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Abstract

Background—Dehydroepiandrosterone (DHEA) and its sulfated ester DHEA-sulfate (DHEA-S), (together DHEA[S]), are the most abundant adrenal steroids in humans and are found in blood and the brain, where they function as neurosteroids with direct receptor affinities. Preclinical studies suggest that DHEA(S) has antidepressant/neuroprotective properties, and exogenously administered DHEA has shown antidepressant efficacy in humans. Nonetheless, the role of endogenous DHEA(S) levels in major depressive disorder (MDD) and antidepressant outcomes remains unclear.

Methods—Morning fasting serum DHEA(S) concentrations were determined in 36 healthy, unmedicated MDD adults with Hamilton Depression (HDRS) ratings ≥ 17, and 75 healthy controls. MDD participants then completed eight weeks of open-label SSRI treatment before DHEA(S) levels were re-sampled; those with post-treatment HDRS ratings ≤ 7 were classified as "Remitters." Pre- and post-treatment DHEA(S) levels of Remitters and Non-remitters were compared, controlling for age, sex, and BMI.

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Conflict of Interest The authors report no conflict of interest.

Results—Pre-treatment HDRS ratings did not differ between Remitters and Non-remitters (p=0.179). Baseline DHEA levels of Remitters were significantly higher than both Non-remitters (p=0.008) and controls (p=0.004); baseline DHEA-S levels of Remitters were also higher than Non-remitters (p=0.040) but did not significantly differ from controls (p=0.096). Non-remitters did not significantly differ from controls. Post-treatment DHEA(S) levels remained higher in Remitters compared to Non-remitters (DHEA: p=0.013; DHEA-S: p=0.040).

Conclusions—These data suggest that higher circulating DHEA(S) levels (while unmedicated and after eight weeks of SSRI treatment) predict SSRI-associated remission in MDD. This raises the possibility that endogenous DHEA(S) abundance is a physiological adjunct to SSRI efficacy, as suggested by prior preclinical and clinical studies.

1. INTRODUCTION

Major depressive disorder (MDD) is a severe and debilitating illness that is estimated by the World Health Organization to affect 350 million people worldwide. Despite the widespread nature and significant costs associated with MDD (Ferrari et al., 2013), its underlying etiology is still not fully understood, nor are the biological predictors and mechanisms of antidepressant treatment outcomes. Clinical "response" is typically defined as a 50% or greater reduction in depressive symptoms after treatment (Lecrubier, 2002). "Remission," however, is defined as post-treatment Hamilton Depression Rating Scale ratings 7 (Lecrubier, 2002), indicating that very few residual symptoms of depression persist. This more stringent criteria has led to remission being considered the "gold standard" of treatment outcomes (Fishbain, 2009). Clinical response that fails to meet standards of remission is associated with earlier relapse into a major depressive episode (MDE), greater lifetime depression chronicity, and significantly poorer psychosocial functioning (Judd, 2001; Kennedy and Paykel, 2004; Paykel, 1998). Antidepressant efficacy studies typically report remission rates of roughly 30–45% and response rates of roughly 50–55% (Rush et al., 2006; Trivedi et al., 2006). The mechanisms related to remission of MDD after pharmacological treatment are not currently known; however, endogenous levels of certain steroid hormones may play a crucial role (Wolkowitz et al., 2001).

Dehydroepiandrosterone (DHEA) and its sulfated ester DHEA-sulfate (DHEA-S), together abbreviated as DHEA(S), are the most abundant adrenal steroids in adult humans and are found in the blood and in the brain (Kroboth et al., 1999), where they function as neurosteroids with direct receptor affinities (Maninger et al., 2009; Mellon, 2007). In preclinical studies, DHEA(S) has been shown to exert several properties consistent with antidepressant or neuroprotective effects, including neurogenesis, neurite enhancement, anti-inflammatory, anti-oxidant, and anti-glucocorticoid effects (Compagnone and Mellon, 1998; Genud et al., 2009; Lazaridis et al., 2011; Maninger et al., 2009; Pinnock et al., 2009; Reddy et al., 1998). Additionally, exogenously administered DHEA has shown antidepressant efficacy in humans; in some cases, subjects who achieved higher circulating DHEA(S) levels achieved better outcomes (Bloch et al., 1999; Maninger et al., 2009; Peixoto et al., 2014;

Rabkin et al., 2006; Schmidt et al., 2005; Wolkowitz et al., 1999; Wolkowitz et al., 1997). Despite such findings with exogenously administered DHEA(S), the role of endogenous DHEA(S) in neuropsychiatric illness in humans and in MDD in particular, remain unclear. Previous findings in depression have found DHEA and/or DHEA-S concentrations to be decreased (Michael et al., 2000; Mocking et al., 2015; Morgan et al., 2010; Zhu et al., 2015), increased (Assies et al., 2004; Kurita et al., 2013; Morita et al., 2014; Takebayashi et al., 1998), or unchanged (Fabian et al., 2001; Kurita et al., 2013; Markopoulou et al., 2009; Mocking et al., 2015; Paslakis et al., 2010; Romeo et al., 1998) (also reviewed in Maninger *et al.*, 2009) in depression, compared to non-depressed controls. The relationship between endogenous serum DHEA(S) levels and likelihood of antidepressant-associated remission also remain unclear.

