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Dehydroepiandrosterone sulfate, cortisol, mood state and smoking cessation: Relationship to relapse status at 4-week follow-up

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Abstract

It has been hypothesized that increased baseline dehydroepiandrosterone sulfate (DHEAS) levels may act as a natural antidepressant to attenuate negative affect during cocaine withdrawal and abstinence, decreasing the probability of relapse. The current study extends this model to assess factors related to risk of relapse in a sample of 68 nicotine dependent participants. Repeated measures ANOVAs were used to examine mood state, salivary DHEAS and cortisol levels across three assessment periods in participants who had relapsed over a 4-week follow-up period ($n=51$, 23 women) compared to those who maintained abstinence ($n=17$, 8 women). Total scores on the Profile of Mood States differed between those who had relapsed and those who maintained abstinence ($p=0.008$). However, DHEAS and cortisol levels, as well as the ratio of cortisol to DHEAS, did not differ significantly between groups. These findings suggest that, although DHEAS-related enhancement of resiliency to withdrawal may occur, the extent of this protective effect may be modulated by additional factors that warrant further research.

Keywords: Dehydroepiandrosterone sulfate; Cortisol; Mood; Smoking; Relapse

1. Introduction

Chronic cigarette smoking is a well known and preventable cause of serious illness and death. However, although various smoking cessation treatments exist, relapse rates remain relatively high. According to the National Institutes of Health, less than 7% of the nearly 35 million individuals per year who attempt unaided smoking cessation will maintain abstinence for more than 1 year (National Institutes on Drug Abuse, 2001). Clearly, additional research is needed to determine factors that may predict treatment success and/or recommend additional approaches to smoking cessation.

Psychosocial stressors, as well as increased negative and decreased positive mood, have been shown to contribute to risk for smoking relapse (Shiffman and Waters, 2004). A potential biological marker of such subjective characteristics was recently examined in the context of addiction to another stimulant drug, cocaine. Alterations in activity of the hypothalamic–pituitary–adrenal (HPA) axis have been observed in the early phases of cocaine abstinence. Buydens-Branchey et al. (2002) assessed changes in cortisol and the neuroexcitatory adrenal steroid hormone, dehydroepiandrosterone sulfate (DHEAS) in hospitalized cocaine abusers after 6, 9, 18 and 21 days of abstinence. Results indicated a decrease in cortisol and increase in DHEAS over the 3 weeks of abstinence, suggesting a gradual return to the individuals' pre-drug state. More recently, Wilkins et al. (2005) examined the relationship between DHEAS and relapse to cocaine use in a population of treatment-seeking cocaine users. DHEAS has been described as an index of physical and mental well being and may positively impact health by antagonizing glucocorticoids, as many disease states are characterized by high cortisol levels with correspondingly low levels of DHEAS (Wolf and Kirschbaum, 1999). The results of Wilkins et al. suggest that

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high DHEAS levels may prolong cocaine abstinence by acting as a natural antidepressant to attenuate stress and negative mood associated with cocaine withdrawal. Thus, it is logical to suggest that DHEAS levels might also be important in recovery from dependence upon other addictive substances, including legal stimulants such as nicotine. However, there is no uniform agreement in the literature with regard to the status of DHEAS as a marker of central nervous system resiliency (Ferrari et al., 2004; Heuser et al., 1998; Legrain and Girard, 2003).

The current investigation extends a previous report by al'Absi et al. (2004), which examined relapse within the first week post-cessation and did not address DHEAS levels. The aim of the current investigation, which followed the same participants over 4 weeks post-cessation, is to examine the relationship between DHEAS level and relapse in a sample of otherwise healthy smokers participating in a smoking cessation program. DHEAS and cortisol levels, as well as subjective mood state, were examined at three time points. Baseline measures were obtained prior to initiation of smoking cessation. A second measure (day 1) was obtained at initial abstinence, and a third measure (day 2) occurred 24 to 28 h following the initial abstinence period. Participants were followed for a period of 4 weeks post-quit date. The authors predicted that, if the theory espoused by Wilkins et al. could be generalized to other substance dependent populations, DHEAS levels would be higher in individuals who maintained abstinence over the 4-week follow-up period compared to those who relapsed.

