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Venous plasma nicotine correlates of hormonal effects of tobacco smoking

Yue Xue [a], Mark Morris [a], Lisong Ni [a], Sally K. Guthrie [b], Jon-Kar Zubieta [c], Kimberly Gonzalez [d], Daniel S. McConnell [d], Edward F. Domino [a,*]

[a] Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-5632, USA
[b] College of Pharmacy, University of Michigan, Ann Arbor, MI, USA
[c] Department of Psychiatry, Radiology, Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA
[d] Clinical Ligand Assay Service Satellite, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

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ABSTRACT

The present study resolves some of the discrepancies in the literature by correlating the effects of tobacco smoking on hormone release with venous plasma nicotine levels. Cortisol, prolactin, and β-endorphin concentrations were measured. Habitual male tobacco users smoked denicotinized (very low nicotine) and average nicotine cigarettes in the morning after overnight tobacco abstinence. Several venous blood samples were withdrawn before and during the smoking sessions for subsequent analyses. The increases in plasma nicotine correlated well with plasma cortisol and prolactin levels (correlation coefficients $r = 0.66$ and 0.53, respectively, $p < 0.05$). This study quantifies the well known increase in plasma cortisol and prolactin after nicotine postsmoking for about 1 h with peak plasma levels up to 35 ng/ml. Contrary to most abused drugs which release dopamine and decrease prolactin, nicotine concentration correlated with increased prolactin release. Increases in maximal plasma β-endorphin levels following tobacco smoking were barely statistically significant with insufficient data to obtain a correlation coefficient.

1. Background

Over the years, a great deal of research has been published on nicotine/tobacco smoking releasing various hormones in animals or humans. However, not all effects are the same between species. For example, rats trained to self-administer nicotine have increased levels of adrenocorticotropin (ACTH) and corticosterone on day 1 but not by day 3. After 20 days of self-administered nicotine, the rats' hormonal response is augmented 2–3 fold to mild foot shock stress but not to moderate shock, lipopolysaccharide or immobilization stress (Chen et al., 2008). Childs and de Wit (2009) compared cortisol, progesterone, allopregnanolone, and catecholamine responses to public speaking stress and a control nonstressful task in male nonsmokers and smokers. Two hours after smoking a cigarette at 8:00 am, compared to nonsmokers the smokers had blunted cortisol responses to the speaking stress as well as greater and prolonged agitation. Stress induced progesterone was similar but lower in the smokers. The allopregnanolone levels were also lower in the smokers. Stress did not alter the levels of the latter neurosteroid. Plasma norepinephrine levels increased in both groups with speaking induced stress. Heart rate and blood pressure increased in both groups subjected to stress. Diastolic blood pressure was less in the stressed smokers. The authors concluded that smoking dampens the hormonal response to stress and prolongs a subjective distressed mood. The results of this study in humans appear to be opposite to the findings in rats that nicotine self-administration cross-sensitizes to mild stress.

In rats, nicotine inhibits the release of prolactin (Muraki et al., 1979; Andersson, 1985), whereas it increases plasma levels of prolactin in humans. Nicotine also produces increased levels of ACTH, vasopressin, ß-endorphin, growth hormone, and cortisol in human subjects (Wilkins, et al., 1982; Seyler, et al., 1986; Fuxe, et al., 1989; Pomerleau and Rosecrans, 1989; Kirschbaum et al., 1994). Increases in ACTH, corticosterone, ß-endorphin, and growth hormone after nicotine have also been observed in rats (Conte-Devolx et al., 1982).

With animal research, the dose of nicotine administered is known. When studying human tobacco users the dose of nicotine absorbed varies markedly even when the nicotine content of the tobacco product is reported. In order to obtain a greater variation in nicotine dose, investigators have studied tobacco with different nicotine content. Imprecise terms such as denicotinized, low, average, or high nicotine tobacco are used for dose–effect studies with differing results. For example, Wilkins et al. (1982) compared levels of cortisol, growth hormone, and prolactin after smoking either low (0.2 mg) or high nicotine (2.0 mg) cigarettes. All three hormone levels were found to be significantly greater after high nicotine cigarettes. Meliska and Gilbert (1991) studied the effects of nicotine on cortisol and β-endorphin in both male and female smokers. Smoking caused increases in cortisol and β-endorphin. However, β-endorphin was elevated after two, but no

* Corresponding author. Tel.: +1 734 764 9115; fax: +1 734 7634450.
E-mail address: efdabcde@umich.edu (E.F. Domino).

