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# Endocrine Responses During Acute Nicotine Withdrawal

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PICKWORTH, W. B., M. H. BAUMANN, R. V. FANT, R. B. ROTHMAN AND J. E. HENNINGFIELD. *Endocrine responses during acute nicotine withdrawal.* PHARMACOL BIOCHEM BEHAV **55**(3) 433–437, 1996.—Acute administration of nicotine increases cortisol and prolactin but the endocrine effects of tobacco withdrawal are unknown. In a residential, double-blind, placebo-controlled, crossover study, volunteers smoked ad lib for 4 days and underwent monitored tobacco abstinence for 3 days. On no-smoking days, patches delivering 0, 10, 20, or 30 mg nicotine were applied for 16 h. Daily plasma samples were analyzed for ACTH, cortisol, and prolactin. During nicotine abstinence (0 mg patch), circulating levels of ACTH, cortisol, and prolactin did not significantly change from ad lib smoking levels. Over all the patch conditions there was a significant effect of day, with modest but significant elevations of cortisol and ACTH levels on the second no-smoking day (Wed, 37 h abstinent). Prolactin levels increased during nicotine abstinence, but this effect was not significant. The observed endocrine changes did not correlate with physiologic, performance, or subjective measures of tobacco withdrawal. Our data indicate endocrine changes during acute tobacco withdrawal are transient and small. Thus, the present results do not support the use of ACTH as a treatment for tobacco cessation. 

Nicotine Transdermal nicotine ACTH Cortisol Prolactin Nicotine abstinence

WITHDRAWAL from chronic use of abused drugs is often associated with endocrine changes. For example, prolactin levels are elevated in abstinent cocaine addicts (16,17), cortisol levels increase during heroin withdrawal (3) and prolactin, growth hormone, and leutinizing hormone levels are altered during alcohol withdrawal (29). However, to our knowledge, there have been no systematic studies of the endocrine effects of acute tobacco withdrawal in humans.

Intense cigarette smoking increased circulating levels of cortisol in nonsmokers (12) and in smokers (28); however, normal smoking did not increase serum cortisol (9). The finding that cigarette smoking increased cortisol suggests that plasma levels of adrenocorticotropic hormone (ACTH) may increase after intense smoking. In a study that systematically measured ACTH, plasma levels did not increase after smoking (20). Puddey et al. (22) reported that 6 weeks after smoking cessation, plasma cortisol levels were decreased. The authors speculated that the suppressed cortisol exacerbated withdrawal. This observation has led to the suggestion and trial of ACTH injections as a treatment for smoking cessation (2).

In rodents (8) and humans (28) the rapid administration of nicotine increases plasma prolactin levels. Chronic administration of nicotine in animals generally lowers plasma prolactin levels (8). Because prolactin secretion is tonically inhibited by hypothalamic dopamine release, plasma prolactin may be an indicator of brain dopaminergic activity (16). For example, hyperprolactinemia in abstinent cocaine addicts has been cited as evidence for impaired dopamine function during cocaine withdrawal (5,17). In support of this proposal, elevated prolactin is reportedly associated with higher risk for relapse in cocaine users (14,26). As with other drugs of abuse, nicotine's reinforcing effects are at least partially modulated through dopamine release (4). Therefore, it seemed possible that plasma levels of prolactin may be a peripheral index of the intensity of tobacco withdrawal.

The purpose of the present study was to determine whether changes in plasma ACTH, cortisol, or prolactin accompany short-term tobacco withdrawal. This study was part of an evaluation of the effects of transdermally delivered nicotine on several measures of acute tobacco withdrawal (18). As a com-

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ponent of that study, the effects of the nicotine patches on endocrine measures of tobacco withdrawal were also examined.

## METHOD

### *Subjects*

Subjects were recruited from the community in response to newspaper advertisements. Nine male and one female volunteer were paid approximately $1000 to participate in this 4-week residential study. The subjects ranged in age from 24 to 41 years (mean = 32). All subjects smoked 20 to 40 cigarettes per day (mean = 29) for at least 2 years (range: 2 to 26 years, mean = 14.3). The nicotine yield of the cigarettes as determined by the FTC method averaged 1.04 mg (range: 0.6 to 1.3 mg). They scored an average of 8.1 (range: 7 to 9) on a test for nicotine dependence (7) where scores of 6 and above indicate a high degree of nicotine dependence. Before their participation in the study, each subject signed an informed consent document that had been approved by the hospital institutional review board and met the Department of Health and Human Services guidelines for the treatment of research volunteers.