2. Methods

2.1. Participants

All participants signed consent forms approved by the Institutional Review Board of the University of Minnesota and received monetary incentives for their participation. Participants were recruited by newspaper advertisements and by posters placed in the university community. Participants endorsed no recent history of medical or psychiatric disorder or medication intake (except contraceptives), and weighed within ±30% of Metropolitan Life Insurance norms. Further, participants consumed two or less alcoholic drinks per day and met minimum smoking requirements (15 cigarettes or more per day for a minimum of 2 years) with significant motivation to quit smoking. Of the 92 participants who initially qualified for the study, 20 (8 male) were discontinued due to failure to attend one or more subsequent appointments. Thus, data from 72 participants (38 male) remained.

Participants began the study with the intent to schedule a specific quit date on which they would stop smoking. For female participants, the quit date was scheduled during the follicular phase (days 3–10) of the menstrual cycle, as determined by self-report. In the laboratory, carbon monoxide (CO; MicroCO™, Micro Direct Inc., Auburn, Maine) and salivary continine (EIA; DRG Diagnostics, Marburg, Germany) samples were obtained for comparison purposes to verify smoking abstinence at a later date. The Profiles of Mood States (POMS; McNair et al., 1992) was also administered between 1200 h and 1300 h. Baseline measurements of salivary DHEAS levels and cortisol levels were collected at 2000 h approximately 2 weeks prior to the quit date (ambulatory smoking measure).

Prior to their quit date, participants attended a 45-min educational session focusing on the negative effects of smoking and the positive impact of cessation. No pharmacological or behavioral interventions were employed. On the quit day, POMS measures were obtained in the laboratory setting between 1200 h and 1300 h. A second assessment of salivary DHEAS and cortisol levels occurred at 2000 h on the first day of abstinence (day 1).

Once participants had attained 24 h of abstinence (day 2), they returned to the laboratory. Following collection of CO and continine samples to verify abstinence, POMS measures and DHEAS and cortisol levels were assessed during the afternoon testing session, which generally occurred between 1200 h to 1500 h.

Participants were then followed for 4 weeks after the quit date. Individuals who reported smoking at least one cigarette during the 4-week period were classified as "relapsed", whereas those who did not relapse were included within the "abstinent" group.

2.2. Dependent measures

Methods for saliva sample collection have been reported previously (see al'Absi et al., 2004). Samples were collected into plastic tubes (Salivette®, Sarstedt, Rommelsdorf, Germany) and stored in −70 °C until assayed for DHEAS and cortisol levels. Cortisol was assayed using a time-resolved fluorescence immunoassay with cortisol-biotin conjugate as a tracer. The inter- and intra-assay coefficients of variation were less than 10% and 12%, respectively. DHEAS was assayed using enzyme immunoassay (Diagnostic Systems Laboratories, Sinsheim, Germany), with inter- and intra-assay coefficients of variation below 9%.

In addition to providing general demographic information, participants completed a number of questionnaires previously reported by al'Absi and colleagues (2004). Instruments included the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991), the Center for Epidemiologic Studies-Depression scale (CES-D; Radloff, 1977) and the State-Trait Anxiety Inventory (Trait-Form; STAI; Speilberger et al., 1983).

2.3. Data analysis

Approximately 75% of participants were included within the relapsed group. The remaining participants comprised the abstinent group. Boxplots (SPSS, version 12) were used to examine the distributions of DHEAS levels, cortisol levels and total POMS scores by group. Four participants were excluded from final analyses due to DHEAS or cortisol levels in excess of three standard deviations of their respective group means. Thus, 68 participants (51 relapsed) were included in the final analyses; *N*'s of less that 68 reflect missing data.

Background characteristics, including age, education, body mass index, smoking rate, years of smoking, level of nicotine dependence (FTND), depression (CES-D) and anxiety (STAI) were examined via separate ANOVAs using relapse status as the grouping factor. Gender distribution was analyzed via Chi-square.

