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A placebo-controlled study of sertraline's effect on cortisol response to the dexamethasone/corticotropin-releasing hormone test in healthy adults

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Abstract

Rationale—The dexamethasone/corticotropin-releasing hormone (Dex/CRH) test is a neuroendocrine probe involving serial blood sampling of cortisol during a standardized pharmacological challenge without inducing psychological distress in humans. Some past studies

in depressed patients have shown a “normalization” or decrease in cortisol response to the Dex/CRH test following successful treatment with an antidepressant. Studies in nondepressed healthy adult samples have also shown aberrant cortisol reactivity to be associated with depression risk factors. These findings prompted research into the use of the Dex/CRH test as a tool for developing antidepressant drugs.

Objectives—In this study, the Dex/CRH test was evaluated with regard to its potential utility for drug development in nonclinical samples.

Methods—The Dex/CRH test was administered before and after 6 weeks of blinded treatment with either sertraline 100 mg/day or matching placebo in 22 healthy adults (13 women, nine men).

Results—Cortisol response to the Dex/CRH test increased following treatment with standard doses of sertraline, compared to placebo, after controlling for age and sex.

Conclusions—The observed pattern of change contrasts with results from published studies in depressed patients and with our initial hypothesis.

Keywords

Sertraline; Dex/CRH test; Cortisol; HPA axis

Introduction

Many have come to associate major depression with findings of excessive output by the hypothalamic–pituitary–adrenal (HPA) system and with glucocorticoid receptor resistance. These biological correlates have been suggested by numerous studies comparing basal and provoked cortisol concentrations in patients and nondepressed controls (Holsboer 2001; Ising et al. 2007). Some research groups have demonstrated “normalization” or dampening of cortisol indices concurrent with clinical improvement, as detected by response to standardized neuroendocrine challenge tests such as the dexamethasone/corticotropin-releasing hormone (Dex/CRH) test (Hatzinger et al. 2002; Heuser et al. 1996; Horstmann et al. 2009; Nickel et al. 2003; Zobel et al. 2001). The convergence of data generated with the Dex/CRH test in depression studies has led some researchers to consider whether the Dex/CRH test cortisol response may represent a trait marker (Holsboer et al. 1995) or a useful endophenotype (Hasler et al. 2004; Ising et al. 2007) for major depression or other psychiatric disorders. Others have suggested that the Dex/CRH test could be helpful in identifying candidate drugs for development as antidepressant medications (Ising et al. 2005a).

Compared with nondepressed controls, individuals with major depressive disorder may possess a differentially reactive HPA axis, both before and during their episodes of depression. Although the amplitude of the effect of an antidepressant drug may be very different in healthy and depressed individuals, it is unlikely that the fundamental mechanism of interaction between the drug and the HPA axis differs between the two groups. The preponderance of evidence suggests that modifications of HPA function occurring in depression are ones of degree rather than of kind (Ising et al. 2005a; Paizanis et al. 2009; Pariante et al. 2003; Schule 2007). Indeed, all preclinical work investigating the effects of

antidepressants on components of the HPA axis, including in vitro and animal studies, assumes that the fundamental effects of the drugs will be the same regardless of individual differences in the system being studied.

Aberrant cortisol reactivity measured with the Dex/CRH test has been reported in adults (without psychopathology) selected on the basis of depression risk factors such as family history (Ising et al. 2005b), chronic work stress (Wirtz et al. 2008), inhibited temperament (Tyrka et al. 2008b), childhood parental loss (Tyrka et al. 2008a), and exposure to trauma in adulthood (Klaassens et al. 2010). The potential utility of characterizing the nature and consequences of these HPA axis reactivity endophenotypes is not known. The paucity of data on antidepressant treatment effects in nondepressed human subjects, including data describing treatment effects on candidate biomarkers such as cortisol reactivity, limits the ability to generate hypotheses about how pharmacological interventions might mitigate risk for developing psychiatric disorders. With these considerations in mind, we examined the effects of a standard antidepressant treatment on cortisol response to the Dex/CRH test in a randomized controlled trial with nondepressed healthy adult subjects. Based on past observations that cortisol response curves were generally reduced following successful antidepressant therapy, we studied healthy individuals with relatively high baseline cortisol responses to the test and hypothesized that 6 weeks of treatment with sertraline would lead to reductions in cortisol response, relative to that observed in subjects given placebo.

Methods

Subjects

Subjects were recruited from the community via flyers and through Internet and newspaper advertisements for healthy adults. Voluntary written informed consent was obtained for the study, which was approved by the Butler Hospital Institutional Review Board.

Phone screens and diagnostic interviews at the first clinic visit were used to exclude subjects meeting diagnostic criteria for current major depression, bipolar disorder, posttraumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, social anxiety disorder, panic disorder, substance use disorders, and all disorders characterized by psychosis. Current and lifetime history of axis I psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID; First et al. 1996). The SCID is a semi-structured diagnostic interview designed to evaluate symptoms corresponding with DSM-IV axis I disorders. Individuals endorsing only symptoms consistent with a diagnosis of dysthymia or specific phobia were not excluded from participation. Subjects with remote mood or substance use disorders were also not excluded, provided the symptoms were not clinically manifest and treatment was not indicated for at least the 1 year prior to participation in this study.