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further increase was observed after four or five tobacco cigarettes. Gilbert et al. (1992) found increases in cortisol and ß-endorphin after smoking, but only when using 2.4 mg cigarettes. Subjects' own brand of cigarettes (1 mg nicotine) did not significantly increase cortisol or β-endorphin levels, even though plasma nicotine levels were significantly increased when compared to nicotine free cigarette smoking. The reports by Mendelson et al. (2005, 2008) are among the best to date on tobacco smoking, hypothalamic, pituitary adrenal axis and cortisol increases, and the significance of these changes.

Prolactin release after tobacco smoking has also been established in research using high, but not low nicotine cigarettes. Seyler et al. (1986) found hormone release after 2.87 mg (high) nicotine cigarettes were smoked, but not after 0.48 mg (medium) nicotine cigarettes. Wilkins et al. (1982) did not find a prolactin response with low (0.2 mg) nicotine cigarettes, but did with high (2.0 mg) nicotine cigarettes. In a more recent study (Mendelson et al., 2003), it was again shown that high nicotine cigarettes (2.3 mg) elicited a prolactin response, but low nicotine cigarettes (0.1 mg) failed to do so. Circulating levels of prolactin have also been observed to be higher in tobacco smokers than in nonsmoking controls, even without smoking before the measurement was taken. Tobacco smokers also have differing plasma concentrations of hormones depending on the number of cigarettes they smoke per day. In a study done by del Arbol et al. (2000), β-endorphin, cortisol, and ACTH plasma concentrations were compared between subjects who consumed different amounts of cigarettes per day vs nonsmoking controls. Blood was drawn in the morning in all subjects after an overnight fast and smoking abstinence. Cortisol levels were significantly higher compared to controls only in subjects who smoked over 20 cigarettes per day. β-endorphin levels were only significantly higher than controls in subjects smoking fewer than 10 cigarettes per day, suggesting that increases in β-endorphin are sustained longer after smoking in lighter smokers. No significant differences in ACTH concentrations were found between groups. ACTH was found by Pomerleau et al. (1983) to have no correlation with plasma nicotine after tobacco smoking. They did, however, find a significant correlation between β-endorphin-β-lipoprotein and plasma nicotine after smoking.

Although nicotine is the major ingredient in tobacco smoke that releases many hormones, precise plasma nicotine concentration–effect relationships bear further scrutiny. The present study quantifies the relationship between plasma nicotine levels and circulating levels of plasma cortisol, prolactin and β-endorphin in overnight abstinent chronic smokers who participated in a brain imaging study.