A total mood disturbance score was derived from the POMS by summing the six subscales with vigor weighted negatively to

produce a possible range of scores from − 40 to 192 (TMD; Glover et al., 2003; McNair et al., 1992). DHEAS levels, cortisol levels and the POMS total mood disturbance score from the three assessment periods were separately analyzed via repeated measures ANOVAs, using relapse status as the grouping factor. Previous literature has recognized the ratio measure of cortisol to DHEAS as a good index of the brain steroidal milieu (Ferrari et al., 2004). Thus, a ratio of cortisol to DHEAS was also calculated and analyzed using the aforementioned strategy. In all analyses, Greenhouse–Geisser corrections were applied to guard against violations of the sphericity assumption, and post-hoc comparisons of repeated variables were Bonferroni corrected. The low number of participants with complete data for all sessions prohibited the inclusion of gender as an additional grouping factor in these analyses. Subsequently, hierarchical linear modeling was conducted to confirm findings from the ANOVAs after adjusting for missing data and accounting for potential violations of ANOVA assumptions. In separate analyses, time of sampling was the within-subject factor, and relapse status served as the independent factor in the prediction of DHEAS, cortisol, cortisol/DHEAS ratio and POMS TMD scores.

In additional analyses, separate univariate ANOVAs were used to examine group differences on the individual POMS subscales at each assessment period.

3. Results

3.1. Background characteristics

As summarized in Table 1, relapsed and abstinent participants did not differ significantly with regard to the number of cigarettes smoked per day, the chronicity of cigarette smoking or level of nicotine dependence as assessed by the FTND. Participant groups also reported a similar number of years of education. Male and female participants were equally distributed across relapsed and abstinent groups, although the small *n* associated with the abstinent group prohibited the inclusion of gender as a grouping factor in subsequent analyses.

However, statistically significant differences between the relapsed and abstinent groups were noted for age ($F(1,66)=6.93$, $p=0.01$), depression ($F(1,66)=5.89$, $p=0.02$) and anxiety ($F(1,66)=4.48$, $p=0.04$).

Table 1
Background characteristics of participants

	Abstinent	Relapsed
Smoking rate (per day)	20.2 (1.0)	18.0 (1.7)
Years of smoking	11.8 (1.6)	16.5 (2.9)
FTND	5.7 (0.3)	5.1 (0.5)
Education (years)	14.5 (0.4)	14.0 (0.7)
Percent male*	47%	45%
Age*	43.8 (3.3)	33.8 (1.9)
CESD*	14.0 (1.3)	7.9 (2.2)
STAI*	38.7 (1.3)	33.2 (2.3)

Entries show estimated marginal means (standard error). BMI: body mass index; FTND: Fagerstrom Test of Nicotine Dependence; CESD: Center for Epidemiologic Studies-Depression; STAI: State-Trait Anxiety Inventory.
* $p<0.05$.

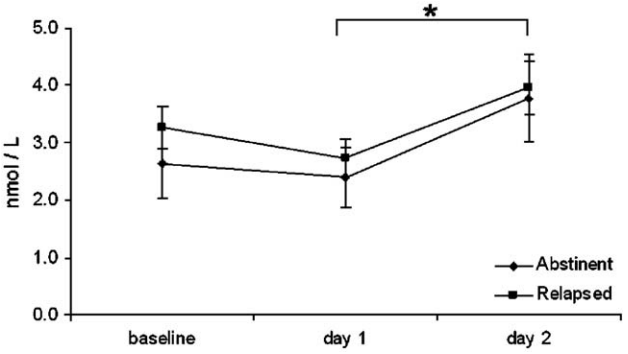

Fig. 1. DHEAS levels changed over time across both abstinent and relapsed groups. *$p<0.05$.

