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ORIGINAL PAPER

5HT1A-mediated stimulation of cortisol release in major depression: use of non-invasive cortisol measurements to predict clinical response

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Abstract The purpose of the present study was to explore 5HT1A-mediated cortisol release in major depressive disorder (MDD) patients in order to determine whether the degree of 5HT1A-receptor sensitivity can predict response to treatment with selective serotonin reuptake inhibitors (SSRIs). We examined whether the sensitivity of the 5HT1A receptor, as measured by the difference in salivary cortisol levels immediately before and 90 min following the administration of a single dose of the 5HT1A-selective agonist buspirone, predicted treatment outcome following an 8-week, fixed-dose, open trial of the SSRI escitalopram in 17 outpatients with MDD. Change in cortisol levels before and 90 min after the administration of buspirone were not found to predict treatment outcome, whether defined as clinical response (50% or greater reduction in symptom severity), or remission of symptoms. In conclusion, in the present study, we did not find that the change in salivary cortisol levels following the administration of a 5HT1A-selective agonist predicted treatment outcome following an 8-week, fixed-dose, open-label trial of the SSRI escitalopram among outpatients with MDD. Although the 5HT1A-desensetization hypothesis is still a valid one, the results of the present study could not provide any evidence in support.

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Introduction

Major depressive disorder (MDD) is a prevalent illness that is associated with significant disability, morbidity, and mortality. Several studies published to date reveal a connection between MDD and hypothalamic–pituitary–adrenal (HPA) axis dysregulation [29]. Specifically, high cortisol levels [24–26, 38], dexamethasone (DST) non-suppression of cortisol release [2, 5, 14, 20], and abnormal 24-h cortisol secretion [11, 30, 39] have been reported in many patients with MDD. Furthermore, the number of CRH secreting-neurons [31] and the levels of CRH in the serum [8] and cerebrospinal fluid [4] are decreased in depressed patients. In parallel, studies have shown that there is also a relationship between steroid dysregulation and poor prognosis in the treatment of MDD. Depressed patients with dexamethasone non-suppression before treatment were found to have a poorer response to treatment with antidepressants [1] or cognitive behavioral therapy (CBT) [37] than MDD patients with dexamethasone suppression [21]. Similarly, patients with elevated pre-treatment cortisol require longer treatment courses to maintain remission [28]. Finally, it also appears that the results of the dexamethasone–corticotropin releasing hormone test (DEX/CRH) can have predictive value with respect to treatment outcome in depression [18, 19], although not all studies have consistently supported this finding [33].

Most importantly, there is evidence to suggest that changes in the activity of the 5HT1A serotonergic inhibitory autoreceptor, a receptor involved in mediating cortisol and ACTH secretion [12] as well as the regulation of

serotonergic neuronal firing [36], play a role in not only the pathophysiology of MDD [13] but also in mediating symptom improvement during antidepressant therapy. Specifically, the selective serotonin reuptake inhibitors (SSRIs) may modulate the serotonergic (5HT) system and the HPA axis by way of their effect on the sensitivity of the 5HT1A autoreceptor [22, 34–36], an effect thought to be a necessary prerequisite in order to achieve clinical response [7, 9, 10, 36]. Berlin and colleagues [6] demonstrated this effect by examining 5HT1A-mediated cortisol responses after 20 days of treatment with the SSRI fluoxetine, ipsapirone CR, or placebo. While acute administration of selective 5HT1A receptor agonists have been shown to stimulate cortisol release [23], Berlin and his coauthors found that cortisol release in response to ipsapirone challenge was reduced in subjects who received long term treatment with SSRI or with ipsapirone CR versus those who received the placebo. Further, the time-course of this desensetization seems to parallel the onset of therapeutic response, suggesting that the desensetization of the 5HT1A presynaptic inhibitory autoreceptor may be the mechanism of action responsible for the therapeutic effects achieved by several antidepressants.

In summary, there is substantial evidence that the activity of the 5HT1A-receptor is influenced by the SSRIs, and that SSRI-induced desensetization of this receptor is the rate-limiting step in achieving clinical response during treatment. In turn, the degree of HPA axis imbalance holds prognostic value in terms of response to treatment and MDD recurrence/relapse; thus, exploring HPA axis dysregulation has potential clinical relevance, as such a predictor could lead to the development of specialized treatment interventions that allow us to identify the risk of relapse/recurrence in MDD patients. A preliminary study by Rausch et al. [32] had suggested that the degree of cortisol secretion following the administration of the 5HT1A-agonist gepirone correlated with depression severity scores among outpatients with MDD. The purpose of the present study was to further explore 5HT1A-mediated cortisol release in MDD patients to determine whether the degree of 5HT1A-receptor sensitivity can predict response to treatment with SSRIs. In order to achieve this, we measured salivary cortisol response to buspirone stimulation on the first and last day of an 8-week, 10 mg, fixed-dose, open-label trial of escitalopram in outpatients with MDD.

