ORIGINAL ARTICLE

Naloxone Challenge in Smokers

Preliminary Evidence of an Opioid Component in Nicotine Dependence

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Background: This study used an opioid antagonist challenge procedure to evaluate the responsivity of the endogenous opioid system in nicotine-dependent individuals, as evidenced by naloxone-induced alterations in both behavioral (withdrawal, craving) and neuroendocrine (cortisol levels) parameters.

Methods: Twenty subjects (9 smokers and 11 nonsmokers) participated in 4 laboratory sessions during which they were challenged with 0, 0.8, 1.6, or 3.2 mg/70 kg of naloxone and then monitored for 1 hour for subjective signs and symptoms of opiate-like withdrawal, nicotine craving, and alterations in cortisol levels.

Results: Nicotine-dependent subjects evidenced naloxone dose-dependent increases in withdrawal signs and symptoms. Lower doses of naloxone also produced increases in urges to smoke (craving) and tiredness in smokers. Smokers, when compared with nonsmokers, had lower prenaloxone baseline levels of cortisol and attenuated cortisol release in response to challenge with naloxone.

Conclusion: These results provide preliminary evidence to suggest that long-term exposure to cigarette smoke is associated with alterations in the responsivity of the endogenous opioid system and the hypothalamic-pituitary-adrenal axis that may contribute to the development of nicotine dependence.

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TOBACCO WITHDRAWAL is one of the most frequently cited reasons for failure to achieve and sustain abstinence in smoking cessation programs.[1] Withdrawal symptoms are mediated, in most instances, by rebound activity in endogenous neural processes that develop adaptations as a result of long-term drug use. Determination of the neurochemical alterations produced by habitual smoking may help to elucidate the mechanisms involved in, and aid in the development of medications for, nicotine withdrawal and craving.

Acute administration of nicotine releases endogenous opioid peptides, in vitro and in vivo, in rats and humans.[2-5] The distribution of nicotinic receptors overlaps with the localization of opioid peptides in several brain regions.[6,7] Acute nicotine administration increases levels of the opioid metenkephalin in the nucleus accumbens, an area that is known to be important in mediating reward.[3,4] Significant increases in messenger RNA for proopioimelanocorticotropin (a precursor for opioid peptides) are seen in the anterior lobe of the pituitary following long-term pulsatile nicotine administration.[8] Cessation of long-term nicotine treatment in rats results in an abstinence syndrome with behavioral signs that closely resemble those observed during rodent opiate abstinence syndromes.[9,10] Acute naloxone treatments precipitates, while morphine treatment reverses, these abstinence signs. Cessation of long-term nicotine treatment in mice results in significantly lower levels of β-endorphin at 24 hours after cessation, with a rebound increase in levels at 14 days after cessation,[11] suggesting that acute nicotine abstinence may be associated with decreased levels of endogenous opioids.

Based on this evidence, we hypothesized that constant stimulation of the endogenous opioids by long-term nicotine exposure in dependent tobacco users may result in altered responsivity of the opioid system, which may partially mediate acute nicotine abstinence effects. Interestingly, acute withdrawal from exogenous opiates has also been proposed to be mediated by absence of exogenous opiates and exogenous opiate-induced down-regulation of

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SUBJECTS AND METHODS

SUBJECTS

Twenty subjects, 9 non–treatment-seeking volunteers who reported smoking between 1 to 1½ packs per day and 11 nonsmoking volunteers, were recruited from advertisements placed in local newspapers and in the community. Subjects provided written informed consent at the initial appointment, following which they were screened to determine eligibility for the study. Subjects did not meet lifetime or current abuse or dependence criteria for other drugs (as evaluated by the Structured Clinical Interview for *DSM-III-R*[15]), and smokers were required to have cotinine levels between 210 and 420 ng/mL. Nicotine dependence was determined using the Fagerstrom Test for Nicotine Dependence.[16] Subjects also had a physical examination, an electrocardiogram, and laboratory tests, including complete blood cell count with differential count, liver function tests, urine toxicology tests, and urine tests for drug use and pregnancy. Subjects with evidence of serious medical conditions or psychiatric illness or urine test results positive for drug use or pregnancy were not enrolled. If eligible, subjects participated in 4 laboratory sessions, each of which was separated by at least 48 hours, during which they were tested with 0, 0.8, 1.6, or 3.2 mg/70 kg of naloxone.