2. Methods

This study was part of a larger ongoing project involving tobacco smoking effects on human dopamine D2 and mu-opioid brain receptors using positron emission tomography (PET). The entire project was approved by the University of Michigan Institutional Review Board for human studies. The PET project required a counterbalanced use of radioisotopes on two separate days. Hence, the endocrine data reported herein were replicated, on the first day in the PET scanner, and then again on day 2. The day 1 and then day 2 endocrine results were obtained with the hope of measuring scanner stress objectively. A total of 24 healthy male subjects, between 20 and 36 years of age (mean 25.8 ± SE 0.93) who smoked 15–40 cigarettes per day were recruited for this portion of the project. When a smaller number of subjects from this group were used for specific hormone analysis, their total number is listed. All subjects were instructed to cease tobacco use overnight, approximately 12 h before study. To assure compliance, exhaled CO levels were <10 ppm prior to the experiment. During the experiment, the subjects were supine and restrained in a PET scanner from about 8:00 am to 12:30 pm. A counterbalanced day 1 and within a week or so day 2 design of PET scans with [^{11}C]carfentanil and [^{11}C]raclopride in trace nonpharmacological doses was used. The subjects smoked as rapidly as possible two pairs of cigarettes for 5 min each while in the PET scanner. All subjects received both radiotracers, in randomized and counterbalanced order. Subjects first smoked denicotinized (0.08 mg nicotine) cigarettes, then smoked average nicotine (1.01 mg nicotine) cigarettes. Through a series of fortunate circumstances, the two different research cigarettes were obtained through the courtesy of Dr. Frank P. Gullota (now retired) and Ms. Cynthia S. Hayes of the Philip Morris Research Center, Richmond, VA. Unfortunately, these cigarettes are no longer available because Philip Morris stopped producing them. The nicotine containing cigarette was prepared with unextracted tobacco (nicotine 1.01 mg/cigarette and tar 9.5 mg/cigarette). The denicotinized cigarette was made with almost 100% extracted tobacco (nicotine 0.08 mg/cigarette and tar 9.1 mg/cigarette). Hence, the word denicotinized refers to very low nicotine containing cigarettes. Both cigarettes contained identical filter tips and were made from the same blend of tobacco with no flavors added. Thus, their tar content was almost identical (9.5 vs 9.1 mg) and only the milligrams of nicotine per cigarette were markedly different (1.01 vs 0.08 mg). Heart rate was monitored during both scans. Blood samples (5 ml) were collected repeatedly in vacutainer tubes before and after the onset of smoking both cigarettes. Blood for nicotine and hormone samples was always drawn at the same time points — at 0, 15, 30, 43, 49, 59, 65, 75, and 95 min into each scan. Cigarettes were smoked at 45 and 55 min into each scan. The samples were placed on ice and centrifuged. The plasma was removed and frozen at −70 °C for nicotine and hormone analyses. Nicotine assay was done by gas chromatography/nitrogen phosphorus detection (GC-NPD) in the Medtox Laboratory, St. Paul, MN. Cortisol and prolactin analyses were performed at the University of Michigan Clinical Ligand Assay Service Satellite Laboratory (CLASS Lab, Ann Arbor, MI). The cortisol assay was a competitive immunoassay performed on Siemen's ADVIA Centaur automated analyzer using chemiluminescent technology. This method had a minimum detectable concentration of 0.2 µg/dl and the assay measured up to 75 µg/dl. The assay was standardized analytically and confirmed by gas chromatography–mass spectroscopy. Prolactin was determined as a two-site chemiluminometric (sandwich) immunoassay run on Siemen's ADVIA Centaur automated analyzer. The minimum detectable concentration was 0.3 ng/ml and the assay measured up to 200 ng/ml. The test results were determined from a calibration curve derived from the standard, WHO 3rd IRP 84/500. β-endorphin was assayed using radioimmunoassay kits (Phoenix Pharmaceuticals, Inc., Burlingame, CA) with a minimum sensitivity of 1 pg/ml.

2.1. Statistical analysis and calculations

The hormone data from two separate experimental days were collected in a parametric format. The SPSS 17.0 System for Windows was used for statistical analysis. Descriptive procedures were used to obtain mean ± SE. A two-way analysis of variance (ANOVA) with repeated measures in a mixed procedure was conducted to compare the differences between the two experimental days. The post hoc comparison and the Sidak multiple comparison adjustment were options used to indicate the significant time points of endocrine change. Linear regression was conducted to establish the relationships between nicotine cortisol and prolactin levels. The latter were in a continuous variable format without predicting the outcome from the nicotine variable. Therefore, a simple correlation coefficient is sufficient for quantifying the relationship of nicotine and cortisol and prolactin. All data were normally distributed and a probability level of less than 5% ($p < 0.05$) was considered significant.