Several studies have examined changes in peripheral endogenous DHEA(S) levels over the course of antidepressant treatment (Berardelli et al., 2010; Deuschle et al., 2004; Fabian et al., 2001; Hsiao, 2006; Markopoulou et al., 2009; Morgan et al., 2010; Morita et al., 2014; Paslakis et al., 2010; Romeo et al., 1998; Schüle et al., 2009; Takebayashi et al., 1998; Zhu et al., 2015) and in relation to treatment response (Deuschle et al., 2004; Fabian et al., 2001; Hsiao, 2006; Markopoulou et al., 2009; Morita et al., 2014; Paslakis et al., 2010; Schüle et al., 2009; Takebayashi et al., 1998). However, to the best of our knowledge, only three previous studies have examined peripheral endogenous DHEA or DHEA-S levels in MDD in relation to clinical response/remission after pharmacological treatment (Fabian et al., 2001; Hsiao, 2006; Markopoulou et al., 2009), and none has examined response to selective serotonin reuptake inhibitors (SSRIs) specifically. These previous studies have had mixed results, likely due to differences in medications, sample size and characterization, and/or the examination of clinical response versus remission. Previously, Markopoulou et al. found that baseline DHEA levels were lower in those with treatment-resistant depression who were responders (not remitters) to inpatient psychotropic treatment with various classes of medications, including antidepressants, mood stabilizers, antipsychotics, benzodiazepines, and buspirone, compared to those who did not respond to treatment (Markopoulou et al., 2009). Fabian et al. reported that baseline DHEA(S) levels did not differ between remitters and non-remitters to treatment with nortriptyline or paroxetine in a mixed inpatient and outpatient sample of elderly (60 years old) MDD patients, although remission to the specific classes of antidepressants was not reported (Fabian et al., 2001). Hsiao compared baseline DHEA levels of MDD patients who remitted after treatment with venlafaxine to those who did not, and did not find any significant between-group differences (Hsiao, 2006).

As previous research is limited, and as other studies have suggested that the mechanisms related to DHEA and antidepressant-response may differ between serotonin/SSRIs, compared to other classes of neurotransmitters and antidepressants (Deuschle et al., 2004; Pérez-Neri et al., 2008; Romeo et al., 1998), the current study sought to assess whether baseline serum DHEA(S) levels predict improvement of depression after SSRI treatment and whether post-treatment DHEA(S) levels are associated with improvement of depression. To accomplish this, we determined morning fasting serum DHEA(S) levels in 36 unmedicated adults (ages 19 – 65) with a current DSM-IV diagnosis of MDD, who were then treated in an open-label manner with an SSRI for eight weeks prior to having serum DHEA(S) levels reevaluated. We predicted that higher DHEA(S) levels at both time points would be

associated with better antidepressant outcome. As a secondary analysis, to compare DHEA(S) levels to norms, we also assessed serum DHEA(S) levels in 75 healthy controls of similar ages.

2. METHODS

2.1. Subjects

Thirty-six unmedicated adults (ages 19 – 65; 24 females, 12 males) with current MDD completed an eight-week, open-label longitudinal study of SSRI treatment, as part of a larger cross-sectional study of MDD (NCT00285935). Data from 75 healthy control subjects (ages 21 – 69; 46 females, 29 males) from this larger cross-sectional study were included in secondary analyses, comparing DHEA(S) levels of control subjects to those of MDD subjects, including comparisons with Remitters (Week 8 HDRS ≤ 7) and Non-remitters separately. All subjects who completed eight weeks of SSRI treatment and who had serum DHEA(S) levels available were included in the analyses. Three MDD subjects did not have follow-up serum samples due to difficulty with venipuncture; these subjects were included in analyses of baseline, but not post-treatment, DHEA(S). Additionally, the DHEA value for one control subject was more than five standard deviations from the mean and was excluded from DHEA (but not DHEA-S) analyses.

Subjects were recruited by flyers, bulletin board notices, Craigslist postings, newspaper ads, and (in the case of MDD subjects) clinical referrals. The Committee on Human Research of the University of California, San Francisco (UCSF) approved the study protocol. All study participants gave written informed consent to participate in this study and were compensated for participating; MDD subjects additionally received free antidepressant treatment.