Methods

Outpatients, 18–65 years of age, with current MDD defined using the DSM-IV criteria were recruited at the Depression Clinical and Research Program of the Massachusetts General Hospital in Boston, Massachusetts. The site's institutional review board (IRB) approved the study, and procedures followed were in accordance with the 1964 Declaration of Helsinki. All participants provided written informed consent. Diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition [15], and a minimum score of 15 on the 17-item Hamilton Depression Rating Scale [17] at the screening and baseline visits was required for inclusion in the study.

Screening was performed, including medical history and physical examination. Patients were excluded from the study if they were at significant risk of suicide; were pregnant or breastfeeding; were women not using effective contraception; had an unstable physical disorder; had a lifetime history of any organic mental disorder, psychotic disorder, or mania; had a history of multiple adverse events, drug reactions or allergy to the study drugs; had mood congruent or mood incongruent psychotic features; had failed to respond during the course of their current major depressive episode to at least four adequate antidepressant trials (defined as 6 weeks or more of treatment with $>$150 mg imipramine or its tricyclic equivalent, $>$60 mg of phenelzine or its monoamine oxidase inhibitor equivalent, $\geq$20 mg of fluoxetine or its SSRI equivalent, $\geq$150 mg of bupropion, $\geq$150 mg of venlafaxine, $\geq$30 mg of duloxetine, $\geq$50 mg of desvenlafaxine, $\geq$15 mg of mirtazapine, $\geq$300 mg of trazodone or nefazodone), or had failed to respond during the course of their current major depressive episode to a course of electroconvulsive therapy (ECT). Patients who had been treated with oral steroids or a steroid inhibitor; had chronically used inhaled steroids; or had failed to respond to and/or tolerate escitalopram were also excluded. Patients being treated with psychotropic medications during the screen visit (save for benzodiazepines) had their psychotropic medications tapered and discontinued before the baseline visit. Patients being treated with benzodiazepines were included if they had been on the present dose for at least 8 weeks, and agreed to continue at this dose for the duration of the 8-week trial.

Patients who continued to meet inclusion criteria during the baseline visit were asked to provide salivary samples for baseline cortisol readings at 9:00 AM in Sarstedt salivettes (provided by the Nathan Kline Institute) at least 30 min after brushing their teeth, and while supine. Patients were asked to avoid consuming breakfast, caffeine, or smoking cigarettes that morning. Patients using steroid inhalers or women on hormonal supplementation or birth control were instructed to take their pills or use their inhaler after the samples were collected. Patients were then given a 30 mg dose of buspirone, and salivary samples were repeated 90 min later. Only samples obtained in Starstedt salivettes were frozen and delivered on ice. All

samples were delivered for analysis every 2 months, to be assayed by RIA at the Nathan Kline Institute (intra/inter-assay variability at 3.1 μg/dl, 19.3 μg/dl, 32.7 μg/dl level is 2.95, 6.0/2.53/3.93, 2.00/2.91%, respectively).

Patients then entered the acute phase of the study: an 8-week course of open-label treatment with escitalopram (10 mg/day). Patients were evaluated by a research psychiatrist every week during the first 4 weeks and biweekly for the second 4 weeks. Patients who experienced an increase in HAM-D17 scores of at least 25% from one visit to the next, or a 40% increase from baseline overall, were discontinued from the study, as were patients who experienced a CGI-I of ≥6 or active suicidal ideation at any visit. Compliance was monitored by counting returned capsules; participants whose adherence to the protocol was judged inadequate by the treating research psychiatrist were removed from the study.

Statistical tests

Cortisol response (delta-cortisol) was defined as the difference between the cortisol value at 9 AM (immediately before the administration of buspirone), and the cortisol value 90 min after buspirone administration. Clinical response was defined as a 50% or greater reduction in HAM-D-17 scores, baseline to endpoint. For patients who prematurely discontinued treatment with escitalopram, endpoint HAM-D-17 scores were defined as the last available score, carried forward (LOCF). The intent-to-treat sample (ITT) was defined as the sample population for the study (defined as all patients who received at least one pill of escitalopram with at least one post-baseline assessment).