3. Results

3.1. Plasma nicotine levels

The baseline and peak mean ± SE of venous plasma nicotine levels for the two separate conditions (see Section 2: counterbalanced design)

smoking denicotinized or average nicotine tobacco cigarettes are given in Table 1. Inasmuch as there were no significant nicotine differences between the two PET imaging results, the overall data were combined. It is obvious that smoking denicotinized cigarettes produced a minor delta venous plasma nicotine increase of only 0.88 ng/ml, whereas smoking average nicotine cigarettes produced a 12.9 ng/ml increase. As described in the Section 2, the denicotinized cigarettes are actually very low nicotine cigarettes. All of the after smoking data shown in the table below were statistically significant ($p<0.001$) including the denicotinized vs average nicotine cigarettes.

Note that the baseline levels of venous plasma nicotine are very low, indicating that the subject volunteer smokers were indeed tobacco abstinent overnight. The fact that the plasma nicotine boost after smoking the average nicotine cigarette is >10 ng/ml is important (see Section **4**).

3.2. Plasma cortisol levels

The normal levels of plasma cortisol related to its diurnal decrease in the morning were absent in a large number of the subjects, indicating possible PET scanner related stress. However, the mean ± SE of all the data indicated that the early morning decrease in plasma cortisol was relatively unaffected by denicotinized cigarette smoking. None of the differences seen in Fig. 1 was statistically significant. In contrast, smoking average nicotine cigarettes clearly increased plasma cortisol levels (Fig. 1). The two-way ANOVA with repeated measures with a mixed model analysis indicated that all of the day 1 and day 2 cortisol values of 23 subjects were not different. In order to adjust for all possible time point comparisons, the Sidak adjustment method was used. There was no interaction effect ($p=0.797$). The trajectory of cortisol by minute was similar between the 2 days. However, the minute effect was highly significant ($F_{1,17}=17.23, p<0.000$). Based on this mixed model analysis, there is no interaction effect. The two lines of the 2 days are statistically similar. Therefore, a reduced mixed model analysis was done without the day*minute interaction. Again, the day effect at any minute was not significant ($F_{1,1}=0.660, p=0.424$). The before/after denicotine smoking data from −5 to 130 min indicated a significant drop in cortisol on both days ($p=<0.000$). In contrast, a pair wise comparison of before/after average nicotine smoking from 130 to 195 min indicated an increase in cortisol ($p<0.000$). The increases were observed at 175 min and 195 min. The increase in cortisol levels was significantly correlated with the increase in plasma nicotine levels ($r=0.66$) as shown in Fig. 2 correlation coefficients (day 1 $r=0.64$ and day 2 $r=0.68$). Therefore, the data were combined as illustrated. A 10 ng/ml boost in venous plasma nicotine gave about a 2.5 μg/dl increase in plasma cortisol. The maximal change (mean ± SE) in plasma cortisol for smoking denicotinized and average nicotine cigarettes was −1.18 ± 0.38 and +4.68 ± 0.81 μg/dl, respectively.

3.3. Plasma prolactin levels

As shown in Fig. **3**, smoking average nicotine cigarettes increased prolactin to an average of 7.74 ng/ml within 30 min. Prolactin levels did not increase after smoking denicotinized cigarettes. The two-way ANOVA with repeated measures in a mixed procedure indicated that days 1 and 2 prolactin values of 17 subjects were not different. There was no interaction effect ($p=0.287$). The trajectory of prolactin by minute was similar between the 2 days. Therefore, a reduced mixed model analysis was done. The day effect at any minute was not significant ($F_{1,1}=0.475, p=0.498$).The minute effect was significant ($F_{1,17}=5.770$, $p<0.000$). The before/after denicotinized smoking data from −5 to 130 min was not significant. The before/after average nicotine smoking increase in prolactin from 130 to 195 min was highly significant ($p<0.005$). The increase in combined prolactin levels correlated with the increase in plasma nicotine levels ($r=0.53$) shown in Fig. 4 (correlation coefficients, day 1 $r=0.53$ and day 2 $r=0.62$). A 10 ng/ml boost in venous plasma nicotine gave about a 1 ng/ml increase in plasma prolactin. The maximal change (mean ± SE) for plasma prolactin after smoking denicotinized and average nicotine cigarettes was 0.20 ± 0.14 and 2.20 ± 0.38 ng/ml, respectively.