### *Procedures*

During their residence on the clinical research ward, subjects ordered food from the hospital menu but were not allowed to consume caffeine-containing products for the duration of the study. Gradual discontinuation of caffeine consumption began 1 week prior to the first study day. Subjects were completely caffeine abstinent for at least 48 h prior to the first study day. They were allowed to smoke their usual brand of cigarettes from Thursday afternoon (1500 h) until Monday at midnight. No smoking was allowed for 63 h between Monday midnight and Thursday afternoon. Tobacco abstinence was monitored by the research staff and confirmed by frequent, random measures of exhaled carbon monoxide (CO).

On each of the nonsmoking days (Tues, Wed, Thurs) at 0800 h, three transdermal nicotine delivery systems (patches) were applied to the forearm. Patches delivered either 0 or 10 mg nicotine over 16 h (Pharmacia Upjohn; Helsingborg, Sweden). Combinations of the 0 and 10 mg patches were used to obtain the four dose conditions of the study: 0 mg (all placebo patches), 10 mg (one active, two placebo patches), 20 mg (one placebo, two active), and 30 mg (all active). Patches were removed at 2300 h on Tuesday and Wednesday night and at 1500 h on Thursday afternoon. The order of the patch conditions was randomized across subjects. Each subject received each dose condition, a different one each week, for 4 consecutive weeks.

Venous blood samples were collected daily on Monday through Thursday at 1300 h through an indwelling catheter placed in the lower arm for at least 2 h prior to the blood withdrawal. The blood samples were centrifuged. The plasma was collected and frozen at −80°C until the time of analysis for cortisol, ACTH, and prolactin. Plasma samples were analyzed in duplicate for levels of nicotine by high-performance liquid chromatographic methods (10).

After collection of the blood samples, physiological (heart rate, EEG, blood pressure) performance and subjective measures of the tobacco withdrawal syndrome were collected as reported elsewhere (18). Heart rate and blood pressure were measured with an automated vital sign monitor (IVAC, Corp., San Diego, CA). Psychomotor performance was estimated using the digit symbol substitution task (DSST) where a random digit appeared on the computer monitor. The subject used the numeric keypad to reproduce a geometric pattern associated with the digit. The geometric digit code was concomitantly displayed on the monitor (11). The intensity of the tobacco withdrawal was estimated using a 12-item self-report tobacco withdrawal scale (13). The items were: craving for cigarettes, irritability/anger, anxious/tense, difficulty concentrating, restlessness, impatient, excessive hunger, insomnia, increased eating, drowsiness, headaches, and "any of the following: tremor, heart racing, sweating or dizzy, stomach, or bowel problems."

### *Endocrine Measures*

Aliquots of plasma (25 μl) were assayed for human ACTH and cortisol using commercially available [$^{125}$I]-radioimmunoassay (RIA) kits (ICN Biomedicals, Irvine, CA). Aliquots of plasma (50 μl) were assayed for human prolactin by double-antibody RIA methods using primary antiserum (hPRL-S-3, lot # AFP-2312C) and reference preparation (hPRL-RP-1, lot # AFP-C11580) generously provided by the National Institute on Diabetes, Digestive and Kidney Disease (NIDDK) and National Hormone and Pituitary Program (Rockville, MD). The [$^{125}$I]-prolactin was obtained from Hazleton Laboratories (Vienna, VA). The lower limit of assay sensitivity for the prolactin assay was 1 ng/ml. All samples were analyzed in duplicate within the same RIA to avoid interassay variability. Average interassay coefficients of variability were 4.5, 6.8, and 10.1% for ACTH, cortisol, and prolactin, respectively.

### *Statistical Analyses*

Analysis of variance (ANOVA) techniques were used to determine the effect of tobacco abstinence on hormone levels (30). Two-way ANOVAs [main factors: day (four levels); treatment (four levels)] were used to determine the effects of the doses of transdermal nicotine across the experimental days on plasma hormone levels. Where there were significant main effects or a significant interaction, pair-wise comparisons were made with Tukey's honestly significant difference (hsd) test (30). Tukey's hsd test was also used to detect differences among experimental days in the 0 mg patch condition (nicotine abstinence) for ACTH, cortisol, and prolactin on an a priori basis. On data from the first day of nicotine abstinence (Tuesday, 0 mg condition) when abstinence was greatest, Pearson's correlational analyses were performed between changes in hormone levels and changes in heart rate, a tobacco withdrawal scale score (13), and the rate of performance on the digit symbol substitution test (11).