3.2. Biological indices

A significant within-subject difference was noted for DHEAS levels over the three assessment periods ($F(1.71,104.19)=4.87$, $p=0.01$). DHEAS levels decreased slightly but not significantly upon initial abstinence. The main effect of assessment period was primarily due to a significant increase in DHEAS at the final assessment period, day 2 ($p=0.02$) to a level more consistent with that of the smoking assessment (baseline). This finding is illustrated in Fig. 1; means are presented by assessment period and relapse status in Table 2. No significant interactions of relapse status and assessment period were noted ($p=0.83$). Further, between-subject differences in DHEAS level were also non-significant ($p=0.50$). Cortisol levels, and the ratio of cortisol to DHEAS, did not significantly vary across the three assessment periods (p's>0.18), and these variables were not significantly associated with relapse status (p's>0.29). Hierarchical linear modeling confirmed the lack of significant relationship between relapse status and DHEAS levels, cortisol levels and the ratio of cortisol to DHEAS in this sample of otherwise healthy smokers.

3.3. Profile of Mood States

Self-reported total POMS scores did not differ significantly over the three assessment periods ($p=0.16$). A significant between-subjects effect of relapse status was observed ($F(1,63)=7.47$, $p=0.008$). Participants within the relapsed group exhibited higher level of total mood disturbance ($M=27.25$, S.E.$=4.52$) compared to those within the abstinent group ($M=2.38$, S.E.$=7.90$). This group effect was confirmed by HLM (estimate of fixed effects$=-24.18$, S.E.$=5.55$, $df=199$, $t=-4.35$, $p<0.001$).

Additional analyses indicated significant group differences in POMS subscale scores at each of the three assessment periods. These findings are shown in Table 2. At baseline, a statistical trend was noted for depression, anger and fatigue subscales (p's≥ 0.08), in which the relapsed group exhibited higher scores compared to the abstinent group. This trend reached statistical significance on the tension ($F(1,66)=4.62$,

Table 2
Cortisol, DHEAS and POMS measures by group and assessment period

	Abstinent	Relapsed
Cortisol (nmol/l)		
Ambulatory smoking	10.8 (1.3)	10.4 (0.7)
Ambulatory abstinent	9.6 (1.6)	12.5 (0.9)
24-h abstinent	9.5 (1.8)	11.3 (1.0)
DHEAS (μg/ml)		
Ambulatory smoking	2.6 (0.6)	3.3 (0.4)
Ambulatory abstinent	2.4 (0.5)	2.7 (0.3)
24-h abstinent	3.8 (0.8)	3.9 (0.5)
Cortisol/DHEAS		
Ambulatory smoking	6.3 (2.1)	7.6 (1.3)
Ambulatory abstinent	8.2 (4.4)	11.9 (2.7)
24-h abstinent	4.5 (3.2)	6.7 (2.0)
POMS		
Total mood disturbance		
Ambulatory smoking	6.8 (7.7)	28.1 (4.4)
Ambulatory abstinent	−2.5 (8.9)	22.7 (5.1)
24-h abstinent	0.6 (9.1)	30.9 (5.2)

Entries show estimated marginal means (standard error). A significant effect of assessment period was noted for DHEAS levels ($p=0.01$), and POMS total mood disturbance scores differed by relapse status ($p=0.008$). All other mean differences were non-significant.

$p=0.04$) and confusion ($F(1,66)=7.08$, $p=0.01$) subscales. On measures of vigor, a trend was noted in which the relapsed group exhibited lower scores relative to the abstinent group ($p=0.09$) (Table 3).

On day 1, significant differences were only noted on the tension subscale ($F(1,64)=4.45$, $p=0.04$), and the aforementioned trends were observed for anger, vigor, fatigue and confusion (p's>0.09). On day 2, relapsed participants exhibited significantly higher scores on measures of tension ($F(1,65)=6.10$, $p=0.02$), anger ($F(1,65)=6.03$, $p=0.02$), fatigue ($F(1,65)=5.19$, $p=0.03$) and confusion ($F(1,65)=8.70$, $p=0.004$). A trend toward significance was noted for the depression subscale ($F(1,65)=3.03$, $p=0.09$). The relapsed group exhibited lower scores on vigor compared to the abstinent group ($F(1,65)=11.45$, $p=0.001$).