Participants completed physical and neurological examinations and laboratory studies, including electrocardiogram, complete blood count, serum electrolytes, thyroid-stimulating hormone (TSH), urine toxicology, and urinalysis. Subjects were excluded from the study if they worked night shifts or if they had acute or unstable medical illness, a history of brain injury, seizure disorder, endocrine disease, or recreational use of illicit substances. 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 2 weeks (or five half-lives, if appropriate) prior to participation. Oral contraceptives and estrogen replacement therapies were allowed.

Assessment instruments

The following additional self-report measures were included to characterize the sample at baseline in terms of symptoms and overall functioning: (1) Inventory of Depressive Symptomatology—Self-Report (IDS-SR; Rush et al. 1996), (2) State-Trait Anxiety Questionnaire (STAI; Spielberger 1983), (3) Perceived Stress Scale (Cohen et al. 1983), (4) Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott et al. 1993), and (5) the 28-item version of the Childhood Trauma Questionnaire (Bernstein et al. 2003).

The Dex/CRH test

During a separate clinic visit, subjects completed the Dex/CRH test. The night before the test, a single oral dose of dexamethasone 1.5 mg was self-administered at 11:00 P.M. The following day, participants arrived at 12:00 P.M. and were given lunch. Topical anesthetic cream containing lidocaine 2.5% and prilocaine 2.5% was applied to the subject's forearm between 12:30 and 12:45 P.M. Participants were queried prior to beginning the Dex/CRH test for any excessive use of alcohol the night prior, and urine toxicology screens were required prior to and on day of test, if use was suspected for any reason. According to our standard procedures, subjects were encouraged to maintain their usual daily habits with regard to consumption of modest amounts of caffeinated and alcoholic beverages and nicotine use before the Dex/CRH tests, to avoid precipitating withdrawal symptoms. Concurrent medication use, recorded at the time of pre-treatment physical exam and at each Dex/CRH test, revealed participants were taking the following: over-the-counter vitamins ($n=7$), inhalers prescribed for use as-needed for mild/intermittent bronchoconstriction ($n=2$; none used during the test procedure), stable maintenance doses of levothyroxine with normal range TSH ($n=2$), and stable use of oral contraceptive tablets ($n=2$) or a contraceptive vaginal ring ($n=1$).

At 1:00 P.M., an indwelling intravenous (IV) catheter was inserted in the forearm by a research nurse with extensive experience with IV catheter placement. Subjects then remained in a semi-recumbent position throughout the procedure except to use the bathroom. They were permitted to read or watch pre-selected movies that did not contain emotionally charged material. Vital signs were monitored throughout the test. At 3:00 P.M., CRH (corticotropin ovine triflutate, Acthrel®, Ferring Pharmaceuticals, Inc.) 100 µg reconstituted in 2 ml 0.9% sodium chloride was infused intravenously over 30 s. Blood samples were drawn at 2:59 P.M. (baseline) and following the CRH infusion at 3:30 P.M. (30 min), 3:45 P.M. (45 min), 4:00 P.M. (60 min), and 4:15 P.M. (75 min). Samples were immediately stored on ice, centrifuged within 45 min, and then stored at -80°C for assay of cortisol.

Plasma cortisol concentration was measured with the double antibody DSL-2000 Cortisol Radioimmunoassay Kit (Diagnostic Systems Laboratories, Webster, TX, USA) according to the manufacturer's instructions. The antiserum has 100% cross-reactivity with cortisol and only 0.38% cross-reactivity with dexamethasone. The intra- and inter-assay coefficients of variation are 5.3% and 7.0%, respectively. Using a 25- μ l sample, the minimum detectable level of cortisol is 4.8 nmol/l. Pre-treatment and post-treatment cortisol response curves were generated for each subject and area under the curve (AUC) calculated with the trapezoidal rule.

Randomization, drug treatment, and follow-up assessments

Subjects were considered eligible, randomized, and instructed to commence study medication approximately 7–10 days following their initial Dex/CRH tests if assay results confirmed a pre-treatment cortisol AUC response of 3,000 nmol/l min or greater. As “normal” reference ranges for Dex/CRH test cortisol response are not known, this criterion for minimum cortisol response was based on descriptive (median and range values) statistics derived from our healthy subject database at the time of study initiation, as well as on practical considerations of feasibility in recruiting healthy subjects with a sufficiently high baseline cortisol response to the Dex/CRH test to permit testing of our a priori hypothesis. The (unblinded) data manager ran a computer-generated randomization procedure (SPSS) to generate a random and unpredictable sequence of allocations to two treatment groups before the trial began. The randomization list was kept in the hospital pharmacy, where prescriptions for study medication were received, assigned to drug or placebo according to serial entry on the list, and filled by the unblinded research pharmacist. The subject assignment list was released by the pharmacist following collection of all data at the end of the study.

