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The association of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) with anxiety sensitivity and electronic diary negative affect among smokers with and without posttraumatic stress disorder

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Abstract

Posttraumatic stress disorder (PTSD) is associated with increased smoking initiation, maintenance and relapse. Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are neurosteroids that have been associated with mood measures as well as smoking status, and nicotine is associated with increased DHEA and DHEAS levels. Given the difficulties with mood experienced by smokers with PTSD, the purpose of the current study was to evaluate the association between negative affect and anxiety sensitivity with DHEA and DHEAS levels. Ninety-six smokers with and without PTSD provided blood samples for neurosteroid analyses, and completed self-report measures of anxiety sensitivity and electronic diary ratings of negative affect. As expected, PTSD smokers reported higher levels of anxiety sensitivity ($F[1,94]=20.67$, partial $\eta^2=0.18$, $p<.0001$) and negative affect ($F[1,91]=7.98$, partial $\eta^2=.08$, $p=.006$). After accounting for age and gender, DHEAS was significantly inversely associated with both anxiety sensitivity ($F[3,92]=6.97$, partial $\eta^2=0.07$, $p=.01$) and negative affect ($F[3,87]=10.52$, partial $\eta^2=0.11$, $p=.002$) across groups. Effect sizes indicated that these effects are moderate to high. No significant interactions of diagnosis and DHEA(S) levels with mood measures were detected. Given that nicotine is known to elevate DHEA(S) levels, these results suggest that DHEAS may serve as a biomarker of the association between mood and nicotine among smokers. Implications for the results include 1) the use of DHEAS measurement across time and across quit attempts; and 2) the potential for careful use of DHEA supplementation to facilitate abstinence during smoking cessation.

Posttraumatic stress disorder (PTSD) is significantly associated with smoking initiation and maintenance^{1,2}. Individuals with posttraumatic stress disorder (PTSD) endorse rates two to three times higher of smoking and heavy smoking, and have more difficulty quitting than

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non-PTSD samples^{3,4}. Research has implicated the hypothalamic-pituitary-adrenal (HPA) axis in both PTSD and smoking, suggesting that acute and chronic smoking-related HPA axis changes may be related to nicotine dependence⁵⁻¹⁰, and particularly to the higher addiction vulnerability among those with PTSD¹¹.

Dehydroepiandrosterone (DHEA) and its sulfated metabolite DHEAS (often referred to together as DHEA(S)) are neuroendocrine hormones of the HPA axis that appear to have protective antiglucocorticoid effects on brain functioning upon exposure to severe or chronic stress^{12,13}. Higher DHEA(S) levels have been associated with increased resiliency or coping among individuals with PTSD¹⁴⁻¹⁶ and cocaine dependence¹⁷. There is some evidence that supplementation with DHEA may improve mood in individuals with depression^{18,19}.

Studies have demonstrated that baseline DHEA(S) levels are higher in smokers than non-smokers^{11,20,21}, and that acute smoking of a single cigarette induces increases in DHEA that are greater than those observed after weeks of DHEA supplementation treatment for depression^{8,18}. In one study with 28 male smokers, DHEAS was significantly inversely correlated with the negative affect subscale of a smoking withdrawal measure and a craving item⁶, and in another study DHEA levels were found to drop 18% in postmenopausal smokers 6 weeks after smoking cessation⁹. PTSD and smoking relapse during quit attempts are both associated with anxiety sensitivity and high negative affect^{5,22-26}, and expectations of relief from negative affect are associated with smoking relapse in those high in anxiety sensitivity generally²⁷ and in those with PTSD specifically^{28,29}.

Given the association of DHEA(S) with lower negative affect, improved mood, and smoking^{6-9,19,30}, and the positive association of DHEA(S) levels and coping among those with PTSD¹³⁻¹⁶, it is possible that smoking-induced increases in DHEA(S) contribute to higher levels of smoking and greater difficulty quitting in individuals with PTSD. The following hypotheses were developed to test in a sample of PTSD and non-PTSD smokers: 1) PTSD status will be associated with increased anxiety sensitivity and negative affect; 2) DHEA and DHEAS will be negatively related to anxiety sensitivity and negative affect; and 3) there will be an interaction of PTSD and neurosteroid levels, such that compared to those without PTSD, smokers with PTSD will have a stronger negative association between DHEA and DHEAS, and anxiety sensitivity and negative affect.