3.4. Post-hoc analyses

Although some degree of circadian rhythm has been reported for DHEAS (Zhao et al., 2003), these effects do not sufficiently explain the findings of the current study. If these changes in DHEAS level were related to nicotine abstinence, one might expect DHEAS levels to continue to decline at the 24-h abstinent measure, although this was not observed. In an attempt to identify variables that might explain this effect, nicotine withdrawal (Minnesota Nicotine Withdrawal Scale; Hughes and Hatsukami, 1986) was considered in post-hoc repeated measures analyses. Although relapsed participants exhibited higher values than those who were abstinent, inclusion of average withdrawal as a covariate in the analysis of DHEAS and cortisol to DHEAS ratio did not alter previous results.

Further, a substantial literature indicates an inverse correlation between DHEAS levels and age (Wolf and Kirschbaum, 1999; Zhao et al., 2003). Given the differences in age between the relapsed and abstinent groups, a separate set of analyses were conducted using age as a covariate in the examination of DHEAS and cortisol/DHEAS. Results indicated no significant relapse-related differences in hormone levels or their ratio. However, the within-subjects differences in DHEAS level was rendered non-significant, suggesting that these findings may have been related, in part, to variability associated with age. Additional research, including repeated DHEAS measures in a larger sample, is needed to determine the implications of these findings.

Finally, the inclusion of both male and female participants is a unique aspect of the current study in relation to previous literature (Buydens-Branchey et al., 2002; Wilkins et al., 2005). Gender-related variations in DHEAS levels have been demonstrated in previous studies (Glei et al., 2004). However, unlike previous studies in which the period of abstinence under consideration was shorter than 4 weeks (i.e., al'Absi et al., 2004), the small number of participants in the current analyses who were able to remain abstinent over a period of 4 weeks resulted in cell sizes too small to support the inclusion of gender as a grouping factor in the main analyses of interest. To further explore this issue, separate post-hoc repeated measures analyses of DHEAS level and the ratio of cortisol to DHEAS were conducted in male participants only. No significant differences were noted over the three assessment periods or between relapsed and abstinent groups. Thus, the relapse-related findings of the current study appear to be valid. However, the issue of gender-related variations in DHEAS levels during the initial

Table 3
Profile of mood states subscale scores by group and assessment period

	Abstinent	Relapsed
Tension		
Ambulatory smoking	6.6 (1.5)	10.5 (0.9)*
Ambulatory abstinent	6.1 (1. 8)	10.4 (1.0)*
24-h abstinent	6.7 (1.7)	11.5 (1.0)*
Depression		
Ambulatory smoking	4.4 (2.0)	8.8 (1.2)
Ambulatory abstinent	3.4 (2.3)	7.1 (1.3)
24-h abstinent	3.6 (2.4)	8.5 (1.4)
Anger		
Ambulatory smoking	4.5 (1.7)	8.0 (1.0)
Ambulatory abstinent	3.1 (2.5)	8.2 (1.4)
24-h abstinent	3.2 (2.4)	10.0 (1.4)
Vigor		
Ambulatory smoking	19.6 (1.3)	17.1 (0.7)
Ambulatory abstinent	20.0 (1.7)	16.7 (1.0)
24-h abstinent	20.9 (1.4)	15.4 (0.8)**
Fatigue		
Ambulatory smoking	5.9 (1.5)	9.0 (0.9)
Ambulatory abstinent	3.6 (1.4)	6.4 (0. 8)
24-h abstinent	4.1 (1.4)	7.9 (0.8)*
Confusion		
Ambulatory smoking	3.9 (1.2)	7.6 (0.7)*
Ambulatory abstinent	3.7 (1.2)	6.4 (0.7)
24-h abstinent	3.9 (1.1)	7.7 (0.7)**

Entries show estimated marginal means (standard error). Significant group differences are noted.
* $p<0.05$.
** $p<0.005$.

phases of smoking cessation warrants further consideration in a larger sample.

