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Dex/CRH test cortisol response in outpatients with major depression and matched healthy controls

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Summary
Background: The dexamethasone/corticotropin releasing hormone (Dex/CRH) test has been proposed as a potential tool for identifying endophenotypes relevant to mood disorders. An exaggerated cortisol response to the test during major depressive episodes has been demonstrated for inpatients with melancholic or psychotic features. A diminished hormone response has been observed in chronically depressed outpatients.
Methods: Following a battery of self-report and interview assessments, 68 adults completed the Dex/CRH test. Thirty-four met structured interview criteria for current major depressive disorder and 34 age- and sex-matched control subjects had no current *or* lifetime DSM-IV depressive disorder. Effect of diagnosis on cortisol response to the Dex/CRH test was examined in a repeated measures general linear model.
Results: The matched groups were equivalent with regard to childhood adversity. Cortisol response to the Dex/CRH test among subjects with current MDD was not significantly different from that seen in matched healthy controls. Independent of diagnosis, an exploratory analysis showed a trend-level association between maltreatment history and diminished cortisol response; no interactive effects with depression diagnosis were detected.
Conclusions: The results do not support the hypothesis that elevated cortisol response to the Dex/CRH test represents a marker for major depressive episodes.

1. Introduction

During the 1980s, the dexamethasone suppression test (DST) became a popular research tool for assessment of hypothalamic—pituitary—adrenal system function in depression (Carroll et al., 1981). Despite its utility in the prediction of clinical outcome in some patients (Greden et al., 1983;

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Ribeiro et al., 1993), especially those with psychotic features (Nelson and Davis, 1997), widespread use of the DST as a diagnostic tool was limited by the test's low sensitivity, ranging between 20% and 50% (Arana et al., 1985).

The DST was extended and refined by combining it with the corticotropin releasing hormone (CRH) stimulation test, which involves placement of an intravenous line for serial withdrawal of blood samples before and after an injected bolus of CRH. Holsboer-Trachsler and colleagues (Holsboer-Trachsler et al., 1987) developed the combined dexamethasone/CRH test to enhance the magnitude of observed differences between healthy controls and depressed patients. The test involves pre-treatment with oral dexamethasone (Dex) 1.5 mg at 11:00 p.m. followed by administration of CRH 100 μg via intravenous bolus at 3:00 p.m. the next day. The Dex/CRH test cortisol response curve incorporates several components, each of which may be uniquely relevant to vulnerability for mood disorders and response to past and current stressors. The post-dex (pre-CRH) baseline cortisol value(s) represent an index of glucocorticoid feedback suppression sensitivity at the level of the pituitary, while the subsequent, post-CRH infusion time-course curve reflects capacity to escape from relative suppression and mount a pituitary–adrenal hormone response to the CRH bolus. In essence, the Dex/CRH test allows examination of an individual's physiological HPA response to a "chemical" stress stimulus (i.e., intravenous CRH bolus) in a psychologically neutral setting, largely bypassing limbic and higher cortical inputs engaged by a physically or emotionally threatening stressor. It provides both baseline and dynamic stress-response system data, and can be easily administered in a standard laboratory setting. As such, the Dex/CRH test may prove to be a useful assessment tool for identification of endophenotypes relevant to risk for mood disorders.

Some of the initial literature related to the Dex/CRH test and depression described *elevated* cortisol and ACTH responses seen among severely ill depressed inpatients, relative to healthy controls (Heuser et al., 1994; Holsboer et al., 1987; Modell et al., 1997), with a tendency for the post-CRH infusion cortisol response curves to diminish or "normalize" with antidepressant treatment and resolution of depressive symptoms (Nikisch et al., 2005). High cortisol Dex/CRH response has been attributed to a change in the adrenal cortex that causes ACTH-independent, disorderly basal cortisol release (Carroll et al., 2007), to amplification of the CRH signal at the level of the pituitary by arginine vasopressin (Scott et al., 1999), and to altered capacity or function of the glucocorticoid receptors in the feedback loop (Holsboer, 2000; Modell et al., 1997). Perhaps most consistently reported in the literature are associations of exaggerated cortisol Dex/CRH response with (1) shortened time to relapse and greater recurrence of depressive episodes (Appelhof et al., 2006; Aubry et al., 2007; Hatzinger et al., 2002) and (2) psychotic and melancholic features (Carroll et al., 2007). However, the finding of cortisol hyper-reactivity to this and other neuroendocrine probe measures, once considered a hallmark of major depressive disorder (MDD), has not been consistently borne out in research examining HPA axis reactivity in a variety of depressive subpopulations.

For example, research in this area has demonstrated that a pattern of relatively "excessive" cortisol release, as measured by the increased response to the Dex/CRH test, is typically not associated with depression in outpatients or in those with chronic course or atypical features (Brouwer et al., 2006; Gervasoni et al., 2004; Oshima et al., 2000; Rydmark et al., 2006; Watson et al., 2002). Suicidal behavior has also been shown to be more characteristic of depressed inpatients with *attenuated*, rather than exaggerated, Dex/CRH responses (Pfennig et al., 2005), and significantly *lower* cortisol and ACTH responses to the Dex/CRH were reported in a study of depressed women with chronic social stressors (Rydmark et al., 2006), a pattern interpreted as reflecting hypoactive central stress-response circuitry.

This apparent inconsistency may suggest two distinct endophenotypes of major depression that manifest clinically with overlapping symptoms (Bremmer et al., 2007; Penninx et al., 2007). Alternatively or additionally, other independent variables associated with HPA axis response, such as exposure to childhood adversity, may be the relevant determinants of the direction of abnormal Dex/CRH findings seen in some patient groups. One investigation that evaluated depressed patients with the Dex/CRH test while considering the effects of early life trauma in men (Heim et al., 2008) found hormone responses associated with MDD in men differed as a function of childhood trauma history. Another study comparing depressed patients with healthy controls on the Dex/CRH test found that patients reporting high levels of childhood emotional neglect had cortisol response patterns similar to those seen among healthy controls, while depressed patients without such histories had relatively elevated levels (Watson et al., 2007). To further investigate the relative effects of depression diagnosis and self-reported early life stress on Dex/CRH response, we compared a group with current MDD and a matched group without any history of depressive disorder. The potential confounding effect of childhood maltreatment was examined in post-hoc analyses.

2. Methods and materials

Sixty-eight adults participated in this study. Control subjects were recruited from the community via flyers as well as through Internet and newspaper advertisements for healthy adults. Outpatients with MDD seeking treatment in clinical trials and individuals in the community responding to newspaper advertisements describing research on depressive symptoms were recruited. Depressed subjects were matched by age and sex to a control group of subjects who reported no current or lifetime mood disorders, as confirmed by diagnostic interview. Subjects underwent physical and neurological examinations. Electrocardiograms and laboratory studies for complete blood count, serum electrolytes, thyroid stimulating hormone, urine toxicology, and urinalysis were conducted. Subjects were excluded if they worked night shifts, or if they had one or more of the following conditions: acute or unstable medical illness, a history of brain injury, seizure disorder, endocrine disease, or current substance abuse. Also excluded were individuals undergoing treatment with drugs which might influence HPA axis function, including psychotropic medications, beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids. Subjects were free of these medications for at least two weeks (6 weeks for fluoxetine) prior to partici-