Depressed subjects were diagnosed with MDD, without psychotic features, according to the Structured Clinical Interview for DSM IV-TR Axis I Disorders (SCID) (First, 1997) (which was the DSM version in use at the time of the study) with a current 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) rating of ≥ 17. All diagnoses were confirmed by clinical interview with a Board-Certified psychiatrist. Depressed subjects were excluded for presence of the following: bipolar disorder, psychotic symptoms during their current major depressive episode, history of psychosis outside of a mood disorder episode, any eating disorder or post-traumatic stress disorder (PTSD) within one month of entering the study, and substance abuse or dependence (including alcohol) within six months of entering the study. Co-morbid anxiety disorders (except PTSD) were allowed if MDD was considered the primary diagnosis. Control subjects had no history of any DSM-IV-TR Axis I disorder, also confirmed by SCID interview. Further, study participants had no acute illnesses or infections, chronic inflammatory disorders, neurological disorders, or any other major medical conditions considered to be potentially confounding (e.g. cancer, HIV, diabetes, history of cardiovascular disease or stroke, etc.), as assessed by history, physical examinations and routine blood screening. All subjects were free of psychotropic medications (including antidepressants), hormone supplements, steroid-containing birth control or other potentially interfering medications, and had not had any vaccinations, for at least six weeks prior to enrollment in the study; additionally, none were taking vitamin supplements above the U.S. recommended daily allowances (e.g. 90 mg/day for Vitamin C).

Short-acting sedative-hypnotics were allowed as needed up to a maximum of three times per week, but none within one week prior to participation. Prior to each study visit, all subjects had to pass a urine toxicology screen for drugs of abuse (marijuana, cocaine, amphetamines, phencyclidine, opiates, methamphetamine, tricyclic antidepressants, and barbiturates) and a urine test for pregnancy in women of child-bearing age.

2.2. Procedures

Subjects were admitted as outpatients to the UCSF Clinical and Translational Science Institute between the hours of 0800 and 1100, having fasted (except water) since 2200 hours the night before. Subjects were instructed to sit quietly and relax for 25 – 45 minutes before blood samples were obtained for hormone assessment and routine clinical labs. The severity of depressive symptoms was then rated in depressed subjects using the 17-item HDRS (Hamilton, 1960). Each rating session was conducted with two raters present who scored within one point of each other; if this was not achieved, a consensus rating was determined.

Following this baseline visit, thirty-six subjects received eight weeks of open-label outpatient treatment with an SSRI antidepressant. The first 28 subjects were treated with sertraline, as this was initially the only SSRI to be studied. The remaining eight subjects were treated under a separate but otherwise identical protocol that allowed treatment with any SSRI (two with sertraline, two with fluoxetine, two with citalopram, and two with escitalopram), as determined to be clinically appropriate by the study psychiatrist. The decision regarding the specific SSRI prescribed was made based on clinical grounds such as medical history, family history, and potential side effects. The prescriber and HDRS raters were blind to serum DHEA(S) levels. Outpatient compliance with the medication regimen, as well as clinical evaluations and assessments of drug tolerability, were assessed by a telephone check-in at the end of Week 1 and an in-person check-in at the end of Week 4 and Week 8, at which time pill counts were performed. Thirteen of the subjects additionally had plasma antidepressant concentrations assessed at Week 4 and Week 8; in each of these subjects, plasma antidepressant concentrations were in the expected clinical range for that antidepressant, suggesting excellent compliance. Medication dosages increased over the course of treatment as tolerated and as warranted by clinical response. Sertraline dosing began with 25 mg per day and increased to a maximum of 200 mg per day; fluoxetine and citalopram dosing began with 10 mg per day and increased to a maximum of 40 mg per day; escitalopram dosing began with 10 mg per day and increased to a maximum of 20 mg per day. See Table 1 for further information regarding SSRI dosing. At the end of the eight weeks of SSRI treatment, MDD subjects were again rated with the HDRS and had blood re-drawn for steroid hormone levels. Subjects with post-treatment HDRS ratings 7 were classified as "Remitters," while those with post-treatment HDRS ratings > 7 were classified as "Non-remitters" (Lecrubier, 2002).

2.3. Steroid Measurement

Serum was collected into serum separator tubes for steroid assay. Assays were performed in two separate batches based on recruitment phases (2006 – 2008 and 2011 – 2014). The first batch consisted of 15 MDD (7 Remitters, 8 Non-remitters) and 20 control samples, and was assayed by radioimmunoassay (DHEA: Diagnostic Systems Laboratories, Inc., Webster, TX;

DHEA-S: Diagnostic Products Corporation, Los Angeles, CA; cortisol: Siemens Medical Solutions Diagnostics, Los Angeles, CA). Intra-assay CV for DHEA, DHEA-S and cortisol was 3.2%, 7.8% and 3.4%, respectively; inter-assay CV for DHEA, DHEA-S and cortisol was 3.6 %, 9.7% and 5.5%, respectively. The second batch consisted of 21 MDD (6 Remitters, 15 Non-remitters) and 55 control samples, and was assayed by Human ELISA (DHEA: American Laboratory Products Co., Salem, NH; DHEA-S and cortisol: Immulite 2000, Siemens Healthcare Global, Erlangen, Germany). Intra-assay CV for DHEA, DHEA-S and cortisol was 5.6%, 7.6% and 5.6%, respectively; inter-assay CV for DHEA, DHEA-S and cortisol was 6.9%, 9.7% and 7.7%, respectively. The use of two different assay batches necessitated a change in assay labs and methods over the course of the study. As noted below, batch was entered as a covariate in all analyses. DHEA was measured in ng/dL with a reportable range of 0.37–30.0 ng/mL. DHEA-S was measured in µg/dL with a reportable range of 15–1000 µg/dL. Cortisol was measured in µg/dL with a reportable range of 1–50 µg/dL. Lab personnel who performed the assay were blind to demographic and clinical data.