Subjects started sertraline at 50 mg (one capsule) or matching placebo each day for 7 days. If no significant side effects occurred, the dose was titrated to 50 mg twice daily for weeks 2 through 6. Compliance, somatic symptoms, and side effects were measured at baseline and after weeks 2, 4, and 6 on drug by spontaneous report, general clinical interview, and with a self-report checklist (Symptom Checklist-90; Derogatis and Cleary 1977). Self-report forms at each assessment included the Adverse Symptoms Checklist (SAFTEE-SI; Levine and Schooler 1986). Following 6 weeks of drug or placebo treatment, the IDS-SR scale and Dex/CRH test were repeated, and cortisol assays were performed. Women were scheduled for their post-treatment Dex/CRH tests after consideration of number of days from last menses and approximate phase of menstrual cycle to enhance consistency of hormonal state across assessment times.

Statistics

Simple descriptive statistics were used to characterize treatment-emergent side effects. *t* test and chi-square statistics were used to compare sample characteristics, and a bivariate correlation matrix was generated to examine relationships between pre-treatment cortisol AUC and other baseline clinical characteristics. For each subject, the change in cortisol AUC from pre-treatment to post-treatment Dex/CRH test (Δ AUC) was calculated. General linear model (GLM) univariate analysis of variance was used to examine the effect of

treatment group on cortisol AUC, controlling for pre-treatment AUC value. Independent samples *t* tests were used to test for baseline sex differences in pre-treatment data, and paired *t* tests were used to compare within-subject data from serial assessments in each treatment group. Post hoc GLMs were constructed to examine the treatment group effect with sex and age as covariates and the durability of main findings when other potential confounds were included in the model (BMI, dichotomized nicotine use, and depression scale scores).

Results

Fifty-five subjects underwent baseline assessments, including Dex/CRH testing. Twenty-three subjects met criteria for minimum baseline cortisol AUC (AUC greater than 3,000 nmol/l min) and were randomized to treatment with either sertraline or placebo; $n=22$ completed the post-drug assessments and repeat neuroendocrine test. Diagnostic interviews determined that nine of the final 22 participants met criteria for “probable” or “definite” past (lifetime) axis I disorders; four of these were randomized to sertraline and five to placebo treatment. A total of three subjects had sought or received past treatment for psychiatric symptoms (two in sertraline and one in the placebo group); one had been treated for substance-induced mood disorder and remote alcohol dependence followed by nearly 10 years sustained remission of both conditions; one subject was treated for symptoms of dysthymia, and one subject was treated for a past single episode of major depression considered to be mild or moderate in severity, followed by full remission over 5 years without subsequent treatment. All previous psychiatric treatments had been undertaken over 5 years prior to the beginning to this investigation.

The distribution of sex across randomized groups included 13 women ($n=6$ [46%] to sertraline and $n=7$ [54%] to placebo) and nine men ($n=5$ [56%] to sertraline and $n=4$ [45] to placebo), a nonsignificant difference on chi-square analysis. There were no significant differences between the sertraline and placebo groups on any of the clinical and demographic variables examined (Table 1), and there were no significant correlations found between pre-treatment cortisol AUC and the other clinical symptom or demographic measures represented as continuous data. Comparison of male and female subjects with independent *t* tests showed pre-treatment cortisol AUC values did not differ by sex. Cortisol concentrations for “time point 0” (following dexamethasone pre-treatment but before infusion of the CRH challenge dose) did not differ between groups at the pre-treatment assessment, between groups as the post-treatment assessment, or within groups over time. There was a wide range of pre-treatment cortisol AUC response values, ranging from 4,201 to 12,393 nmol/l min, but the means did not differ significantly between groups (mean $\pm$ SD, 8,089 $\pm$ 2,363 vs 8,858 $\pm$ 2,203; $p=0.44$). The post-treatment cortisol AUC ranged from 1,035 to 23,279 nmol/l min.

The GLM revealed a significant effect of treatment group ($F=6.7$, $p=0.02$), such that mean cortisol AUC was greater for those who took active sertraline than for those in the placebo group. As graphed in Fig. 1, sertraline treatment was associated with an overall *increase* in mean cortisol response to the test. Pre-treatment cortisol AUC, entered in the model as a covariate, was associated with AUC ($F=5.8$, $p=0.03$) in a fashion suggesting greater

changes over time among those who had relatively lower pre-treatment cortisol responses to the Dex/CRH test. A post hoc model which also included age and sex as covariates retained the significant treatment group effect ($F=10.2$, $p=0.005$), after controlling for the effect of sex ($F=9.1$, $p=0.008$). Use of estrogen was not significantly related to pre-treatment cortisol AUC values or to cortisol AUC in either group.

Several other potentially confounding variables were subsequently examined. There were no statistically significant effects of age or BMI on the outcomes, and analyses re-run with nicotine use ($n=1$ smoker in placebo group, $n=2$ smokers in sertraline) included as a covariate in the model also retained their statistically significant main finding of treatment group effect. We did not detect a significant change in (subclinical) depressive symptom scores following drug treatment in either group. The magnitude of cortisol AUC with treatment did not correlate with corresponding change in IDS-SR scores over time.