Materials and Methods

Participants and Procedures

Data presented here are baseline measures administered as part of a larger smoking cessation study investigating mechanisms of relapse in smokers with and without PTSD. Neuroendocrine and anxiety sensitivity measures were available for 41 smokers with PTSD and 55 smokers without PTSD; of these participants, five did not have electronic diary negative affect data. Eligible participants were between 18 and 65 years of age and currently smoking at least 10 cigarettes/day. Because the larger smoking cessation study focused on a counseling intervention (Beckham et al., 2012), participants were excluded if they were using non-cigarette forms of nicotine or bupropion. In addition, participants were excluded for major unstable medical problems (because this could affect quitting smoking); using non-cigarette forms of nicotine; current alcohol or drug abuse/dependence (as this can effect smoking craving and behavior); schizophrenia or current manic syndrome (as these psychiatric disorders are associated with additional difficulty with quitting smoking); and lifetime but not current PTSD (because these individuals would not have been representative of a non-PTSD group). In addition, because acoustic startle responses and prepulse inhibition measures were evaluated in the larger trial, individuals with current

benzodiazepine use were excluded. This study was approved by the Durham Veterans Affairs Institutional Review Board (IRB) and Research and Development Committees and the Duke University School of Medicine IRB.

Measures

Clinician-Administered PTSD Scale (CAPS) and Structured Clinical Interview for DSM-IV Disorders (SCID)—The CAPS³¹ was used to determine PTSD diagnosis during a screening visit. This instrument is a clinical structured interview that is considered the “gold standard” for PTSD assessment. PTSD symptoms were considered present based on the CAPS frequency 1/intensity 2 rule^{31,32}. The Structured Clinical Interview for DSM-IV³³ was used to determine Major Depressive Disorder (MDD) diagnosis. The CAPS and the SCID were administered by clinical raters trained using standardized SCID training. Inter-rater reliability for diagnoses based on videotapes of patient interviews was high ($\kappa = .96$).

The Anxiety Sensitivity Index-R (ASI-R)³⁴ is a 36-item measure that assesses an individual's concerns about the emotional and physical consequences of experiencing anxiety symptoms. Participants rate each item on a 5-point Likert scale, with total scores ranging from 0 to 144. AS is considered to be a stable endophenotypic trait associated with the development of anxiety disorders³⁵. The ASI has demonstrated excellent psychometric properties in both clinical and nonclinical samples^{34,36–39}. The ASI-R was administered at the baseline visit.

Positive and Negative Affect Schedule (PANAS)—Negative affect was measured over a 7-day baseline using the PANAS^{40,41}, a 10-item positive affect and 10-item negative affect scale designed to measure both types of affect. The two scales are largely uncorrelated with one another and are reliable over a two-month period⁴⁰. Participants used electronic diaries to complete mood ratings several times daily upon randomly administered alarm cues, for an average of 22 PANAS ratings over the 7 days (range of 1 to 49 ratings, SD = 11.2).

Fagerström Test of Nicotine Dependence (FTND)—Baseline nicotine dependence was assessed with the FTND, which has been shown to be a valid assessment of heaviness of smoking as reflected in biochemical measures such as cotinine levels⁴².

Endocrine testing—Blood for serum analyses was drawn between 10am and 2pm on the day of screening. Samples were centrifuged at 3000 rpm for 15 minutes and frozen within 60 minutes of venipuncture, and were stored in at -80°C until they were shipped on dry ice to the Clinical Assay Ligand Service Satellite (CLASS) Laboratory in the School of Public Health, Department of Epidemiology, at the University of Michigan for analysis.

DHEAS levels were measured using the ADVIA Centaur DHEA-S assay, a competitive immunoassay using direct chemiluminescent technology. CLASS lab DHEAS analyses are automated and are therefore conducted in singleton; in-house intra- and inter-assay CV's for DHEAS are between 3.2% - 6.5% and 3.3% - 5.8%, respectively. Plasma DHEA samples were analyzed in duplicate using the DRG DHEA ELISA Kit, a solid phase enzyme-linked immunosorbent assay (ELISA); intra-assay CV for DHEA was 4.5%.

Statistical Analysis

Log transformations were used to normalize the distributions for DHEA and DHEAS. General linear models were used to evaluate all hypotheses. Both DHEA and DHEAS are age and gender dependent: secretion levels of both hormones decline from early adulthood

through old age, and the ratio of DHEA to DHEAS is higher in women than in men¹². Therefore, age and gender were entered as covariates in all models. Bonferroni corrections were applied to account for multiple comparisons, and $p < .0125$ (.05/4 comparisons) was adopted as the significance threshold.