4. Discussion

The current study revealed no significant differences between smokers who relapsed in the 4-week period following their quit date and those who maintained abstinence throughout this period in DHEAS, cortisol or cortisol to DHEAS ratio. However, individuals who relapsed exhibited higher POMS total mood disturbance scores compared to those who maintained abstinence. In addition, the relapsed group exhibited higher levels of tension, depression, anger fatigue and confusion, as well as lower levels of vigor, at each of the three assessment periods. Such findings of differences in mood state are consistent with results noted in earlier phases of the study (al'Absi et al., 2004), as well as an extensive earlier literature linking stress and negative affect with nicotine relapse (Baer et al., 1989; Baer and Lichtenstein, 1988; Brandon et al., 1990; O'Connell and Martin, 1987). It has long been known that individuals with a history of conditions characterized by a high degree of negative affect often have more difficulty in quitting smoking (Rabois and Haaga, 2003). In fact, medications designed to address this aspect of smoking cessation have yielded increased abstinence rates (Hayford et al., 1999; Hall et al., 1998; Rabois and Haaga, 2003).

Although the current results do not replicate those of Wilkins and colleagues (2005), these findings are not inconsistent with the theory that high DHEAS levels may enhance resiliency to the effects of stimulant withdrawal. It is important to note that the differential findings in the current study could have a pharmacological basis. Although nicotine and cocaine ultimately activate the dopaminergic reward system, the substances act via different mechanisms. Further, addictive impact of cocaine may be more subjectively intense as compared to cigarette smoking (Mendelson et al., 2003). Further, although cocaine and nicotine are both addictive stimulants, individuals in treatment for cocaine dependence frequently exhibit co-morbid physical and psychological pathology that could lead to variation in DHEAS levels (Hill et al., 2005; Michael et al., 2000). In contrast to Wilkins et al. (2005), the current study examined DHEAS levels in a population of otherwise healthy control participants without concurrent abuse or dependence upon alcohol or illicit substances. This sample was free of health problems or co-morbid psychopathology that might be expected to influence DHEAS levels in a clinical sample. Thus, although the notion of DHEAS as a marker of CNS resiliency remains valid, the current study suggests that this relationship may be mediated or modulated by additional factors.

Additional methodological differences also warrant consideration. For instance, Wilkins and colleagues reported on male veterans, predominantly African American, who enrolled in an inpatient treatment program for cocaine dependence. A comparison group of matched non-substance abusers was also recruited. In contrast, the current study included healthy community dwellers, both male and female, without a history dependence on substances other than nicotine. No comparison group of non-smokers was included. Further, Wilkins and colleagues followed their research participants for 6 months as outpatients in recovery, whereas the current study covers only the first 4 weeks following smoking cessation. Given the methodological differences in the two investigations, the null results of the current study should be interpreted with caution in relation to the findings of Wilkins et al. (2005).

In addition to these issues, participants in the current study also differed on a number of relevant background characteristics. However, several factors should be considered in the practical interpretation of these statistical differences. First, it is important to note that although statistically significant differences were noted in self-reported responses on the CES-D and STAI instruments, all participants were screened for clinically significant depression and anxiety prior to inclusion in the study. Thus, although statistical differences are present, individual levels of anxiety and depression were not clinically significant. Further, although a substantial literature indicates an inverse correlation between DHEAS levels and age (Wolf and Kirschbaum, 1999; Zhao et al., 2003), it is important to note that the mean ages of the relapsed and abstinent groups in the current study are generally within what is considered to be the peak level of DHEAS within the lifespan (see Wolf and Kirschbaum, 1999).

Finally, a number of issues remain to be addressed in future research. It is possible that many of the null findings of the current study could be related to issues of statistical power; thus, future studies should include a larger sample of participants with proportional numbers of male and female participants. In addition, recent research suggests that the timing of assessments may also be an important issue to be considered in future studies of DHEAS. For instance, reports by Goel and Grasso (2004) suggest that variations in mood state throughout the day may vary significantly according to gender, as well as the season in which testing occurs (e.g., winter vs. spring).

5. Conclusion

The current study addressed levels of DHEAS, cortisol and self-reported mood in otherwise healthy smokers over the course of 4 weeks of attempted abstinence from tobacco. Results indicated that the relapsed group exhibited a higher level of withdrawal-related mood disturbance relative to the abstinent group. Relapsed and abstinent groups did not differ with respect to biological measures, suggesting that the proposed role of DHEAS as a marker of CNS resiliency to drug withdrawal may be mediated or modulated by other factors.

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