Naloxone, administered intravenously at a dose of 0.8 mg/70 kg, is normally used to reverse the effects of opiate drugs. Initially we tested the effects of 0, 0.8, and 1.6 mg of naloxone. After 10 subjects participated in this paradigm, we included a higher dose of 3.2 mg/70 kg, and for safety reasons restricted challenge with this dose to the fourth and last laboratory session. The results presented in this article are based on 20 subjects who received all 4 naloxone doses and do not include the data from the first 10 subjects who received only 3 naloxone doses.

GENERAL PROCEDURES

Subjects were admitted to the General Clinical Research Center of Yale–New Haven Hospital, New Haven, Conn, at 9 PM on the evening prior to each laboratory session. They were required to spend the night in the hospital and remain abstinent from cigarettes, caffeine, and food from the time of admission until completion of the session. Prior to each session, urine tests for pregnancy and drug use (to confirm abstinence from cocaine, opiates, and marijuana) were conducted; carbon monoxide levels of less than 10 ppm were required to confirm overnight abstinence from cigarettes. Procedures for all laboratory sessions were similar. Specifically, baseline assessments were conducted from 8:30 to 9 AM. At 9 AM, a dose of naloxone or saline was administered intravenously during a 1-minute period, following which withdrawal symptoms were evaluated until 10 AM. The 1-hour observation period was chosen based on the 60-minute half-life of naloxone and earlier evidence indicating that naloxone-precipitated opiate withdrawal is generally resolved in 1 hour.[14,17,18]

LABORATORY ASSESSMENTS

All assessments were administered by a single observer, who was blinded to whether the subject was a smoker or nonsmoker and to the dose of drug being administered. Withdrawal signs and symptoms were assessed using a modified version of the Clinical Institute for Narcotic Withdrawal Scale (CINA), a 12-item withdrawal instrument that has been reliably used to assess opiate dependence following naloxone challenges in opiate addicts.[13] This scale, administered during a 5-minute period, rates the following items on a 0 to 4 scale: lacrimation, nasal congestion, yawning, sneezing/coughing/throat clearing, restlessness, nausea/vomiting, gooseflesh, sweating, stomach cramps, muscle cramps, and feeling hot/cold. Other nicotine withdrawal symptoms (including feeling tired, irritable, anxious, or having difficulty concentrating) were assessed using a drug effects scale. The CINA and the drug effects scale were administered at 30 and 5 minutes prior to naloxone challenge, every 5 minutes in the first half hour, and every 10 minutes in the second half hour following naloxone administration. Craving was assessed using the Tiffany scale of smoking urges[19] prior to naloxone administration and at 20, 40, and 60 minutes after naloxone administration. Cortisol levels were determined from blood samples obtained from an indwelling catheter placed in the forearm at least 1 hour prior to the first blood draw. Blood samples drawn at 30 and 10 minutes prior to and 10, 20, 30, 40, and 60 minutes after naloxone administration were centrifuged and plasma was collected and stored at −70°C until the time of analysis. Cortisol analyses were conducted at the General Clinical Research Center laboratory using commercially available radioimmunoassay kits (Diagnostic Products Corp, Los Angeles, Calif).

STATISTICAL ANALYSIS

We were primarily concerned with potential naloxone dose–dependent differences between smokers and nonsmokers in (1) intensity of withdrawal symptoms as measured using the CINA and the drug effects scale and (2) intensity of naloxone-induced HPA activation as measured by cortisol levels. To rule out any baseline differences between smokers and nonsmokers, a *t* test was conducted on the prenaloxone values for all biochemical and behavioral measurements. If any differences were found, then all further analyses were conducted on change from baseline scores. Total and individual scores on the CINA, individual scores on the drug effects scale, and cortisol levels were analyzed using a mixed model with both dose (0, 0.8, 1.6, and 3.2 mg/70 kg) and time of measurement as random effects and group (smoker or nonsmoker) as a fixed effect. This model, which was determined to be a better fit for our repeated-measures study design with unequally spaced measurements, is also better at dealing with incomplete data sets.[20,21] Changes in craving for cigarettes were analyzed using a mixed model with dose of naloxone and time of measurement as within-subject factors. In cases of significant effects, multiple comparisons were conducted using least-square (adjusted) means. $P<.05$ was considered significant. Unless otherwise indicated, data are presented as mean ± SE.