2.4. Statistical Analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) v.22 (IBM Corp., Armonk, NY). All tests were 2-tailed with an alpha=0.05. Comparisons of demographic and clinical characteristics between-groups were performed using Kruskall Wallis, Mann-Whitney U, and Chi-Square tests. Non-parametric tests were used (Mann-Whitney U, Kruskal-Wallis, Chi-Square, and Spearman's Correlations, as appropriate), since DHEA(S) levels were non-normally distributed. Age, sex, and body mass index (BMI) were defined *a priori* as possible confounders due to their reported impact on DHEA(S) (Kroboth et al., 1999) and were corrected for in all analyses by utilizing residual values of DHEA(S); additionally, as DHEA(S) was analyzed in two separate assay batches, all analyses were also corrected for assay batch. Cohen's *d* effect sizes were calculated using residual data.

To assess whether pre- and post-treatment DHEA(S) levels were related to SSRI-associated remission, pre-treatment DHEA(S) levels were compared between Remitters and Non-remitters, as were post-treatment DHEA(S) levels. Since the majority, but not all subjects received sertraline, sensitivity analyses were performed, only including those subjects who were prescribed sertraline; all results remained unchanged. Secondarily, differences in DHEA(S) levels between controls and both groups of MDD subjects (Remitters and Non-Remitters) were explored to determine the relationship of the MDD hormone levels of those with controls. To determine the specificity of the association of DHEA(S) with SSRI-associated remission, and to examine the relationship of related steroids, pre- and post-treatment cortisol levels were compared using the same statistical methods used in DHEA(S) analyses. Receiver operating characteristic (ROC) curve analyses were performed using residual data to calculate area under the curve (AUC) of significant between-group findings.

3. RESULTS

3.1. Participant Characteristics

Demographic and clinical characteristics of the sample are summarized in Table 1. Remitters and Non-remitters did not differ in baseline HDRS scores, age, sex, years of education, race, current tobacco use, lifetime depression chronicity, length of current MDD episode, or final SSRI dose (based on dose-equivalency of sertraline (Preskorn, 2009)). Non-remitters had significantly higher BMI than both Remitters (p=0.009) and controls (p<0.001); Remitters' BMI did not differ from controls (p=0.663). Controls were well-matched to both Remitters and Non-remitters in regards to age, sex, years of education, and race. Tobacco use was more prevalent in both Remitters (p=0.017) and Non-remitters (p=0.006), in comparison to controls.

3.2. DHEA(S) and Remission of MDD

In comparison to Non-Remitters, Remitters had significantly higher pre-treatment DHEA and DHEA-S levels (DHEA: U=70.0, p=0.008, Cohen's d=1.11; DHEA-S: U=87.0, p=0.040, Cohen's d=0.83; Figure 1). Pre-treatment DHEA(S) showed good predictive ability in separating Remitters from Non-Remitters (DHEA: AUC=0.766, p=0.009; DHEA-S: AUC=.709, p=0.040). At the end of eight weeks of SSRI treatment, DHEA and DHEA-S levels remained significantly higher in Remitters compared to Non-remitters (DHEA: U=63.0, p=0.013, Cohen's d=0.98; DHEA-S: U=74.0, p=0.040, Cohen's d=0.67; Figure 1). DHEA(S) levels after SSRI treatment continued to significantly distinguish these two groups (DHEA: AUC=0.758, p=0.014; DHEA-S: AUC=0.715, p=0.039). Sensitivity analyses were performed, only including those subjects who were prescribed sertraline and results remained unchanged. Group means and standard deviations of DHEA(S) levels are presented in Table 2.

3.3. DHEA(S) and Absolute Improvement of MDD Severity

Correlational analyses showed that absolute improvement in HDRS ratings (across all MDD subjects) was not significantly associated with pre-treatment DHEA (rho=−0.081, p=0.639; Figure 2a) or DHEA-S levels (rho=−0.288, p=0.088; Figure 2b). Improvement in HDRS ratings was, however, significantly associated with higher post-treatment DHEA (rho=−0.432, p=0.012; Figure 2c) and DHEA-S levels (rho=−0.590, p<0.001; Figure 2d).

There was no significant change in pre-to-post-treatment DHEA or DHEA-S levels in the whole group (p=0.922 and 0.469, respectively), Remitters (p=0.422 and 0.522, respectively), or in Non-remitters (p=0.681 and 0.601, respectively). Further, changes in DHEA(S) were not significantly correlated with changes in HDRS (p=0.717 and 0.589, respectively).