## RESULTS

As shown in Fig. 1, plasma levels of nicotine on the ad lib smoking day (Monday) averaged (mean ± SEM) 18 ± 2.4 ng/ml. During nicotine abstinence (0 mg condition) levels were below 3 ng/ml. Patch combinations that delivered 10 mg of nicotine maintained plasma nicotine levels at 9.2 ± 0.7 ng/ml. The 20 and 30 mg patch conditions maintained plasma nicotine levels at or above (17.9 ± 1.1, 25.3 ± 1.1 ng/ml, respectively) those of ad lib smoking. A two-way ANOVA indicated there was a significant effect of treatment, $F(3, 27) = 117.3$, $p < 0.001$, day, $F(3, 27) = 4.03$, $p < 0.02$, and the treatment by day interaction, $F(9, 81) = 27.61$, $p < 001$.

All hormones seemed to show a trend for increased levels on the first and second day of abstinence [Tues (13 h abstinent) and Wed (37 h abstinent)] and a return to baseline (smoking) levels by the third day of abstinence [Thur (61 h abstinent)].

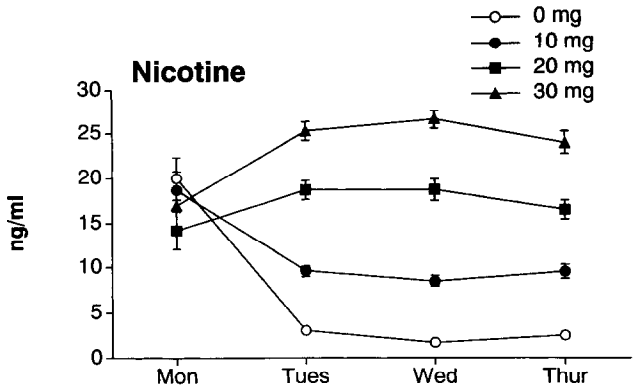


FIG. 1. Mean plasma levels of nicotine on ad lib smoking day (Mon) and on nonsmoking days (Tues to Thur). Subjects were tobacco abstinent for 13, 37, and 61 h on Tues, Wed, and Thur, respectively. Plasma samples were collected at 1300 h. On nonsmoking days, patches delivering a total of 0, 10, 20, or 30 mg of nicotine daily were applied at 0800 h and removed at 2300 h.

Plasma ACTH levels are shown in Fig. 2A. On the ad lib smoking day (Monday), ACTH levels averaged 60 ± 5.7 pg/ml. Analyses indicated there were no significant differences across days in ACTH levels during nicotine abstinence (0 mg condition). The two-way ANOVA indicated no significant effect of treatment, $F(3, 27) = 0.42$, NS, and no significant day by treatment interaction, $F(9, 81) = 0.52$, NS; however, there was a significant day effect, $F(3, 27) = 3.84$, $p < 0.02$. Post hoc analyses indicated that over all patch conditions ACTH levels were significantly elevated on Wednesday compared to Thursday.

Plasma cortisol levels are shown in Fig. 2B. On the ad lib smoking day (Monday) plasma cortisol levels averaged 21 ± 2.0 μg/ml. Analyses indicated there were no significant differences across days in cortisol levels during nicotine abstinence (0 mg condition). The two-way ANOVA indicated no significant effect by treatment, $F(3, 27) = 0.20$, NS, or the treatment by day interaction, $F(9, 81) = 0.89$, NS. However, as occurred with ACTH, over all patch conditions there was a significant difference in cortisol between days, $F(3, 27) = 3.96$, $p < 0.05$. Post hoc analyses indicated there was a significant elevation of cortisol levels on Wednesday compared to all other days.

Plasma prolactin levels averaged 7.7 ± 0.7 ng/ml on the ad lib smoking day. Analyses indicated there were no significant differences across days in prolactin levels during nicotine abstinence (0 mg condition). The two-way ANOVA indicated no significant effect of treatment, $F(3, 27) = 1.76$, NS, day, $F(3, 27) = 0.78$, or the treatment by day interaction, $F(9, 81) = 0.97$, NS.