the functional status of the endogenous opioids. Moreover, many of the signs and symptoms of tobacco withdrawal are similar to those observed during both spontaneous and opiate antagonist–precipitated withdrawal.[12] The current study used the naloxone challenge test, commonly used to establish opiate dependence,[13,14] to establish evidence of alterations in endogenous opioid responsivity in human nicotine-dependent smokers compared

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with nonsmokers, by evaluating (1) precipitated opiate-like withdrawal symptoms and craving for cigarettes and (2) cortisol levels as an indicator of naloxone-induced hypothalamic-pituitary-adrenal (HPA) axis activation.

RESULTS

DEMOGRAPHICS

Smokers did not differ from the nonsmokers on age, sex, race, or caffeine use. Smokers (n = 9, 5 men) had a mean age of 28.8 ± 1.6 years with baseline cotinine levels of 268.3 ± 24 ng/mL and average Fagerstrom scores of 6.9 ± 0.3, indicating a high level of nicotine dependence. Nonsmokers (n = 11, 7 men) had a mean age of 31.7 ± 2.4 years and reported no smoking in the past 5 years.

CINA SCORES

Analysis of the total CINA scores (**Figure**, A and B) indicated a significant main effect of dose of naloxone ($F_{3,51} = 3.37$, $P<.05$) and time of assessment ($F_{8,136} = 4.17$, $P<.001$). The effect of dose and time was modified by the individual's group status (smoker or nonsmoker) (group × dose, $F_{3,51} = 3.75$, $P<.01$ and group × time, $F_{8,136} = 3.42$, $P<.05$). Multiple-comparison procedures revealed that the CINA scores for nonsmokers were not altered by naloxone dose. However, in smokers, the increases in CINA scores observed with the 1.6-mg and the 3.2-mg doses were significantly greater than the placebo ($P<.05$ and $P<.001$, respectively), and the 3.2-mg dose produced greater withdrawal than the 0.8-mg ($P<.05$) and the 1.6 mg ($P<.05$) doses. Furthermore, CINA scores were significantly higher for smokers compared with nonsmokers at the 2 highest naloxone doses ($P<.05$).

Further analysis of individual items on the CINA scale revealed that smokers, when compared with nonsmokers, had significantly higher scores on tearing (group, $F_{3,51} = 3.75$, $P<.01$), and feeling hot/cold (group, $F_{1,17} = 5.50$, $P<.05$). Smokers also had naloxone dose–related increases in tearing (dose, $F_{3,51} = 3.21$, $P<.05$), yawning (dose, $F_{3,51} = 2.19$, $P<.01$), and muscle tension (dose, $F_{3,51} = 2.71$, $P<.05$). Moreover, smokers experienced greater naloxone dose–related increases in muscle twitching ($F_{3,51} = 5.01$, $P<.01$) and muscle tension ($F_{3,51} = 2.71$, $P<.05$) when compared with nonsmokers. Restlessness displayed time-dependent increases in smokers but not in nonsmokers (group × time, $F_{8,136} = 2.61$, $P<.01$) and was not altered by naloxone.

DRUG EFFECTS SCALE

Smokers were more irritable than nonsmokers ($F_{1,17} = 5.45$, $P<.03$) regardless of the dose of naloxone administered. We observed a significant main effect of naloxone dose ($F_{3,51} = 2.79$, $P<.05$) on "feeling tired," which was modified by time of assessment and by whether subjects were smokers or nonsmokers (group × dose × time, $F_{21,357} = 1.71$, $P<.05$). Further examination of the data within each group revealed that nonsmokers did not experience naloxone-induced alterations in tiredness (Figure, D). Conversely, smokers had significant increases in tiredness following administration of the 0.8-mg ($P<.05$) and 1.6-mg ($P<.01$) doses, when compared with placebo, but not following the highest dose (3.2 mg) of naloxone (Figure, C).