Treatment-emergent side effects reported by the subjects were consistent with those reported in clinical trials and in typical clinical practice. Two of the 11 sertraline subjects rated several related adverse effects as “severe”: One participant endorsed trouble sleeping, nightmares, drowsiness, and loss of sex interest, while another reported problems with sex arousal and interest, and orgasm. One additional subject reported drowsiness and one reported trouble sleeping. Cortisol AUC was not significantly different in these four subjects compared to the other sertraline subjects. There were no side effects ranked as “severe” by the placebo group, but a number of side effects were rated as “mild” or “moderate” by both groups.

Discussion

In contrast to our hypothesis, results of this study suggest that sertraline treatment at standard doses significantly *increases* the cortisol response to the Dex/CRH test in healthy adults with relatively high initial cortisol responses to the Dex/CRH test. A significant change in cortisol response to serial administration of the Dex/CRH test was not observed for those who received placebo.

It is unlikely that nonspecific stress effects of the test were inducing greater cortisol release at the post-treatment assessment, as all subjects were familiar with the laboratory procedure at that time and none reported subjective distress. Use of a design involving sequential within-subjects Dex/CRH tests compared across treatment groups, in conjunction with the finding that pre-infusion cortisol concentrations did not vary following the course of treatment, supports the inference that observed changes during sertraline treatment reflect the coordinated HPA axis response to the CRH infusion challenge rather than basal concentrations or the cortisol response to dexamethasone. The dose and duration of sertraline used in this study are consistent with standard clinical practice, though the absence of plasma sertraline and dexamethasone blood levels may be considered a limitation, especially in light of the unexpected findings.

Enrichment of the sample with individuals showing relatively high baseline cortisol response to the Dex/CRH test produced a sample whose proposed HPA reactivity

endophenotype was similar to that reported for other at-risk populations (Ising et al. 2005b; Zobel et al. 2004). The use of a minimal pre-treatment cortisol reactivity criterion might also represent a limitation of the current study design, since it was intended to exclude healthy subjects whose baseline cortisol response to the test was already too low to show treatment-induced reduction. However, this maneuver would not likely account for the sertraline-associated *increase* in cortisol we observed.

Prior studies in healthy adults have involved acute challenge with selective serotonin reuptake inhibitors (Carpenter et al. 2003; Laakmann et al. 1988; Petraglia et al. 1984; Seifritz et al. 1996; Skene et al. 1994; von Bardeleben et al. 1989), and these typically suggest stimulation of HPA axis as reflected by elevation in cortisol concentrations following a single dose administration. In healthy men, both resting state cortisol concentration and provoked cortisol response (to physical exercise challenge on a treadmill) measured 8.5 h following a single oral dose of sertraline 100 mg were greater than those following placebo administration (Ahrens et al. 2007). Increased cortisol secretion following acute sertraline challenge has also been observed in animal studies, particularly among females (Broadbear et al. 2004).

However, divergent neuroendocrine effects are commonly generated from experiments involving acute versus chronic exposure to antidepressant drugs in preclinical studies (Bano et al. 2010; O'Donnell and Grealy 1992), and enhanced cortisol reactivity is typically not seen in investigations of chronic antidepressant treatment effects in humans. A report by Heuser et al. (1996) included data from 14 age-matched healthy comparison subjects, whose pre- and post-amitriptyline treatment (6 week) cortisol data were contrasted with similar data obtained from 39 elderly patients with depression. While amitriptyline appeared to attenuate cortisol concentrations in the Dex/CRH test for a subset of depressed patients, the same pattern of change was not seen in healthy control subjects. That study did not include any controls with relatively “high” baseline cortisol reactivity, and no statistically significant relationship emerged between changes in cortisol response over time and resolution of depression symptoms.

One study of chronic sertraline treatment also examined acute HPA axis response to steroid challenge (Cooney and Dinan 2000). In six patients with melancholic depression, basal cortisol concentrations were significantly higher before 4 weeks of treatment with sertraline, compared to those obtained after treatment; all patients were considered clinical responders. Cortisol response curves (provoked by intravenous hydrocortisone infusion over 60 min) did not show change over time associated with antidepressant treatment in these patients, leading the authors to conclude that acute phase negative feedback mechanisms are intact in depression, even in the presence of relative basal hypercortisolism. A number of investigations in depressed patients have highlighted a pattern of *diminished* Dex/CRH test cortisol response over time as a correlate or predictor of clinical improvement during antidepressant therapy (Sagud et al. 2002; Schule et al. 2006), with persisting patterns of elevated cortisol response to the test despite clinical remission predicting enhanced risk for future relapse. Very few have found *increased* cortisol reactivity in depressed patients associated with chronic pharmacotherapy, though two studies reported increased cortisol

reactivity following lithium augmentation of antidepressants (Adli et al. 2009; Bschor et al. 2002).