Changes in plasma levels of ACTH, cortisol, and prolactin in individual subjects were correlated with changes in measures of tobacco withdrawal collected on the first day of tobacco abstinence (0 mg, Tues). Heart rate decreased in 8 of the 10 subjects but the change in heart rate was not significantly correlated with changes in ACTH ($r = 0.14$), cortisol ($r = 0.03$), or prolactin ($r = -0.18$). Similarly, tobacco abstinence increased scores on a tobacco withdrawal scale (13) in eight of the subjects, but these changes were not significantly correlated with changes in ACTH ($r = -0.09$), cortisol ($r = 0.03$), or prolactin ($r = -0.37$). Finally, eight of the subjects showed a decrease in the attempts on the digit symbol substitution test (DSST), indicating that performance was slowed on the first day of tobacco withdrawal. However, the changes in the DSST were not significantly correlated with changes in the plasma concentrations of ACTH ($r = -0.38$), cortisol ($r = 0$), or prolactin ($r = -.07$).

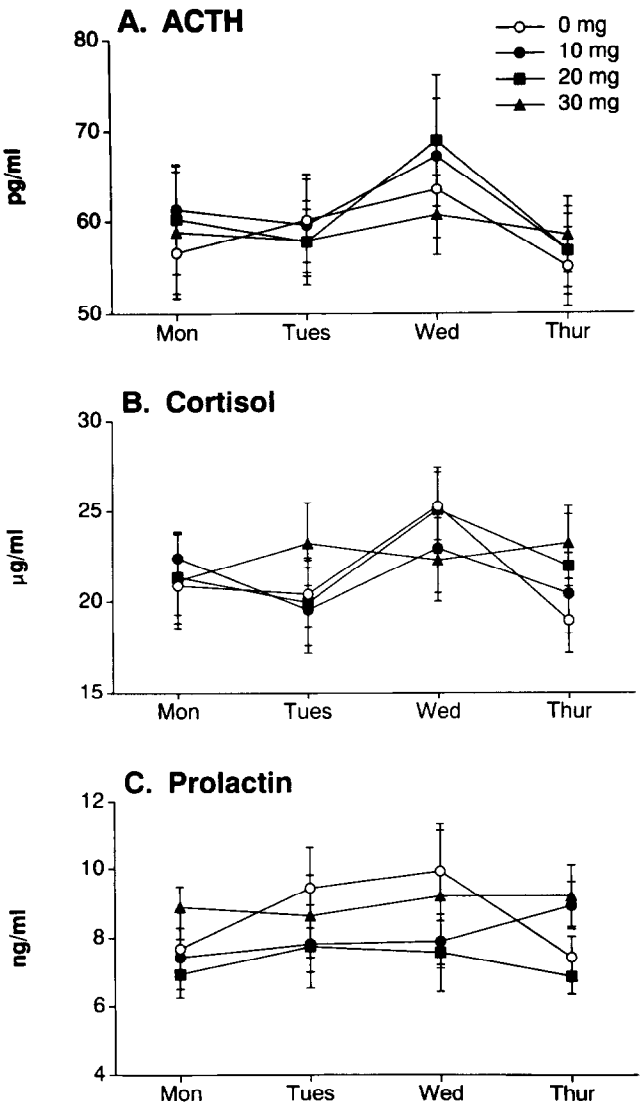


FIG. 2. Mean plasma levels of ACTH (A), cortisol (B), and prolactin (C) on the ad lib smoking day (Mon) and on nonsmoking days (Tues to Thur). Subjects were tobacco abstinent for 13, 37, and 61 h on Tues, Wed, and Thur, respectively. On nonsmoking days, patches delivering a total of 0, 10, 20, or 30 mg of nicotine daily were applied at 0800 h and removed at 1100 h. Plasma samples were collected at 1300 h.

## DISCUSSION

The neuroendocrine effects of nicotine administration have been studied in a variety of animal and clinical experiments [for review, see (8,19,21)]. Although nicotine causes measurable changes in plasma concentrations of several hormones, the mechanisms responsible for these effects and their clinical significance are not well understood. There have been no studies of the endocrine consequences of acute tobacco with-

drawal. In the present study, the effects of 3 days of tobacco deprivation on plasma levels of ACTH, cortisol, and prolactin were determined in a protocol designed to evaluate the effects of transdermal nicotine on acute signs of tobacco withdrawal.

During the placebo treatment (nicotine abstinence), nicotine plasma levels decreased to less than 3 ng/ml and signs and symptoms of tobacco withdrawal emerged; these included decreased heart rate, EEG slowing, and performance impairment (18). Nicotine patch application caused dose-dependent replacement of plasma nicotine to levels that equaled (20 mg) or exceeded (30 mg) those measured on the ad lib smoking day (Monday). Furthermore, the physiologic, performance, and subjective changes associated with tobacco withdrawal were diminished in the active patch conditions (18).