3.4. Plasma β endorphin

Before smoking average nicotine cigarettes, mean ± SE peak plasma β-endorphin levels were 20.45 ± 1.93, and after smoking 26.97 ± 2.18 pg/ml, which was surprisingly significant ($p<0.05$). There was a great deal of individual variability after smoking so the data were not as consistent as with cortisol and prolactin. Only maximal changes are reported. Due to the minor and variable effects, the effects of denicotinized cigarettes were not determined.

4. Discussion

Plasma cortisol levels increased after smoking average nicotine compared to denicotinized cigarettes. These data are consistent with previous reports that cigarette smoking induces an increase in plasma cortisol levels (Cryer et al., 1976; Gossain et al., 1986; Mendelson et al., 2005, 2008; Pickworth and Fant, 1998; Seyler et al., 1984; Spohr et al., 1979; Wilkins et al., 1982; Winternitz and Quillen, 1977).

The absolute increase in plasma cortisol on day 1 was 4.74; on day 2 it was 3.31 μg/dl (both days $p<.001$). These absolute changes are relatively small in comparison to the increases in corticosterone in rats given nicotine. The biological significance of this minimal increase deserves further study. The extent of nicotine dependence, tolerance, diurnal cycle, and behaviorally equivalent doses of nicotine, etc. need to be controlled.

The increase in cortisol levels was less closely correlated with the increase in plasma nicotine levels ($r=0.66$) than expected, but clearly significant. Perhaps the additional stress effect of the PET scanner on the first compared to the second day was a factor. A review of the literature on the cortisol response to stressors indicates that most physical and psychological challenges produce increased cortisol concentrations (Kirschbaum and Hellhammer, 1994). Tasks that included social-evaluative threat or uncontrollable conditions consistently elevate cortisol levels (Dickerson and Kemeny, 2004). Furthermore, marked increases in hypothalamic–pituitary activity have been observed in animals and humans exposed to novel environments (Davis et al., 1999; Hennessy et al., 2000). The novel radiologic environment associated with magnetic resonance imaging (MRI) and PET scanners is well known to induce claustrophobia, fear, and

Table 1
Effects of tobacco smoking on venous plasma nicotine levels after overnight abstinence.

Condition	Plasma nicotine after smoking denicotinized cigarettes (ng/ml)		Plasma nicotine after smoking average cigarettes (ng/ml)	
	Borderline baseline	After peak	Before baseline	After peak
[^{11}C]carfentanil	2.58 ± 0.30	3.58 ± 0.41	2.52 ± 0.25	15.9 ± 1.72
[^{11}C]raclopride	2.78 ± 0.34	3.57 ± 0.41	2.59 ± 0.25	15.0 ± 1.63
Combined	2.69 ± 0.23	3.57 ± 0.29	2.56 ± 0.18	15.5 ± 1.19