One criticism of investigations into the usefulness of the Dex/CRH test as a predictor of antidepressant response has involved the ascertainment of “baseline” neuroendocrine data from depressed inpatients that are not free of psychotropic medications. Post hoc analyses from a multicenter study (Kunugi et al. 2006) indicated that concurrent medication use did not diminish the ability of the Dex/CRH test results to predict outcome at the time of hospital discharge. The results we report here for sertraline underscore the possibility that “baseline” Dex/CRH test values could be elevated or otherwise altered as a function of the underlying drug treatment, even if the antidepressant has been unsuccessful in producing symptom relief. Furthermore, a pattern of relatively “excessive” cortisol release to this neuroendocrine challenge has not proven characteristic of all severely depressed inpatients (Carroll et al. 2007; Pfennig et al. 2005; Schule et al. 2009) and is typically not associated with depression in outpatients or in those with atypical features (Brouwer et al. 2005; Carpenter et al. 2009a; Gervasoni et al. 2004; Oshima et al. 2000; Rydmark et al. 2006; Watson et al. 2002). Additional evidence of limited or no predictive utility comes from one recent report of serial Dex/CRH tests in depressed men, which found that relatively *low* cortisol response values before initiation of treatment predicted best outcome with fluoxetine (Paslakis et al. 2010).

In summary, our findings indicate that cortisol response to the Dex/CRH in healthy nondepressed adults does not appear to decrease over time with chronic antidepressant treatment. While we acknowledge the potential impact of the small sample size, there are no previous controlled studies to examine this effect in healthy subjects. These findings are important, given the extensive use of the Dex/CRH test for assessing HPA axis function in a variety of pathological conditions and for studying the mechanism of action of numerous therapeutic agents. A growing literature has identified a collection of clinical and demographic variables exerting significant effects on the cortisol response to the Dex/CRH test, including age (Kunugi et al. 2006), sex (Haefner et al. 2008), temperament (Tyrka et al. 2008b), coping style (Hori et al. 2010), early life adversity (Carpenter et al. 2009b; Heim et al. 2008), quality of parental care (Tyrka et al. 2008a), adult trauma exposure (Klaassens et al. 2009), social support (Tsuru et al. 2008), psychiatric comorbidity (Veen et al. 2009), and genotype (Binder et al. 2010; Tyrka et al. 2009; Zobel et al. 2010). Assumptions about qualitatively similar cellular and system-level responses to receptor activation by sertraline across depressed and healthy subjects supported the rationale for this investigation. Our unexpected findings lead us to speculate about contributions from the many complex effects involved in HPA axis reactivity and to conclude that the Dex/CRH test cortisol response may not be a useful tool for evaluating the potential effectiveness of antidepressants on HPA axis downregulation in healthy volunteers. Recent data describing gene–gender effects on Dex/CRH test response (Haefner et al. 2008) suggest a further avenue of research inquiry for understanding our results.

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References

- Adli M, Bschor T, Bauer M, Lucka C, Lewitzka U, Ising M, Uhr M, Mueller-Oerlinghausen B, Baethge C. Long-term outcome after lithium augmentation in unipolar depression: focus on HPA system activity. *Neuropsychobiology*. 2009; 60:23–30. [PubMed: 19684420]
- Ahrens T, Frankhauser P, Lederbogen F, Deuschle M. Effect of single-dose sertraline on the hypothalamus–pituitary–adrenal system, autonomic nervous system, and platelet function. *J Clin Psychopharmacol*. 2007; 27:602–606. [PubMed: 18004127]
- Bano S, Gitay M, Ara I, Badawy A. Acute effects of serotonergic antidepressants on tryptophan metabolism and corticosterone levels in rats. *Pak J Pharm Sci*. 2010; 23:266–272. [PubMed: 20566438]
- Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl*. 2003; 27:169–190. [PubMed: 12615092]
- Binder EB, Owens MJ, Liu W, Deveau TC, Rush AJ, Trivedi MH, Fava M, Bradley B, Ressler KJ, Nemeroff CB. Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. *Arch Gen Psychiatry*. 2010; 67:369–379. [PubMed: 20368512]
- Broadbear JH, Hutton LC, Clarke IJ, Canny BJ. Sex differences in the pituitary–adrenal response following acute antidepressant treatment in sheep. *Psychopharmacol Berl*. 2004; 171:450–457.
- Brouwer JP, Appelhof BC, Hoogendijk WJ, Huyser J, Endert E, Zucketo C, Schene AH, Tijssen JG, Van Dyck R, Wiersinga WM, Fliers E. Thyroid and adrenal axis in major depression: a controlled study in outpatients. *Eur J Endocrinol*. 2005; 152:185–191. [PubMed: 15745924]
- Bschor T, Adli M, Baethge C, Eichmann U, Ising M, Uhr M, Modell S, Kunzel H, Muller-Oerlinghausen B, Bauer M. Lithium augmentation increases the ACTH and cortisol response in the combined DEX/CRH test in unipolar major depression. *Neuropsychopharmacology*. 2002; 27:470–478. [PubMed: 12225704]
- Carpenter LL, Anderson GM, Siniscalchi JM, Chappell PB, Price LH. Acute changes in cerebrospinal fluid 5-HIAA following oral paroxetine challenge in healthy humans. *Neuropsychopharmacology*. 2003; 28:339–347. [PubMed: 12589387]
- Carpenter LL, Ross NS, Tyrka AR, Anderson GM, Kelly M, Price LH. Dex/CRH test cortisol response in outpatients with major depression and matched healthy controls. *Psychoneuroendocrinology*. 2009a; 34:1208–1213. [PubMed: 19375869]
- Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, Price LH. Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biol Psychiatry*. 2009b; 66:69–75. [PubMed: 19375070]
- Carroll BJ, Cassidy F, Naftolowitz D, Tatham NE, Wilson WH, Iranmanesh A, Liu PY, Veldhuis JD. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand Suppl*. 2007; 115:90–103. [PubMed: 17280575]
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983; 24:385–396. [PubMed: 6668417]
- Cooney JM, Dinan TG. Hypothalamic–pituitary–adrenal axis early-feedback responses are preserved in melancholic depression: a study of sertraline treatment. *Hum Psychopharmacol*. 2000; 15:351–356. [PubMed: 12404313]
- Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977; 16:347–356. [PubMed: 588890]