Among the symptoms of tobacco abstinence, several including irritability, anxious, tense, tremor, heart racing, and insomnia (13) are characteristic of the stress response (23). Stress is associated with increases in plasma levels of cortisol and ACTH (23). If tobacco withdrawal is a stressful event, one would predict that nicotine abstinence would lead to increases in the plasma levels of ACTH and cortisol. However, ACTH and cortisol levels did not significantly increase during nicotine abstinence (placebo treatment) over ad lib smoking levels. The two-way ANOVA indicated that ACTH and cortisol levels changed as a function of day but not as a function of treatment. As seen in Fig. 2A and B, ACTH and cortisol levels on Wednesday were higher than those on Thursday regardless of the treatment condition.

Prolactin levels are an indirect peripheral index of hypothalamic (tuberoinfundibular) dopamine activity; however, the extent to which plasma prolactin levels indicate dopamine activity in other brain areas including the mesolimbic area is uncertain (1,27). Corrigall et al. (4) reported nicotine administration in the rat increases release of dopamine in mesolimbic regions. In humans, smoking causes an initial increase in plasma prolactin levels but chronic smoking is associated with decreased plasma prolactin (8). These findings suggest that chronic smoking may increase dopamine release in the hypothalamus and possibly other brain areas. Mesolimbic dopamine release has been associated with the rewarding effects of various classes of drugs (6). It is possible that the cigarette craving and dysphoria of the tobacco withdrawal syndrome is related to decreased mesolimbic dopamine release, but plasma prolactin levels are not an index of mesolimbic dopamine activity.

In the present study there were nonsignificant increases in plasma prolactin levels on the first and second days of tobacco abstinence. On the third day of abstinence, prolactin levels were similar to those of ad lib smoking. The increase in plasma prolactin tended to be attenuated by the application of nicotine patches; however, the effect was not statistically significant. These results do not resolve the role of dopamine in cigarette craving and other symptoms of tobacco withdrawal.

Endocrine changes have been reported after withdrawal from several classes of drugs including the opiates (3), cocaine (16,17), and ethanol [for review, see (29)]. During clonidine- and guanfacine-treated heroin withdrawal, salivary levels of cortisol were 150% above those of ex-addicts (3). Mendelson et al. (17) and others (14) reported that prolactin levels were up to three times above normal levels during cocaine withdrawal; although this elevation has not always been observed (15,24,25). We hypothesized that tobacco abstinence would engender significant increases in plasma ACTH, cortisol, and prolactin; however, this hypothesis was not confirmed. Although the endocrine changes were in the directions predicted by the hypothesis, they did not always reach statistical significance. One limitation of the present study was that hormone levels were sampled at one time point on each of the 3 days of tobacco abstinence. A more thorough analysis of diurnal hormone levels over an extended period of tobacco abstinence may have revealed significant changes during the course of the abstinence. Furthermore, the power of the study may have been diminished by the small sample size.

Nonsignificant correlation analyses between physiological (heart rate), subjective (tobacco withdrawal score), and performance (DSST test) measures and plasma levels of the hormones indicated that hormone changes did not covary with well-established measures of tobacco withdrawal. The analysis confirmed that subjects with the largest change in plasma hormones were not those with the largest changes in conventional measures of tobacco withdrawal. Puddey et al. (22) reported a significant decrease in plasma levels of cortisol and epinephrine but no significant changes in prolactin levels in 13 smokers who successfully stopped smoking for 6 weeks. The authors interpreted these results to indicate that epinephrine and cortisol are maintained at elevated levels during smoking by continuous stimulation of the adrenal medulla and adrenal cortex. However, because the Puddey et al. study did not include a nonsmoking control group, it is difficult to determine if the levels of hormones were actually elevated by smoking as the authors proposed.

Bourne (2) assessed the effectiveness of corticotrophin gel (180 units) in a preliminary study of 10 patients attempting to stop smoking. Nine of the patients stopped smoking after the injection. In three patients, a second injection was administered a few days later to control exacerbation of the tobacco abstinence syndrome. All of the patients continued to be smoke-free after 7 months. The author speculated that tobacco abstinence was associated with decreases in levels of cortisol. Bourne further suggested that diminished cortisol leads to hypoglycemia and adrenaline release that are responsible for the tension, anxiety, and other manifestations of the tobacco withdrawal syndrome. The results of the present study do not confirm that proposal. The endocrine changes we observed were small, short-lived, and not correlated with other well-established indices of tobacco withdrawal.

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