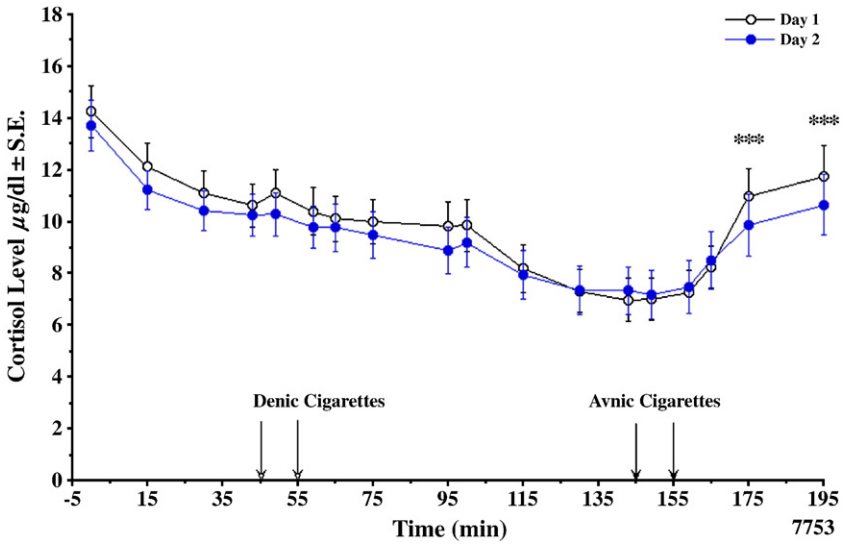

Fig. 1. Effects of smoking tobacco cigarettes on plasma cortisol. In this and subsequent figures, the morning data from day 1 (open circles) and day 2 (closed circles) sessions (usually within one week or so) in overnight abstinent tobacco smokers are illustrated from about 8:00 am. Time −5 min is when the first venous blood samples were drawn and 195 min when the last samples were drawn. A total of 16–23 subjects' data were included. Note that day 1 cortisol levels are statistically significant and consistently slightly higher than on day 2 from −5 to 115 min in the PET scanner. In this and in Fig. 3 significant time differences are noted by $^{**}p<.01$, and $^{***}p<.001$.

anxiety (Melendez and McCrank, 1993; Goyen and Klewer, 1997; McIsaac et al., 1998; Westerman et al., 2004; Eshed et al., 2007; Thorpe et al., 2008). Tessner et al. (2006) also demonstrated that the MRI scanning environment can induce cortisol elevations. Individuals undergoing MRI for the first time exhibited increased post-scan salivary cortisol levels compared to subjects familiar with the MRI environment and procedure. Our observation that plasma cortisol release on day 1 was slightly greater than that on day 2 is consistent with their findings. However, it is surprising that the cortisol changes observed are so similar in this small group of male tobacco smokers exposed to the PET facilities on day 1 vs day 2.

Pickworth et al. (1996) reported that during tobacco abstinence smokers with a 0 mg control path had no significant change in ACHT, cortisol, or prolactin. However, Frederick et al. (1998) found that cortisol levels dropped significantly 2 weeks post-quit and returned to a level below baseline 1 month later. The initial drop in cortisol was strongly related to post-quit distress. Subsequently, Ussher et al. (2006) and al'Absi et al. (2004) showed decreases in cortisol after smoking abstinence. In the latter study, these were associated with a higher rate of relapse during the first week. The importance of cortisol for the reinforcing effects of cocaine has also been demonstrated in rodents (Goeders, 2002).

Most drugs of abuse that release brain dopamine inhibit prolactin release. These include cocaine (Mendelson et al., 2003), amphetamine (Lurie and O'Quinn, 1991; Overtoom et al., 2003) and methylphenidate (Overtoom et al., 2003; Shaywitz et al., 1990; Weizman et al., 1987). In contrast, in our study average nicotine cigarette smoking produced significant and sustained elevations in venous prolactin. The contribution of high prolactin levels to the maintenance of smoking behavior is still debated. Seyler et al. (1986) showed that malaise or nausea induced by smoking could increase prolactin release. Although it is possible that discomfort associated with high nicotine cigarette smoking may produce increased prolactin levels, the subjects in our study never reported feeling sick or uncomfortable. Furthermore, some animal