Unpaired t tests were used to evaluate differences in pre-treatment cortisol, post-treatment cortisol, and delta-cortisol values between responders and non-responders, remitters and non-remitters, and between males and females. Logistic regression was used to evaluate the relationship between delta-cortisol and clinical response status after adjusting for gender. Logistic regression was used to evaluate the relationship between delta-cortisol and remission status after adjusting for gender. Statistical significance was set at the alpha = 0.05 level (two tailed tests).

Results

17 patients (10 women, mean age 42.1 ± 13.4, mean baseline HAM-D-17 score 19.4 ± 2.9) enrolled in the study. All 17 patients had not received any prior antidepressant course during their current major depressive episode. 12 (70.5%) patients completed 8-weeks of open-label treatment, while five patients discontinued prematurely (two patients discontinued treatment because they did not perceive any symptom improvement during the course of the escitalopram trial, two patients were lost to follow-up and one patient discontinued treatment due to worsening suicidal ideation). 8 (47.0%) patients met criteria for clinical response at endpoint, and 6 (35.2%) for remission. Mean baseline salivary cortisol levels at 9 AM were (1.2 ± 1.8), and 90-min post-buspirone administration (2.9 ± 4.2) ($p = 0.14$). There was no statistically significant difference in baseline (1.59 ± 2.34 vs. 0.8 ± 0.33; $p = 0.39$), post-buspirone cortisol levels (2.55 ± 6.78 vs. 3.48 ± 6.03; $p = 0.66$), or in the change in cortisol levels from baseline following the administration of buspirone (0.96 ± 3.28 vs. 2.68 ± 5.88; $p = 0.44$) between women and men.

There was no statistically significant difference in baseline (1.66 ± 2.46 vs. 0.81 ± 0.45; $p = 0.35$), post-buspirone cortisol levels (2.03 ± 2.42 vs. 3.95 ± 5.61; $p = 0.35$), or in the change in cortisol levels from baseline following the administration of buspirone (0.36 ± 3.27 vs. 3.13 ± 5.32; $p = 0.21$) between non-responders and responders. There was no statistically significant difference in baseline (1.60 ± 2.21 vs. 0.65 ± 0.39; $p = 0.32$), post-buspirone cortisol levels (3.75 ± 4.85 vs. 1.43 ± 2.29; $p = 0.29$), or in the change in cortisol levels from baseline following the administration of buspirone (2.15 ± 5.33 vs. 0.78 ± 2.23; $p = 0.56$) between non-remitters and remitters. A logistic regression, with clinical response as the dependent variable and the change in cortisol levels from baseline following the administration of buspirone as well as gender as the two independent variables, did not demonstrate the change in cortisol levels from baseline following the administration of buspirone to significantly predict clinical response ($p = 0.58$, $R^2 = 0.093$, odds ratio for response status per unit of change in cortisol was 1.20 with 95%CI = 0.9–1.59). A logistic regression, with remission as the dependent variable and the change in cortisol levels from baseline following the administration of buspirone as well as gender as the two independent variables, did not demonstrate the change in cortisol levels from baseline following the administration of buspirone to significantly predict clinical response ($p = 0.70$, $R^2 = 0.026$, odds ratio for remission status per unit of change in cortisol was 0.92 with 95%CI = 0.70–1.21).

These regressions were repeated for completers only, utilizing response ($p = 0.58$, $R^2 = 0.093$, odds ratio for response status per unit of change in cortisol was 1.13 with 95%CI = 0.64–1.97), and remission ($p = 0.85$, $R^2 = 0.021$, odds ratio for response status per unit of change in cortisol was 0.85 with 95%CI = 0.50–1.45) as outcomes.

Figure 1 graphically depicts the relationship between change in Cortisol levels and change in HAM-D-17 scores.

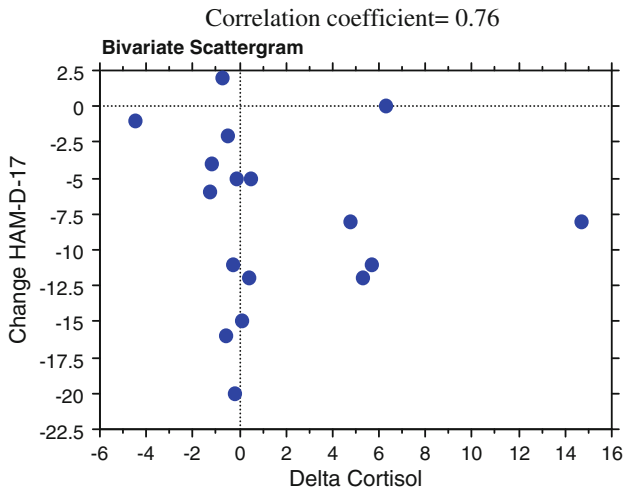

Fig. 1 Change in HAM-D-17 scores during the trial (*x*-axis) versus change in cortisol levels following the buspirone challenge (*y*-axis). Correlation coefficient = 0.76