3.4. Comparisons with Healthy Controls

There were no group differences in baseline DHEA and DHEA-S levels between controls and all MDD subjects (DHEA: U=1181.0, p=0.336, Cohen's d=0.31; DHEAS: U=1221.0, p=0.416, Cohen's d=0.22). However, power calculations indicate that an effect size of 0.57 or greater would be necessary to detect differences in a sample of this size, with a power of 0.80. When comparing baseline DHEA(S) levels of controls to those of Remitters and Non-

remitters separately, Remitters had significantly higher baseline DHEA than controls (U=242.0, p=0.004, Cohen's d=0.98; AUC=0.748, p=0.004) and a trend toward the same relationship with DHEA-S (U=346.0, p=0.096, Cohen's d=0.56; AUC=0.645, p=0.096); Figure 3. Levels of DHEA and DHEA-S did not differ significantly between Non-remitters and controls (DHEA: U=763.0, p=0.455, Cohen's d=0.17; DHEA-S: U=850.0, p=0.917, Cohen's d=0.03; Figure 3). Group means and standard deviations of DHEA(S) levels are presented in Table 2.

3.5 Cortisol and Remission of MDD

To determine the specificity of the association of DHEA(S) with SSRI-associated remission, and to examine the relationship of related steroids, pre- and post-treatment cortisol levels were compared, also correcting for age, sex, BMI and assay batch. There were no significant differences in pre- or post-treatment cortisol levels between Remitters and Non-remitters; comparisons with healthy controls were also not significant. Statistics are presented in Table 2.

4. DISCUSSION

To the best of our knowledge, this is the first study to examine endogenous serum DHEA(S) levels specifically in relation to SSRI-induced remission of MDD. We found that pre-treatment, as well as post-treatment, serum DHEA(S) levels were higher in MDD subjects who achieved remission during eight weeks of SSRI treatment compared to those who did not achieve remission; these relationships were of a large effect size and remained significant when only including participants who were taking sertraline (n=30). Similar relationships were not found with cortisol, suggesting that DHEA(S) concentrations specifically were related to MDD remission.

As reviewed in the Introduction, three previous studies examined baseline circulating DHEA(S) levels in relation to likelihood of antidepressant-associated response/remission, with somewhat mixed results. Markopoulou et al. found that baseline DHEA levels were lower in those who went on to respond to inpatient pharmacotherapy with a variety of psychotropics, including thyroid medications, antidepressants, mood stabilizers, antipsychotics, benzodiazepines, and buspirone; response to antidepressants alone was not reported (Markopoulou et al., 2009). The comparability of these previous findings with those of this current study is limited, however, as it (i) was specifically in treatment-resistant depression, (ii) examined clinical response rather than remission, (iii) included participants with comorbid diagnoses that were exclusionary in the present study (e.g. bipolar, PTSD, bulimia, psychosis), (iv) included inpatient subjects, and (v) the medication interventions involved different classes of drugs. Fabian et al. found no differences in baseline DHEA(S) levels when comparing remitters and non-remitters to treatment with nortriptyline (a tricyclic antidepressant) or paroxetine (an SSRI) in elderly MDD patients (Fabian et al., 2001); however, response to these two medications were not examined separately, making it unknown whether the relationship between remission and DHEA(S) levels differed between the two classes of antidepressants. Additionally, the study by Fabian et al. differed from ours in that it (i) was limited to elderly MDD patients (60+ years of age), (ii) employed a

different classification of remission (post-treatment HDRS 10), (iii) involved 12 weeks of treatment rather than eight, (iv) included inpatient subjects, and (v) many subjects were taking multiple medications throughout the study (Fabian et al., 2001). Hsiao compared baseline DHEA levels of those who remitted after treatment with venlafaxine (a serotonin-norepinephrine reuptake inhibitor [SNRI]) to those who did not remit and did not find any significant differences between these groups (Hsiao, 2006). Though there are many similarities between the present study and that by Hsiao, there are certain key differences that could explain the discrepancies between those findings and our own. The study by Hsiao (i) involved 12 weeks of treatment rather than eight, perhaps impacting the classification of Remitters; (ii) did not correct for BMI, though they acknowledge the effects of BMI on DHEA levels (Mazza et al., 1999); (iii) imposed a shorter medication-free period prior to baseline measurement (two weeks rather than six); and (iv) involved the use of a different class of antidepressants (i.e. SNRIs).

Though the primary aim of the present study was to examine DHEA(S) levels in MDD subjects before and after undergoing open-label SSRI treatment, we additionally examined whether DHEA(S) levels changed after SSRI treatment and whether the change in DHEA(S) levels related to the change in depression severity. We did not find any significant changes in pre-to-post-treatment DHEA(S) levels in the whole MDD sample or in the Remitters or Non-remitters separately, nor did we find a significant correlation between change in DHEA(S) and change in depression severity. Several studies have examined the association between change in DHEA(S) levels and clinical improvement after antidepressant treatment (Deuschle et al., 2004; Fabian et al., 2001; Hsiao, 2006; Markopoulou et al., 2009; Morita et al., 2014; Paslakis et al., 2010; Romeo et al., 1998; Schüle et al., 2009; Takebayashi et al., 1998), several of which have reported decreases in pre-to-post treatment DHEA(S) levels in depressed patients (Schüle et al., 2009; Takebayashi et al., 1998; Zhu et al., 2015), at least in those who responded to treatment (Deuschle et al., 2004; Fabian et al., 2001; Hsiao, 2006; Morita et al., 2014; Paslakis et al., 2010; Schüle et al., 2009); however, findings are mixed (Markopoulou et al., 2009; Morgan et al., 2010; Romeo et al., 1998). The reasons for these inconsistencies are uncertain, however, few of these studies had similar designs to ours, including differences in age groups, medication status, measurements of improvement, etc., making direct comparisons difficult. One more potential reason for these discrepant findings may be the differences in the classes of antidepressants used in each study (as discussed in the Introduction).