TIFFANY SCALE OF SMOKING URGES

We observed a significant main effect of naloxone dose ($F_{3,88} = 4.38$, $P<.01$) on smoking urges (craving), with maximal increases in scores at the 1.6-mg dose (4.18 ± 0.6) which was significantly different from saline (–0.24 ± 0.2; $P<.05$) and the 0.8-mg (0.2 ± 0.2, $P<.05$) dose of naloxone, but not following the 3.2-mg dose (2.56 ± 0.7) (Figure, G).

CORTISOL LEVELS

Cortisol levels at baseline (prior to naloxone) were significantly lower in smokers (11.97 ± 0.87 µg/dL; $P<.05$) when compared with nonsmokers (14.17 ± 0.66 µg/dL). Naloxone produced dose-dependent increases in cortisol levels over time as evidenced by a main effect of dose ($F_{3,42} = 9.14$, $P<.001$) and time ($F_{5,75} = 9.14$, $P<.001$) and a significant interaction of dose × time ($F_{15,203} = 5.28$, $P<.001$) in both smokers and nonsmokers (Figure, E and F). Post hoc comparisons indicate that the 1.6- and 3.2-mg doses were significantly different from both the placebo ($P<.001$) and the 0.8-mg ($P<.01$) conditions but were not significantly different from each other. Nonsmokers experienced greater increases in cortisol levels over time when compared with smokers (group × time, $F_{5,75} = 3.14$, $P<.05$), suggesting that the ability of the HPA axis to respond to the naloxone stimulus was attenuated in smokers. The intensity of naloxone-induced cortisol increases did not correlate with increases in total CINA scores as examined within each group or across the whole sample ($r<0.05$). There were no sex differences in naloxone-induced cortisol responses.

COMMENT

This study provides previously undocumented preliminary evidence for alterations in responsivity of the endogenous opioids in nicotine-dependent subjects, which may be one of the underlying biological mechanisms for the development of nicotine dependence. Indirect support for these results comes from previous reports of significant increases in adverse mood (depression, irritability, restlessness and poor concentration) following administration of naltrexone to smokers.[22] In the current study, withdrawal symptoms were assessed using the CINA, an opiate withdrawal scale, based on the premise that withdrawal precipitated by endogenous opioid antagonism should be similar to that observed during exogenous opiate withdrawal. Smokers experienced significant naloxone-induced increases in symptoms like tearing, feeling hot/cold, yawning, muscle tension, and muscle twitching, many of which are also increased following withdrawal in opiate addicts. How-

