunctional in a subgroup of mood disorders.
Methods: We compared cortisol and adrenocorticotropic hormone (ACTH) responses in major depression and healthy volunteers to the combined dexamethasone suppression–corticotrophin-releasing hormone stimulation (DEX–CRH) test. Unlike other published studies, the study patients were medication-free and the healthy volunteers did not have first-degree relatives with a mood or psychotic disorder. Demographics, DSM-IV diagnoses and other clinical parameters were evaluated in major depressive disorder (MDD) and healthy control groups. Participants received an oral dose of 1.5 mg dexamethasone at 11 pm the day before CRH administration. On the following day, at 3 pm, 100 μg of ovine CRH was infused. Blood samples for determination of cortisol and ACTH were collected every 15 min from 3 pm to 4:15 pm. Cortisol and ACTH responses were calculated as areas under the curve.
Results: Controlling for age, *baseline* (i.e., post-dexamethasone) ACTH levels were higher in depressed patients compared to controls ($p=0.01$). There was a trend for higher ACTH responses in depressed patients compared to the control group ($p=0.08$). In depressed patients, cortisol and ACTH responses correlated positively with age, duration of illness and number of hospitalizations.
Limitations: Because of the cross-sectional study design we can only evaluate the nature of potential HPA axis disturbances that were present in patients when they are acutely depressed.
Conclusions: Feedback inhibition of ACTH secretion by cortisol is compromised in MDD, and this is independent of an age effect on the HPA axis function.

1. Introduction

The HPA axis is dysfunctional in mood disorders (Lloyd and Nemeroff, 2011; Ströhle and Holsboer, 2003; Watson and Mackin, 2006). The pattern of the HPA axis dysregulation in major depression includes impaired inhibition of cortisol release by dexamethasone, higher baseline cortisol values, greater 24 h excretion of cortisol and an overactive response to psychological stressors. It has been suggested that some of these observations are related to abnormalities in the HPA axis' negative feedback system and corticotrophin-releasing hormone (CRH) production (Lloyd and Nemeroff, 2011; Ströhle and Holsboer, 2003; Watson and Mackin, 2006). Adrenal hypertrophy can contribute to cortisol hypersecretion in some patients with major depression. Compared with non-depressed controls, individuals with major depressive disorder may possess a differentially reactive HPA axis, both between and during their episodes of depression (Lloyd and Nemeroff, 2011; Ströhle and Holsboer, 2003; Watson and Mackin, 2006).

A number of tests have been developed to assess the HPA axis activity, and one of the most common is the dexamethasone suppression test (DST) (Rush et al., 1996; Sher and Mann, 2003). During normal HPA axis activity, administration of dexamethasone, an exogenous synthetic glucocorticoid hormone, inhibits release of CRH and release of adrenocorticotropic hormone (ACTH), and both effects result in less release of cortisol from the adrenal gland. Considerable evidence suggests that resistance to dexamethasone suppression of cortisol levels is seen in more severe forms of major depression (Dratcu and Calil, 1989; Rush et al., 1996). A combined dexamethasone suppression–CRH stimulation (DEX–CRH) test has also been developed as a potentially more sensitive measure of HPA axis dysfunction in mood disorders

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(Heuser, 1998; Holsboer, 2000). In this test, dexamethasone is administered orally at night to suppress cortisol, and then subjects receive an i.v. bolus of CRH in the afternoon of the following day. This approach measures HPA function downstream from CRH, including cortisol feedback or dexamethasone inhibition of ACTH.

The results of the DEX–CRH studies in depression have been inconsistent. Some report greater cortisol and ACTH responses in depressed patients compared to healthy controls (Heuser et al., 1994a; Holsboer et al., 1987; Modell et al., 1997). High cortisol DEX–CRH response has been attributed to three potential effects: adrenal cortical hypertrophy that causes ACTH-independent, elevated but disorderly basal cortisol release (Carroll et al., 2007); amplification of the CRH signal at the level of the pituitary by arginine vasopressin (Scott et al., 1999); and altered function of the glucocorticoid receptors in the feedback loop at the level of ACTH release (Modell et al., 1997; Spijker and van Rossum, 2012). However, the finding of cortisol hyper-reactivity to this and other neuroendocrine probe measures, once considered a hallmark of major depressive disorder (MDD) with melancholic features, has not been consistently observed in depressive populations. For example, in one study, cortisol response to the DEX–CRH test in subjects with current MDD was comparable to that seen in matched healthy controls (Carpenter et al., 2009).

We compared cortisol and ACTH level in subjects with DSM-IV MDD and off psychotropic medications with healthy volunteers. Our study differed from published studies in that our patients were *medication-free* and our controls *did not have* a history of a mood or psychotic disorder in their first-degree relatives.