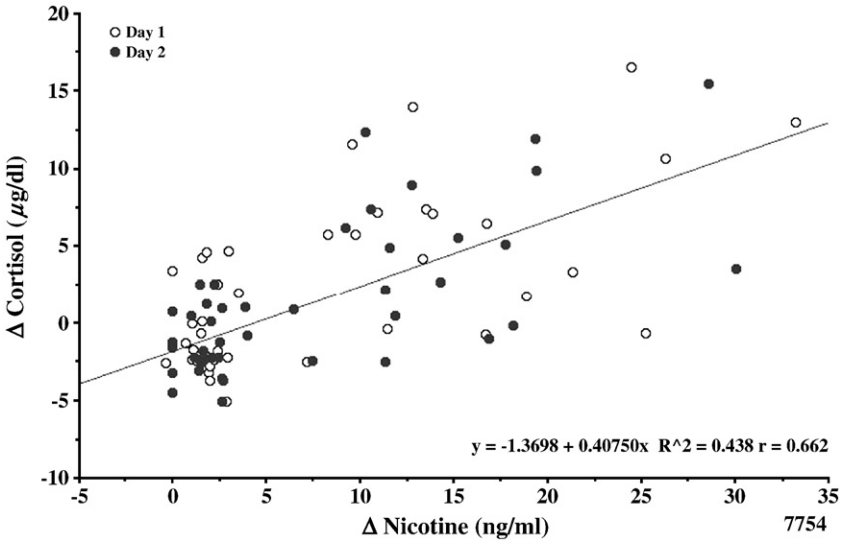

Fig. 2. Correlation of plasma nicotine and cortisol levels. Note that day 1 and day 2 data are very similar. Plasma nicotine and cortisol levels after denic and avnic cigarette smoking were combined. A total of 16–23 subjects with complete data were studied. The delta increase in nicotine and cortisol levels were both calculated by using the peak value after smoking minus the value just before smoking. The correlation coefficient $r=0.66$. Time 0 in this and Fig. 4 is immediately after smoking.

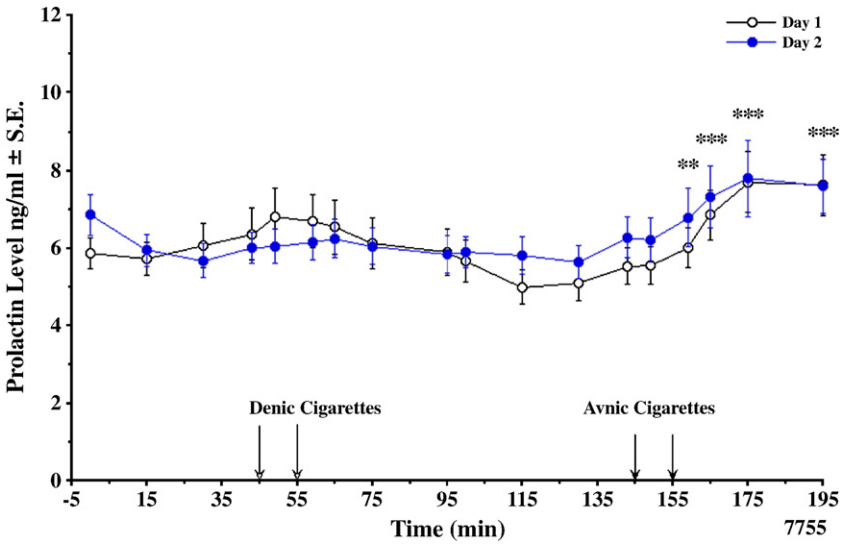

Fig. 3. Effects of tobacco cigarette smoking on plasma prolactin. A total of 16 subjects were included with complete data. Note that there is a trend for a slight increase after smoking denic and a greater increase after avnic cigarettes on the two different days.

studies showed that acute administration of nicotine by intravenous, intracerebroventricular, and intraperitoneal routes each consistently resulted in dose-dependent increases in prolactin (Hulihan-Giblin et al., 1990; Sharp and Beyer, 1986). Average nicotine cigarette smoking may stimulate release of prolactin by increasing endogenous opioids (Pomerleau et al., 1983; Seyler et al., 1986), which in turn may inhibit dopamine release (Shah et al., 1988). Chronic use of nicotine may dysregulate the hypothalamic–pituitary–adrenocortical (HPA) axis. This dysregulation may have an important relationship to addiction and relapse (Lovallo, 2006), as well as adverse health consequences (Rohleder and Kirschbaum, 2006). Cortisol levels are generally higher throughout the day in smokers on both working and weekend days, and cortisol responses to waking are also greater in smokers (Steptoe and Ussher, 2006; Badrick et al., 2007). As mentioned above, cortisol levels usually decrease in smokers upon quitting smoking. It is possible that a greater decline in cortisol after quitting may be used to predict relapse (Ussher et al., 2006). Badrick et al. (2007) reported that eventually ex-smokers' and never-smokers' cortisol levels do not differ significantly, indicating that nicotine's effect on the endocrine system is not permanent. Yu et al. (2008) have demonstrated that nicotine self-administration in rats differentially regulates hypothalamic corticotrophin-releasing factor and arginine vasopressin mRNAs. This is a key mechanism for chronic nicotine to cross-sensitize the hypothalamic–pituitary–adrenal (HPA) response to stress. This rat study suggests that tobacco smoking may augment HPA responsiveness to specific human stressors as a longer term consequence to its continued use.