- Endicott J, Nee J, Harrison W, Blumenthal R. Quality of life enjoyment and satisfaction questionnaire: a new measure. *Psychopharmacol Bull.* 1993; 29:321–326. [PubMed: 8290681]
- First, M.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P). New York State Psychiatric Institute, Biometrics Research; New York: 1996.
- Gervasoni N, Bertschy G, Osiek C, Perret G, Denis R, Golaz J, Rossier MF, Bondolfi G, Aubry JM. Cortisol responses to combined dexamethasone/CRH test in outpatients with a major depressive episode. *J Psychiatr Res.* 2004; 38:553–557. [PubMed: 15458850]
- Haefner S, Baghai TC, Schule C, Eser D, Spraul M, Zill P, Rupprecht R, Bondy B. Impact of gene–gender effects of adrenergic polymorphisms on hypothalamic–pituitary–adrenal axis activity in depressed patients. *Neuropsychobiology.* 2008; 58:154–162. [PubMed: 19088492]
- Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology.* 2004; 29:1765–1781. [PubMed: 15213704]
- Hatzinger M, Hemminger UM, Baumann K, Brand S, Holsboer-Trachsler E. The combined DEX-CRH test in treatment course and long-term outcome of major depression. *J Psychiatr Res.* 2002; 36:287–297. [PubMed: 12127596]
- Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry.* 2008; 63:398–405. [PubMed: 17825799]
- Heuser IJ, Schweiger U, Gotthardt U, Schmider J, Lammers CH, Dettling M, Yassouridis A, Holsboer F. Pituitary–adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. *Am J Psychiatry.* 1996; 153:93–99. [PubMed: 8540599]
- Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J Affect Disord.* 2001; 62:77–91. [PubMed: 11172875]
- Holsboer F, Lauer CJ, Schreiber W, Krieg JC. Altered hypothalamic–pituitary–adrenocortical regulation in healthy subjects at high familial risk for affective disorders. *Neuroendocrinology.* 1995; 62:340–347. [PubMed: 8544947]
- Hori H, Ozeki Y, Teraishi T, Matsuo J, Kawamoto Y, Kinoshita Y, Suto S, Terada S, Higuchi T, Kunugi H. Relationships between psychological distress, coping styles, and HPA axis reactivity in healthy adults. *J Psychiatr Res.* 2010; 44:865–873. [PubMed: 20334880]
- Horstmann S, Dose T, Lucae S, Kloiber S, Menke A, Hennings J, Spieler D, Uhr M, Holsboer F, Ising M. Suppressing effect of mirtazapine on the HPA system in acutely depressed women seems to be transient and not related to antidepressant action. *Psychoneuroendocrinology.* 2009; 34:238–248. [PubMed: 18926641]
- Ising M, Kunzel HE, Binder EB, Nickel T, Modell S, Holsboer F. The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005a; 29:1085–1093. [PubMed: 15950349]
- Ising M, Lauer CJ, Holsboer F, Modell S. The Munich vulnerability study on affective disorders: premorbid neuroendocrine profile of affected high-risk probands. *J Psychiatr Res.* 2005b; 39:21–28. [PubMed: 15504420]
- Ising M, Horstmann S, Kloiber S, Lucae S, Binder EB, Kern N, Kunzel HE, Pfennig A, Uhr M, Holsboer F. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression—a potential biomarker? *Biol Psychiatry.* 2007; 62:47–54. [PubMed: 17123470]
- Klaassens ER, van Noorden MS, Giltay EJ, van Pelt J, van Veen T, Zitman FG. Effects of childhood trauma on HPA-axis reactivity in women free of lifetime psychopathology. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009; 33:889–894. [PubMed: 19389455]
- Klaassens ER, van Veen T, Giltay EJ, Rinne T, van Pelt J, Zitman FG. Trauma exposure and hypothalamic–pituitary–adrenal axis functioning in mentally healthy Dutch peacekeeping veterans, 10–25 years after deployment. *J Trauma Stress.* 2010; 23:124–131. [PubMed: 20146391]
- Kunugi H, Ida I, Owashi T, Kimura M, Inoue Y, Nakagawa S, Yabana T, Urushibara T, Kanai R, Aihara M, Yuuki N, Otsubo T, Oshima A, Kudo K, Inoue T, Kitaichi Y, Shirakawa O, Isogawa K, Nagayama H, Kamijima K, Nanko S, Kanba S, Higuchi T, Mikuni M. Assessment of the

dexamethasone/CRH test as a state-dependent marker for hypothalamic–pituitary–adrenal (HPA) axis abnormalities in major depressive episode: a multicenter study. *Neuropsychopharmacology*. 2006; 31:212–220. [PubMed: 16123748]