In addition to examining differences in DHEA(S) levels in Remitters and Non-remitters, we explored the relationship of these hormone levels to absolute changes in HDRS. We found that, whereas baseline DHEA(S) levels were not significantly associated with absolute changes in HDRS, Week 8 DHEA(S) levels were significantly associated with absolute changes in HDRS. Though the reasons for the differences in these measures are not known, remission indicates the absence of significant depressive symptoms and is considered the "gold standard" outcome (Fishbain, 2009). Further larger scale studies will be needed to validate the differences in these measures.

In addition to examining differences in DHEA(S) levels in MDD subjects, we further explored differences between depressed individuals and healthy controls. Previous findings

in depression have found DHEA and/or DHEA-S concentrations to be decreased (Michael et al., 2000; Mocking et al., 2015; Morgan et al., 2010; Zhu et al., 2015), increased (Assies et al., 2004; Kurita et al., 2013; Morita et al., 2014; Takebayashi et al., 1998), or unchanged (Fabian et al., 2001; Kurita et al., 2013; Markopoulou et al., 2009; Mocking et al., 2015; Paslakis et al., 2010; Romeo et al., 1998) (also reviewed in Maninger *et al.*, 2009) in depression in comparison to non-depressed controls. There is no simple way of reconciling these discrepant findings; however, it is likely that participant demographics (including age and gender), comorbid psychiatric and medical conditions, medication status, and time of blood collection are relevant. The current study did not find any significant differences in DHEA or DHEA-S levels between MDD and healthy control subjects; however, MDD subjects who went on to become Remitters after SSRI treatment had significantly higher baseline DHEA(S) levels when compared to controls. Non-remitters' baseline DHEA(S) levels did not differ from healthy controls, suggesting that baseline DHEA(S) levels may be related to prognosis rather than diagnosis of MDD *per se*.

Though specific pathways by which DHEA(S) levels may relate to SSRI-induced remission are not known, possible mechanisms may be postulated. Prior experiments in adult rats by Pinnock et al. have shown that DHEA, administered subcutaneously, can increase the efficacy of fluoxetine-induced neurogenesis in the dentate gyrus by rendering fluoxetine doses that were previously ineffective to be as effective as a dose four times greater (Pinnock et al., 2009). This finding suggests that DHEA may have a synergistic effect with fluoxetine, promoting hippocampal neurogenesis, at least in rats. To the extent this is true in humans with MDD as well, it is plausible that DHEA may augment SSRIs' ability to promote hippocampal neurogenesis, thereby increasing the likelihood of inducing remission.

One limitation of the present study is the use of a relatively small sample, although, we had more than sufficient power to detect the effect sizes of our main comparisons, which ranged from 0.67 – 1.11. However, our between-group comparisons with cortisol were generally underpowered, with observed effect sizes ranging from 0.23 – 0.60. Additional limitations of the present study include (i) the use of multiple SSRIs, though sensitivity analyses revealed no change in findings when only examining subjects taking sertraline; (ii) the sole use of SSRIs, which may limit generalizability to other classes of antidepressants; (iii) the open-label nature of the antidepressant therapy, which can confound drug response with placebo response (though an open-label design more closely resembles clinical settings); (iv) the assessment of antidepressant remission after eight weeks of treatment, rather than additionally including longer duration time points; and (v) the use of single time-point and single time-of-day (morning) blood draws for DHEA(S) determination pre- and post-SSRI treatment, which fails to account for diurnal and day-to-day fluctuations. Strengths of the present study include (i) our use of well-characterized, rigorously diagnosed, physically healthy, unmedicated MDD subjects; (ii) a minimum six-week medication-free period before baseline; (iii) an eight-week period of antidepressant treatment that was verified by pill counts in all subjects and by plasma antidepressant assays in a subset; and (iv) the use of a single class of antidepressant medication to increase sample homogeneity.

5. CONCLUSIONS

The present study suggests that higher circulating DHEA(S) levels (both while unmedicated and after eight weeks of SSRI treatment) are associated with remission of depression after SSRI treatment. Due to our modest sample size and somewhat conflicting prior findings in the literature, these data bear replication with a larger sample. These data indicate that endogenous DHEA(S) abundance may be a physiological adjunct to SSRI efficacy, as suggested by prior preclinical and clinical studies (Bloch et al., 1999; Maninger et al., 2009; Pinnock et al., 2009; Rabkin et al., 2006; Schmidt et al., 2005; Wolkowitz et al., 1999; Wolkowitz et al., 1997). Should these findings be replicated, serum DHEA(S) levels could represent a novel biomarker for depression remission with SSRI antidepressants, although our small-scale study was not designed to establish sensitivity or specificity of DHEA(S) as a biomarker in individual patients. Additional future clinical trials might further examine whether exogenously administered DHEA can serve as a useful adjunct to SSRI treatment.