To test hypothesis 1, two general linear models (GLM) were conducted with age and gender as covariates and PTSD status as the independent variable. For the first model the outcome variable was the total ASI score, and for the second the outcome variable was the total PANAS negative affect score. To test hypothesis 2, two GLM analyses with age and gender as covariates, and DHEA as the independent variable were conducted: in the first model total ASI score was the dependent variable, and in the second mean negative affect across the seven days was the dependent variable. The same models were then re-run with DHEAS as the independent variable. As a test of hypothesis 3, the models were re-run with the addition of the interaction term of PTSD $\times$ DHEA and PTSD $\times$ DHEAS.

Results

Clinical and Demographic Characteristics

Gender distribution, age, minority status, education level, employment status, and veteran status are presented in Table 1. No significant differences were detected between participants with and without PTSD on these variables other than employment status. Most participants in the sample had experienced at least one significant trauma accompanied by fear, helplessness, and horror at some time in their lives; however, participants with PTSD had experienced significantly more such traumas compared to those without.

Key clinical characteristics and mean hormone levels for PTSD and non-PTSD groups are also presented in Table 1. Participants with PTSD were significantly more likely to have current MDD, though no significant differences were observed between the groups on comorbid anxiety disorder diagnoses. As expected, the PTSD group had significantly higher scores for ASI Total and PANAS negative affect. There were no significant differences in FTND scores, and the groups did not differ on DHEA or DHEAS levels. As DHEA(S) may be impacted by antidepressant use⁴³ and possibly by lifetime substance use via dopaminergic mechanisms⁴⁴, we examined the correlation of DHEA and DHEAS levels with these two variables (22% of the sample endorsed current antidepressant use; 50% of the sample met lifetime criteria for substance abuse/dependence). These correlations failed to be significant.

Results examining the association of DHEA(S) with anxiety sensitivity and negative affect revealed that after accounting for age and gender, DHEAS was significantly associated with both ASI total score, $F(3,92)=6.97$, partial $\eta^2=0.07$, $p=.01$, and with PANAS negative affect, $F(3,87)=10.52$, partial $\eta^2=0.11$, $p=.002$. DHEA was associated with PANAS negative affect, $F(3,87)=6.25$, partial $\eta^2=0.07$, $p=.014$, but this did not survive Bonferroni corrections. DHEA was not significantly associated with ASI total score.

The hypothesis that there would be a stronger negative association of DHEA(S) with anxiety sensitivity and negative affect among participants with PTSD was not supported. Consistent with the significant differences in means reported in Table 1, GLM analyses revealed significant main effects in the association between PTSD and ASI total score, $F(1,94)=20.67$, partial $\eta^2=0.18$, $p<.0001$, and between PTSD and PANAS negative affect, $F(1,91)=7.98$, partial $\eta^2=.08$, $p=.006$. Those with PTSD reported higher anxiety sensitivity and experienced more negative affect during the baseline monitoring period than those without PTSD. Though there was an interaction between DHEA and PTSD and ASI

sensitivity ($p=.02$), this did not survive Bonferroni corrections. No other interactions were detected.

Discussion

This study examined the association of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) with anxiety sensitivity and negative affect in smokers with and without PTSD. As predicted, PTSD was positively associated with both anxiety sensitivity and negative affect, and DHEAS levels were significantly inversely associated with anxiety sensitivity and negative affect. Effect sizes were in the moderate to high range⁴⁵. However, the interaction hypothesis was not supported: The negative association between DHEAS, anxiety sensitivity and negative affect was similar across both PTSD and non-PTSD smoker groups. DHEA levels were not significantly associated with either of the mood measures after Bonferroni corrections.

The observation that PTSD was positively associated with anxiety sensitivity and negative affect in smokers replicates previous findings^{46,47}. Among all smokers, the negative association of DHEAS with anxiety sensitivity and negative affect is consistent with and extends previous findings of an inverse relationship between DHEAS and the negative affect scale of a smoking withdrawal measure⁶. Taken together, these findings suggest that DHEAS levels may be associated with increased coping among smokers. Increased DHEA(S) levels and associated improvement in functioning have been observed in response to both psychotherapy and DHEA supplementation. As cigarette smoking is related to increased DHEA(S) levels⁷, DHEAS elevations may reflect one of the reinforcing effects of smoking.