Laakmann G, Blaschke D, Hippus H, Schewe S. Double-blind randomized trial of the benzodiazepine derivative metaclozepam as compared with placebo treatment of outpatients with anxiety syndromes. *Pharmacopsychiatry*. 1988; 21:136–143. [PubMed: 2900514]

Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 1986; 22:343–381. [PubMed: 3774930]

Nickel T, Sonntag A, Schill J, Zobel AW, Ackl N, Brunnauer A, Murck H, Ising M, Yassouridis A, Steiger A, Zihl J, Holsboer F. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol*. 2003; 23:155–168. [PubMed: 12640217]

O'Donnell JM, Grealy M. Neuroendocrine response to clonidine and 8-OH-DPAT in rats following chronic administration of desipramine or sertraline. *Br J Pharmacol*. 1992; 105:863–868. [PubMed: 1387021]

Oshima A, Yamashita S, Owashi T, Murata T, Tadokoro C, Miyaoka H, Kamijima K, Higuchi T. The differential ACTH responses to combined dexamethasone/CRH administration in major depressive and dysthymic disorders. *J Psychiatr Res*. 2000; 34:325–328. [PubMed: 11104845]

Paizanis E, Renoir T, Lelievre V, Saurini F, Melfort M, Gabriel C, Barden N, Mocaer E, Hamon M, Lanfumey L. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. *Int J Neuropsychopharmacol*. 2009; 13:759–774. [PubMed: 19775499]

Pariante CM, Kim RB, Makoff A, Kerwin RW. Antidepressant fluoxetine enhances glucocorticoid receptor function in vitro by modulating membrane steroid transporters. *Br J Pharmacol*. 2003; 139:1111–1118. [PubMed: 12871829]

Paslakis G, Heuser I, Schweiger U, Deuschle M. A single DEX/CRH test in male drug-free depressed patients is associated with the clinical response to treatment with fluoxetine. *J Psychiatr Res*. 2010; 44:1154–1157. [PubMed: 20447650]

Petragnia F, Facchinetti F, Martignoni E, Nappi G, Volpe A, Genazzani AR. Serotonergic agonists increase plasma levels of beta-endorphin and beta-lipotropin in humans. *J Clin Endocrinol Metab*. 1984; 59:1138–1142. [PubMed: 6092410]

Pfennig A, Kunzel HE, Kern N, Ising M, Majer M, Fuchs B, Ernst G, Holsboer F, Binder EB. Hypothalamus–pituitary–adrenal system regulation and suicidal behavior in depression. *Biol Psychiatry*. 2005; 57:336–342. [PubMed: 15705348]

Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996; 26:477–486. [PubMed: 8733206]

Rydmark I, Wahlberg K, Ghatan PH, Modell S, Nygren A, Ingvar M, Asberg M, Heilig M. Neuroendocrine, cognitive and structural imaging characteristics of women on longterm sickleave with job stress-induced depression. *Biol Psychiatry*. 2006; 60:867–873. [PubMed: 16934773]

Sagud M, Pivac N, Muck-Seler D, Jakovljevic M, Mihaljevic-Peles A, Korsic M. Effects of sertraline treatment on plasma cortisol, prolactin and thyroid hormones in female depressed patients. *Neuropsychobiology*. 2002; 45:139–143. [PubMed: 11979064]

Schule C. Neuroendocrinological mechanisms of actions of antidepressant drugs. *J Neuroendocrinol*. 2007; 19:213–226. [PubMed: 17280595]

Schule C, Baghai TC, Eser D, Zwanzger P, Jordan M, Buechs R, Rupprecht R. Time course of hypothalamic–pituitary–adrenocortical axis activity during treatment with reboxetine and mirtazapine in depressed patients. *Psychopharmacol Berl*. 2006; 186:601–611.

Schule C, Baghai TC, Eser D, Hafner S, Born C, Herrmann S, Rupprecht R. The combined dexamethasone/CRH test (DEX/CRH test) and prediction of acute treatment response in major depression. *PLoS ONE*. 2009; 4:e4324. [PubMed: 19177168]

Seifritz E, Baumann P, Muller MJ, Annen O, Amey M, Hemmeter U, Hatzinger M, Chardon F, Holsboer-Trachsler E. Neuroendocrine effects of a 20-mg citalopram infusion in healthy males. A placebo-controlled evaluation of citalopram as 5-HT function probe. *Neuropsychopharmacology*. 1996; 14:253–263. [PubMed: 8924193]