Acknowledgements

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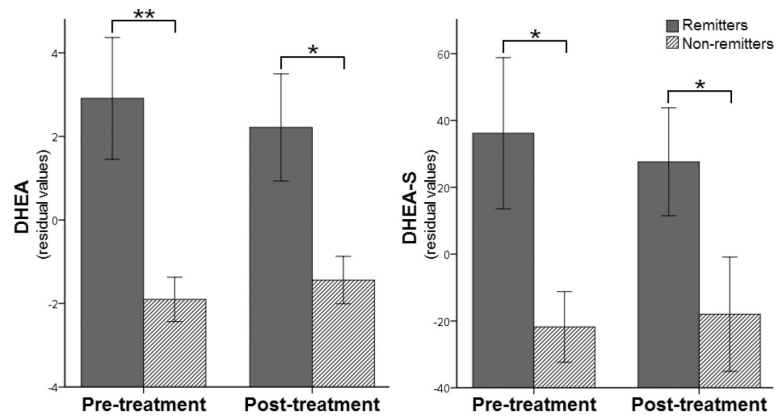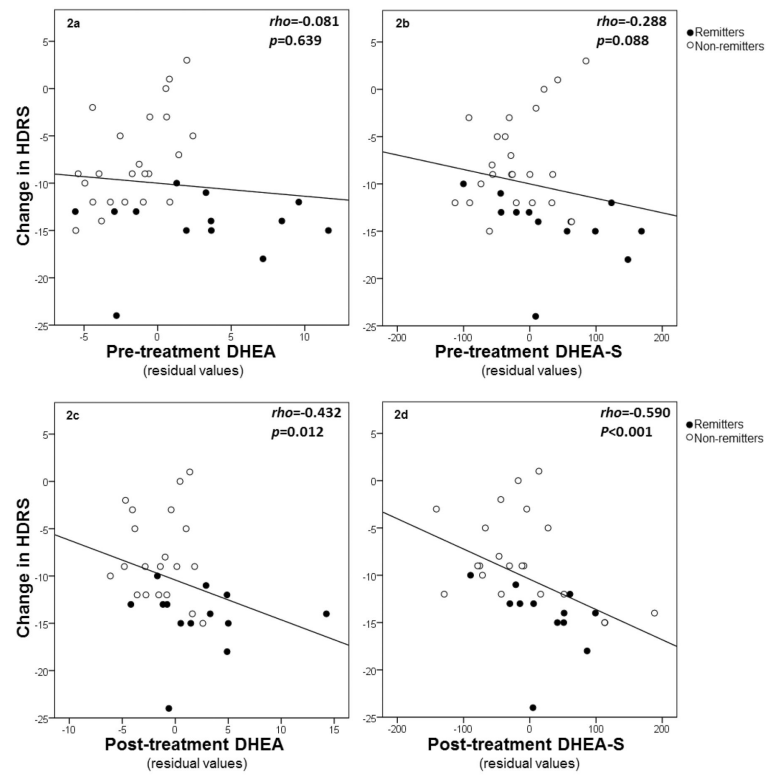
Figure 1. Pre- and Post-treatment DHEA(S) in Remitters and Non-remitters
DHEA and DHEA-S levels were significantly higher in Remitters compared to Non-remitters before SSRI treatment (p=0.008 and 0.040, respectively) and after SSRI treatment (p=0.013 and 0.040, respectively). DHEA was measured in ng/dL and DHEA-S was measured in µg/dL. Data represent residual values after correcting for age, sex, BMI, and DHEA(S) assay batch, therefore, values may be positive or negative.

Figure 2. Spearman correlations between pre- and post-treatment DHEA(S) and absolute change in HDRS Depression Severity over the eight weeks of treatment (Week 8 minus Baseline)

DHEA was measured in ng/dL and DHEA-S was measured in μg/dL. Data represent residual values after correcting for age, sex, BMI, and DHEA(S) assay batch, therefore, data may be positive or negative. The outlier with the greatest decrease in HDRS ratings did not significantly affect the results, as results were not significantly changed with post-hoc exclusion of that subject and as the analyses were non-parametric.
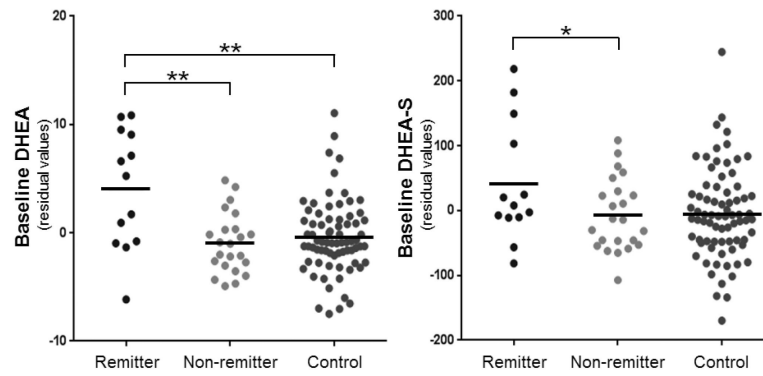
Figure 3. Baseline (pre-treatment) DHEA(S) levels in Remitters, Non-remitters, and controls
Baseline DHEA levels of Remitters were significantly higher than Non-remitters (p=0.008) and controls (p=0.004). Baseline DHEA-S levels of Remitters were significantly higher than Non-remitters (p=0.040), with a trend toward the same relationship when compared to controls (p=0.096). DHEA was measured in ng/dL and DHEA-S was measured in μg/dL. Data represent residual values after correcting for age, sex, BMI, and DHEA(S) assay batch, therefore, data may be positive or negative.