The relationship between endogenous opioids and nicotine has been studied intensively. In mice exposed to nicotine, endogenous opioid levels are increased in the nucleus accumbens and striatum (Davenport et al., 1990; Dhatt et al., 1995; Houdi et al., 1991; Pierzchala et al., 1987; Pomerleau and Pomerleau, 1984). Several clinical studies have demonstrated that levels of β-endorphin were elevated in response to differences in nicotine exposure (Backon, 1989; Gilbert et al., 1992; Meliska and Gilbert, 1991; Seyler et al., 1986). Interestingly, plasma levels of β-endorphin in light but not heavy smokers were reported to be significantly higher than in nonsmokers (del Arbol et al., 2000). However, Osaki et al. (2003) showed that acute exposure of rats to cocaine, amphetamine, and alcohol increases β-endorphin in the nucleus accumbens, but acute exposure to nicotine does not. Moreover, in the mediobasohypothalamus of rats, mRNA for pro-opiomelanocortin

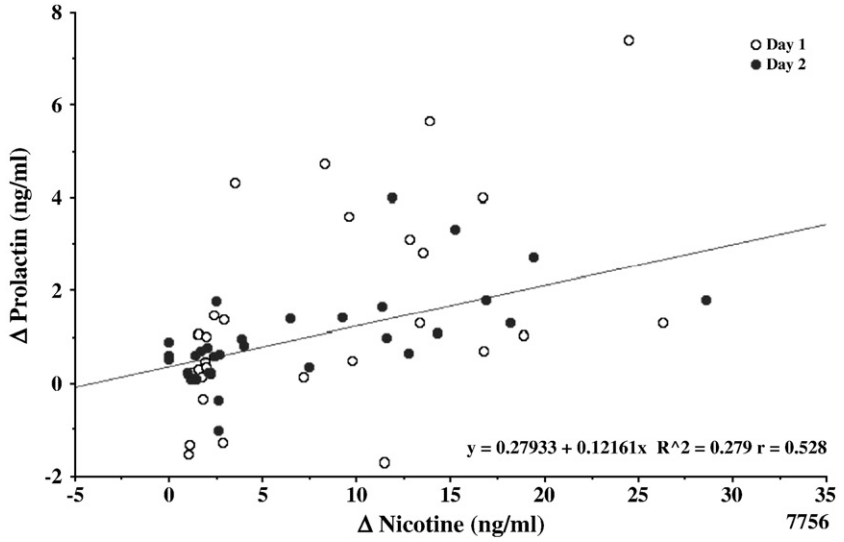

Fig. 4. Correlation of plasma nicotine and prolactin levels. Plasma nicotine and prolactin levels after denic and avnic cigarette smoking are correlated ($r = 0.53$) but less than with plasma cortisol.

decreases following long-term nicotine administration, a decrease that persists for 21 days after withdrawal (Rasmussen, 1998). In another study, nicotine exposure caused no change in β-endorphin plasma levels (Wewers et al., 1994). In the present study, after smoking average nicotine cigarettes, plasma β-endorphin changes were highly variable and barely significant. In view of previously published findings cited above, this was an unexpected but not to be ignored lack of dramatic effect. A limitation to the present study is that the volunteers were not interested in quitting smoking so we were not able to examine the effects of smoking on hormone levels.

5. Conclusions

This study confirms an increase in plasma cortisol, prolactin, and nicotine following tobacco smoking. A good plasma nicotine–hormone (cortisol and prolactin) correlation was obtained. Contrary to most studies, the effects of smoking average nicotine cigarettes on increased plasma β-endorphin levels were very variable and barely statistically significant. Additional work is needed to further clarify the precise concentration effect relationship between plasma nicotine and β-endorphin release.

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