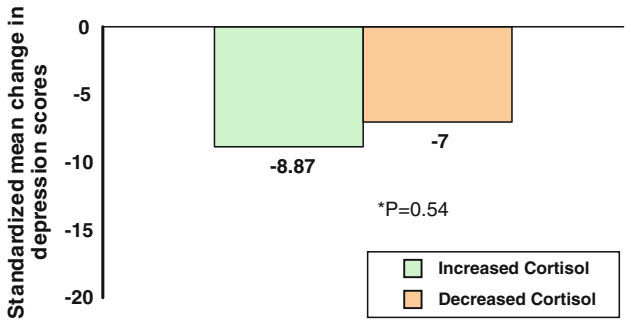

Fig. 2 Mean change in HAM-D-17 scores for patients who demonstrated an increase ($n = 8$) versus those who demonstrated a decrease ($n = 9$) in cortisol levels during treatment $^*P = 0.54$

Figure 2 depicts the mean change in HAM-D-17 scores during the trial for patients who demonstrated an increase ($n = 8$) versus decrease ($n = 9$) in cortisol values following the buspirone test.

Discussion

Several researchers have hypothesized that the desensetization of the 5HT1A-receptor during antidepressant therapy in patients with MDD may be a prerequisite for the resolution of depressive symptoms. In order to test this hypothesis, we examined whether the sensitivity of the 5HT1A receptor, as measured by the difference in salivary cortisol levels immediately before and 90-min following the administration of a single dose of the 5HT1A-selective agonist buspirone, predicted treatment outcome following an 8-week, fixed-dose, open trial of the SSRI escitalopram. In the present study, we did not find that the change in cortisol levels predicted treatment outcome, whether defined as clinical response (50% or greater reduction in symptom severity), or remission of symptoms. Although the 5HT1A-desensetization hypothesis is still a valid one, the results of the present study could not provide any evidence in support.

There may be several reasons that could explain our findings. One possibility is that our study, with only 17 patients enrolled, was underpowered to detect a relationship between 5HT1A-mediated cortisol stimulation and symptom improvement in MDD, although the large standard deviations of measurement obtained using the present assay suggest that lack of adequate sample size alone cannot account for the absence of statistically significant findings. Alternatively, it is quite possible that salivary cortisol measures, although relatively easy to obtain, may not have been as sensitive to changes in cortisol secretion as serum cortisol levels (i.e. in a study of similar design employing plasma rather than salivary measures, Navinez et al. did find a significant relationship between buspirone-induced cortisol and adrenocorticotrophic hormone (ACTH) release and response to the SSRI citalopram in MDD [27]), although studies have suggested excellent correlation between serum and salivary cortisol levels in MDD patients [3, 16].

A third possibility is that the hypothesis put forth may, simply, not hold, namely that 5HT1A-desensetization is not a major factor in achieving resolution of symptoms during the treatment of MDD. Alternatively, whether the current paradigm used to measure the degree of 5HT1A-receptor sensitivity (buspirone-mediated cortisol release) is sensitive enough a measure of central (i.e. CNS) 5HT1A-receptor sensitivity is unclear. Alternative measures of 5HT1A-receptor sensitivity (i.e. neuroimaging—[13], or the measurement of ACTH rather than cortisol [27] may have been much preferable. In addition, it is also quite possible that a single measurement of buspirone-induced cortisol secretion conducted before treatment may have not been sufficient to accurately measure 5HT1A-receptor sensitivity. Multiple pre-treatment measurements may have provided more accurate results. Another limitation of the present study was that compliance was assessed by pill count. Plasma levels of escitalopram may have provided an additional, perhaps more accurate way of assessing whether some patients may not have been taking their study medication.

In conclusion, in the present study, we did not find that the change in salivary cortisol levels following the administration of a 5HT1A-selective agonist predicted treatment outcome following an 8-week, fixed-dose, open-label trial of the SSRI escitalopram among outpatients with MDD. Although the 5HT1A-desensetization hypothesis is still a valid one, the results of the present study could not provide any evidence in support.

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