Table 1

Demographics and clinical characteristics of the sample.

	All MDD (n=36)	Remitters (n=13)	Non-remitters (n=23)	Remitters vs. Non-remitters	Controls (n=75)	Three Group Comparison
Age (years; M±SD)	37.92± 12.11	37.77± 12.60	38.00± 12.11	U=138.5 p=0.717	37.33± 13.29	χ^2=0.35 p=0.840
Sex (% females)	66.7	61.5	69.6	χ^2=0.24 p=0.624	61.3	χ^2=0.53 p=0.768
Ethnicity (% Caucasian)	83.3	84.6	82.6	χ^2=0.02 p=0.877	70.7	χ^2=2.09 p=0.352
Body Mass Index (kg/m2; M±SD)	26.78± 5.00	24.03± 12.60	28.34± 4.59	U=71.0 p=0.010	24.48± 4.60	χ^2=14.07 p=0.001 *[1]
Tobacco Use (% tobacco users)	30.6	30.8	30.4	χ^2=0.00 p=0.983	8.0	χ^2=9.54 p=0.008 *[2]
Years of education (M±SD)	16.17± 2.11	16.38± 1.94	16.04± 2.23	U=138.0 p=0.697	16.73± 1.83	χ^2=2.03 p=0.362
HDRS pre-treatment (M±SD)	19.50± 3.01	18.92± 3.04	19.83± 3.01	U=109.5 p=0.179	--	--
HDRS post-treatment (M±SD)	9.53± 5.09	4.62± 1.34	12.30± 4.23	U=0.00 p<0.001*	--	--
Current MDE Length (months; M±SD)	70.87± 124.68	46.55± 117.91	83.55± 128.77	U=108.5 p=0.310	--	--
Lifetime Depression Chronicity[3] (months; adjusted M±SD)	123.05± 118.00 (n=35)	106.49± 112.30 (n=12)	139.61± 112.14	F=0.68 p=0.414	--	--
Final SSRI Dose[4] (mg/day; M±SD)	108.33± 36.84	105.77± 27.30	109.78± 41.79	U=141.0 p=0.763	--	--

*
Significant at the p<0.05 level.

[1]
Post-hoc analyses indicate that the BMI of Non-remitters was significantly higher than that of controls (p<0.001); BMI of Remitters did not differ from controls (p=0.663).

[2]
Post-hoc analyses indicate that tobacco use was more prevalent in both Remitters (p=0.017) and Non-remitters (p=0.006), in comparison to controls.

[3]
Lifetime Depression Chronicity data was not available for one MDD Remitter. Adjusted means and standard deviations were calculated using analysis of covariance (ANCOVA) while covarying for age.

[4]
Final SSRI Dose is based on dose-equivalency of sertraline (Preskorn, 2009).

Table 2

Mean steroid concentrations and group comparisons.

	Remitters (n=13)	Non-remitters (n=23)	Remitters vs. Non-remitters	Controls (n=75)	Controls vs. Remitters	Controls vs. Non-Remitters
Pre-treatment (Baseline) DHEA (ng/dL; M±SD)	12.49±8.12	6.17±3.69	U=70.0 p=0.008[*]	6.45±4.38[1]	U=242.0 p=0.004	U=763.0 p=0.455
Pre-treatment (Baseline) DHEA-S (µg/dL; M±SD)	207.46±134.92	157.30±83.47	U=87.0 p=0.040[*]	159.00±89.40	U=346.0 p=0.096	U=850.0 p=0.917
Post-treatment DHEA (ng/dL; M±SD)	10.54±7.26	5.73±3.43[2]	U=63.0 p=0.013[*]	--	--	--
Post-treatment DHEA-S (µg/dL; M±SD)	200.44±120.58	162.95±115.85[2]	U=74.0 p=0.040[*]	--	--	--
Pre-treatment (Baseline) cortisol (µg/dL; M±SD)	11.91±5.89	8.08±3.23	U=115.0 p=0.267	9.68±6.00	U=415.0 p=0.394	U=762.0 p=0.400
Post-treatment cortisol (µg/dL; M±SD)	10.91±5.53	8.24±3.19[2]	U=111.0 p=0.501	--	--	--

Means presented reflect raw data, however, group comparisons were run on residual data corrected for age, sex, BMI and DHEA(S) assay batch.

[*] Significant at the p<0.05 level.

[1] n=74

[2] n=20