Contrary to hypotheses, DHEA(S) levels were not more strongly inversely associated with mood measures in smokers with versus without PTSD. This suggests that smokers use smoking to improve mood across a range of dimensions and levels of functioning, and that this is not limited to those who meet a clinical threshold. Such an interpretation would be consistent with findings of the association of smoking with subthreshold symptoms of attention-deficit/hyperactivity disorder, which is also linked to high rates of nicotine dependence⁴⁸. As such, smokers with subthreshold symptoms of a range of psychiatric disorders may derive mood-related benefits associated with smoking-related elevations in DHEA(S) levels. Taken together, these results and the literature suggest that DHEA(S) may serve as a biomarker for the association of nicotine and mood across smokers, and that varying levels are quantitative rather than qualitative.

Inverse correlations of negative affect and craving with DHEA levels in smokers have led researchers to suggest that supplementation with DHEA may help mitigate mood-related withdrawal symptoms in smokers during a cessation attempt⁶. Our findings support this conclusion. However, the timing and context of DHEA supplementation may be important if used to facilitate abstinence. For example, DHEA supplementation with individuals in an outpatient cocaine dependence treatment program resulted in increased cocaine use, and the authors suggested that this may have been due to the augmentation by DHEA of cocaine's euphoric effects during lapses⁴⁹. As such, it will be important to determine whether such effects also occur with nicotine, and to carefully consider when and under what circumstances DHEA may be helpful or harmful in the treatment of nicotine dependence.

Though we found DHEAS levels to be inversely associated with both negative affect and anxiety sensitivity, we did not find an association of DHEA levels with our mood measures. Circulating levels of DHEAS are 250 times higher than levels of DHEA in women, and 500 times higher than levels of DHEA in men¹², potentially allowing for a more sensitive

measure of association. As such, DHEAS may be a more sensitive biomarker of mood among smokers than DHEA.

These findings must be considered in light of the study's limitations. Even though the DHEA(S) measurement was restricted to a four hour window, it is possible that there was unintended diurnal variation during the restricted time period. Other variables known to affect DHEA(S), such as exercise⁵⁰ and previous treatment with serotonergic compounds⁵¹, were unavailable for evaluation. Further, because there are varying trajectories associated with PTSD⁵², different PTSD symptom patterns across time could potentially have some effect on the associations reported here. In future research it may be useful to monitor DHEA(S) levels across baseline smoking, quit attempts and relapse periods to determine how the association may vary. Finally, it could be helpful to investigate DHEA(S) supplementation and the effect of antidepressant medications on the association between DHEA(S) and negative affect/anxiety sensitivity to explore improved methods for smoking cessation interventions.

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Table 1

Demographics and Clinical Characteristics

	PTSD (n=41)	W/out PTSD (n=55)	Test Statistic	Effect Size
Gender (female)	51.2%	41.8%	$\chi^2=.83, p=.36, ns$	$V=.09$
Age (years)	42.9 (9.5)	41.9 (10.0)	$t=-.48, p=.63, ns$	$d=.10$
Minority	70.7%	69.1%	$\chi^2=.03, p=.86, ns$	$V=.02$
Education	12.3 (1.8)	12.6 (2.9)	$t=.50, p=.62, ns$	$d=-.12$
Employed	34.1%	60%	$\chi^2=6.3, p=.01$	$V=.26$
Veteran	26.8%	21.8%	$\chi^2=.32, p=.57, ns$	$V=.06$
# Trauma types with fear, helplessness, or horror	9.8 (3.4)	4.4 (3.9)	$t=-7.08, p<.0001$	$d=1.48$
Current MDD diagnosis	26.8%	3.6%	$\chi^2=10.8, p=.001$	$V=.34$
FTND score	6.0 (1.9)	5.3 (2.1)	$t=-1.47, p=.14, ns$	$d=.35$
ASI Total score	69.2 (32.8)	38.3 (32.9)	$t=-4.55, p<.0001$	$d=.94$
Negative affect	14.2 (4.3)	12.0 (3.0)	$t=-2.7, p=.001$	$d=.59$
DHEA level*	5.8 (3.3)	6.5 (3.4)	$t=.98, p=.33, ns$	$d=-.21$
DHEAS level*	139.5 (73.9)	180.7 (110.7)	$t=.97, p=.33, ns$	$d=-.44$

* DHEA and DHEAS levels reported here are raw values; statistical analyses to address hypotheses were conducted on log values.