2. Methods

2.1. Subjects

Participants were recruited through advertising and referrals. After a description of the study, all subjects gave written informed consent as required by the Institutional Review Board. Forty-two subjects participated in the study: 17 patients with major depressive disorder (MDD) and 25 healthy volunteers.

All depressed subjects met the following inclusion criteria: (1) age 18–65 years; (2) DSM-IV criteria for a current major depressive episode (MDE); and (3) ≥two week medication-free period prior to the DEX–CRH test (four weeks for oral neuroleptics and six weeks for fluoxetine). Healthy controls were 18–65 year-old and required to have no psychiatric history, be medically free from signiticant illness and no history of a mood or psychotic disorder in their first-degree relatives.

All subjects were free from alcohol or substance use disorders for at least 2 months prior to study entry. The duration of the drug-free status of the subjects was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the participant, the participant's family and the referring physician. At enrollment, all subjects were free of acute or serious medical illness, based on history, physical examination and laboratory tests, including liver function tests, hematologic profile, thyroid function tests, urinalysis and toxicology.

2.2. Clinical Measures

MDD was diagnosed using the Structured Clinical Interview (SCID) for DSM-IV (Spitzer et al., 1996). Current severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). Lifetime aggression and impulsivity were assessed with the Aggression History Scale (Brown and Goodwin 1986) and the Barratt Impulsivity Scale, respectively (Barratt, 1965). Hostility (lifetime) was rated with the Buss-Durkee Hostility Inventory (Buss and Durkee, 1957). The Scale for Suicide Ideation (SSI) was used to measure the severity of suicidal ideation (Beck et al., 1999), and hopelessness during the previous week was measured with the Beck Hopelessness Scale (BHS) (Beck et al., 1974). A lifetime history of all suicide attempts, including number of attempts and the method of the attempt, was recorded on the Columbia Suicide History Form (Oquendo et al., 2003). A suicide attempt was defined as a self-destructive act that was committed with some intent to end one's life. Additionally, the Medical Lethality Rating Scale was used to measure the degree of medical damage caused by each suicide attempt (Beck et al., 1975). The scale was scored from 0 to 8 (0=no medical damage, 8=death), with anchor points for different suicide attempt methods. The degree of suicide intent for the worst suicide attempt was rated with the Suicide Intent Scale (Beck et al., 1979). Interviewers were Masters or PhD-level psychologists. Inter-rater reliability was good to excellent (ICC 0.71-0.97).

2.3. The combined dexamethasone suppression–corticotropin releasing hormone stimulation (DEX–CRH) test

Participants received an oral dose of 1.5 mg dexamethasone at 11 pm the day before the CRH administration. On the following day, at 1:30 pm they rested supine on a bed. An intravenous forearm catheter was placed. At 3 pm, 100 μg of ovine CRH (corticorelin ovine triflutate, Acthrel®, Ferring Pharmaceuticals, Inc.) reconstituted in 0.9% saline was infused within 30 s. Blood samples for cortisol and ACTH determination were collected from 3 pm to 4:15 pm every 15 min. Cortisol and ACTH levels at 3 pm were regarded as baseline levels in this study. Samples were immediately centrifuged and stored at –80 °C (ACTH) and –20 °C (cortisol). Cortisol was measured using a commercial radioimmunoassay. Plasma ACTH was measured by immunoradiometric assay.

2.4. Statistical analysis

Demographic and clinical data were compared using Student's *t*-test and chi-square test, as appropriate. Cortisol and ACTH responses were calculated as areas under the curve. Baseline cortisol and ACTH levels, cortisol and ACTH responses were compared using Student's *t*-test. A univariate model was used to compare baseline cortisol and ACTH levels controlling for age, and cortisol and ACTH responses controlling for age and controlling for age and baseline levels. SPSS 19.0 program was used to perform statistical analyses.

3. Results

Demographic and clinical characteristics of depressed patients and healthy volunteers are presented in Table 1. Healthy volunteers were younger compared to patients. As expected, Hamilton Depression Rating Scale, Beck Depression Inventory, Beck Hopelessness Inventory, Buss-Durkee Hostility Inventory, Suicide Ideation Scale, Reasons for Living Scale, and Ramsey Life Events Scale scores were significantly higher in MDD patients compared to healthy controls.

In depressed patients, cortisol and ACTH responses positively correlated with age ($r=0.63$, $p=0.007$, and $r=0.65$, $p=0.005$, respectively) and duration of illness ($r=0.49$, $p=0.04$, and $r=0.55$, $p=0.02$, respectively). We could not separate the effects of age from duration of illness due to their high positive correlation within patients ($r=0.9$, $p<0.001$). In contrast, there was no