- Skene DJ, Bojkowski CJ, Arendt J. Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans. *Br J Clin Pharmacol*. 1994; 37:181–186. [PubMed: 8186063]
- Spielberger, C. State–Trait Anxiety Inventory (Form Y). Consulting Psychologists Press; Palo Alto: 1983.
- Tsuru J, Akiyoshi J, Tanaka Y, Matsushita H, Hanada H, Kodama K, Hikichi T, Ohgami H, Tsutsumi T, Isogawa K, Nagayama H. Social support and enhanced suppression of adrenocorticotrophic hormone and cortisol responses to hypothalamic–pituitary–adrenal function and thyrotropin-releasing hormone tests in patients with major depressive disorder. *Biol Psychol*. 2008; 78:159–163. [PubMed: 18359551]
- Tyrka AR, Wier L, Price LH, Ross N, Anderson GM, Wilkinson CW, Carpenter LL. Childhood parental loss and adult hypothalamic–pituitary–adrenal function. *Biol Psychiatry*. 2008a; 63:1147–1154. [PubMed: 18339361]
- Tyrka AR, Wier LM, Price LH, Rikhye K, Ross NS, Anderson GM, Wilkinson CW, Carpenter LL. Cortisol and ACTH responses to the Dex/CRH test: influence of temperament. *Horm Behav*. 2008b; 53:518–525. [PubMed: 18294637]
- Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL. Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: effects on hypothalamic–pituitary–adrenal axis reactivity. *Biol Psychiatry*. 2009; 66:681–685. [PubMed: 19596121]
- Veen G, Derijk RH, Giltay EJ, van Vliet IM, van Pelt J, Zitman FG. The influence of psychiatric comorbidity on the dexamethasone/CRH test in major depression. *Eur Neuropsychopharmacol*. 2009; 19:409–415. [PubMed: 19327969]
- von Bardeleben U, Steiger A, Gerken A, Holsboer F. Effects of fluoxetine upon pharmacoenocrine and sleep-EEG parameters in normal controls. *Int Clin Psychopharmacol*. 1989; 4(Suppl 1):1–5. [PubMed: 2536765]
- Watson S, Gallagher P, Del-Estal D, Hearn A, Ferrier IN, Young AH. Hypothalamic–pituitary–adrenal axis function in patients with chronic depression. *Psychol Med*. 2002; 32:1021–1028. [PubMed: 12214783]
- Wirtz PH, Siegrist J, Rimmel U, Ehlert U. Higher overcommitment to work is associated with lower norepinephrine secretion before and after acute psychosocial stress in men. *Psychoneuroendocrinology*. 2008; 33:92–99. [PubMed: 18023536]
- Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. *J Psychiatr Res*. 2001; 35:83–94. [PubMed: 11377437]
- Zobel A, Barkow K, Schulze-Rauschenbach S, Von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic–pituitary–adrenocortical system in healthy volunteers. *Acta Psychiatr Scand*. 2004; 109:392–399. [PubMed: 15049775]
- Zobel A, Schuhmacher A, Jessen F, Hofels S, von Widdern O, Metten M, Pfeiffer U, Hanses C, Becker T, Rietschel M, Scheef L, Block W, Schild HH, Maier W, Schwab SG. DNA sequence variants of the FKBP5 gene are associated with unipolar depression. *Int J Neuropsychopharmacol*. 2010; 13:649–660. [PubMed: 20047716]

Fig. 1. Mean plasma cortisol concentrations (with standard error bars) during the Dex/CRH test, administered before and after 6 weeks of blinded treatment with either sertraline 100 mg/day or matching placebo in 22 healthy adults

Table 1

Demographic and clinical characteristics of healthy sample

	Sertraline (<i>n</i> =11)	Placebo (<i>n</i> =11)
Age, years		
Mean (SD), range	30.18 (8.5), 20–46	28.73 (10.6), 20–54
Sex, <i>n</i> (%)		
Female	6 (55%)	7 (63%)
Menstrual cycle phase ^a		
Luteal phase, <i>n</i> (% of women)	1 (16.7%)	1 (14.3%)
Follicular phase, <i>n</i> (% of women)	3 (50.0%)	3 (42.9%)
Post-menopausal, <i>n</i> (% of women)	0 (0.0%)	1 (14.3%)
Menses	2 (33.3%)	2 (28.6%)
Male	5 (45.5%)	4 (36.4%)
Use of estrogen		
<i>n</i> (% of women)	3 (50.0%)	1 (14.3%)
Depression symptoms (IDS-SR score), mean (SD)		
Pre-treatment	6.82 (3.28)	11.73 (9.32)
Post-treatment	8.64 (4.69)	12.55 (7.71)
State Anxiety (STAI) Scale		
Mean (SD)	31.45 (9.52)	29.55 (7.20)
Trait Anxiety (STAI) Scale		
Mean (SD)	32.09 (6.82)	31.72 (10.87)
Perceived Stress Scale		
Mean (SD)	16.90 (3.56)	19.36 (7.33)
Childhood Trauma Questionnaire Total, 28-item version		
Mean (SD)	7.02 (2.39)	7.04 (4.11)
Quality of Life and Satisfaction, Short Form Total		
Mean (SD)	4.20 (0.63)	4.18 (0.75)

No significant differences ($p < 0.05$) were detected between groups with chi-square and *t* tests

^a Steps were undertaken to enhance consistency of menstrual cycle phase at time of pre- and post-treatment Dex/CRH testing