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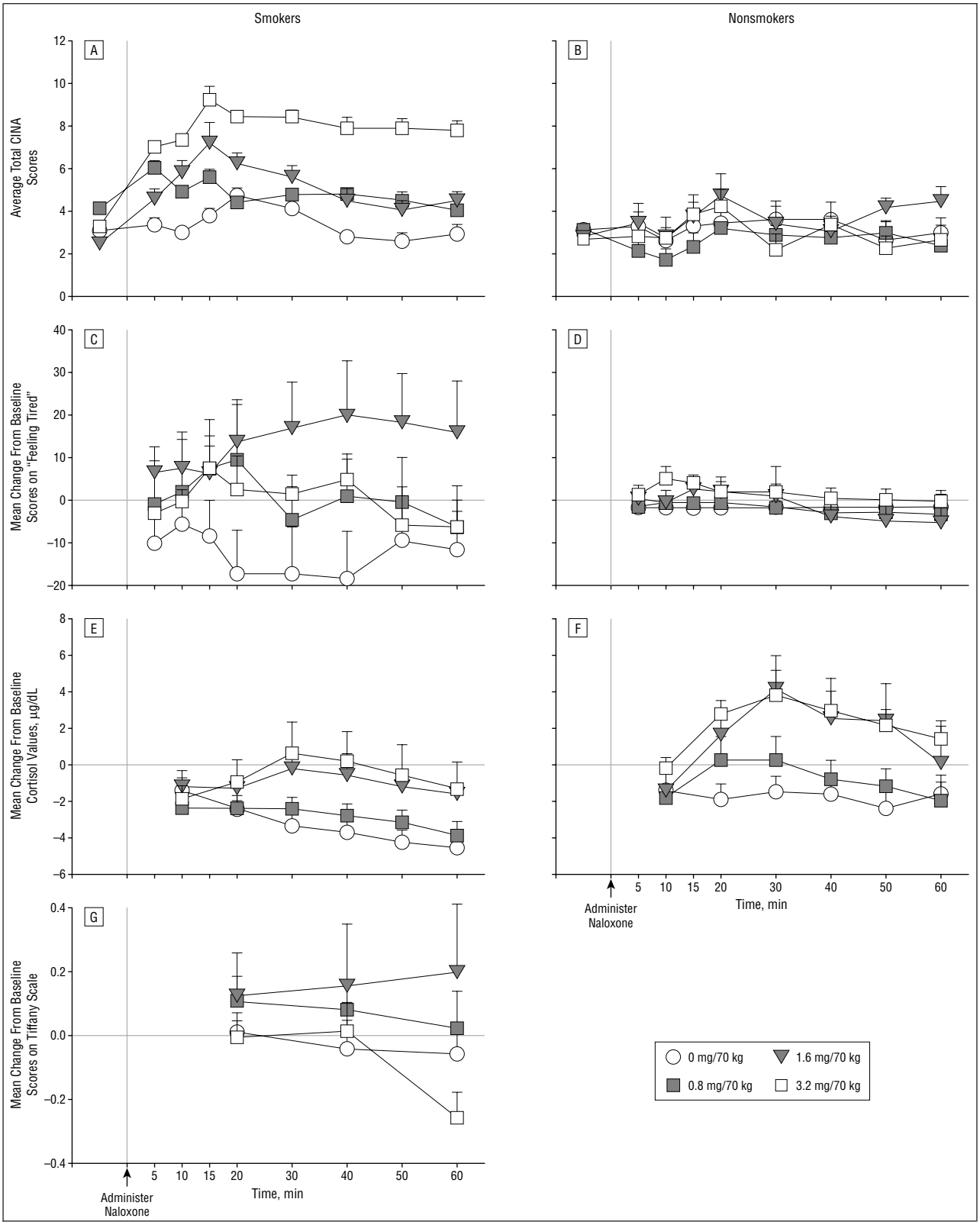

Effect of intravenous naloxone in smokers (n = 9; left panels) and nonsmokers (n = 11; right panels). A and B, Total Clinical Institute for Narcotic Withdrawal Scale (CINA)[13] scores. C and D, "Feeling tired." E and F, Cortisol levels. G, Tiffany scale of smoking urges[19] "urge to smoke" scores. All data are presented as mean ± SE.

ever, the intensity of the antagonist-precipitated changes is milder than in opiate withdrawal. This could be due to differences between nicotine- and opiate-dependent subjects in either the degree of opioid dysregulation, differential alterations in opioid receptor affinity, or in the levels of opioid receptors (μ and δ) that mediate these effects. Alternatively, these differences may also reflect a role for other neurochemical systems such as the

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nicotinergic-cholinergic system in mediating these effects.

As opposed to the unequivocal naloxone dose–dependent increases in classic opiate withdrawal signs in the smokers, other measures showed less clear naloxone-induced and group differences. Restlessness and irritability, which are commonly observed during both opiate and nicotine withdrawal,[12] were always higher in smokers compared with nonsmokers and were not influenced by naloxone, possibly due to a "ceiling" effect since subjects were already in mild nicotine withdrawal prior to naloxone administration. "Tiredness" was increased in smokers but not in nonsmokers following administration of the lower naloxone doses and not at the highest (3.2-mg) dose. Naloxone had a similar effects on the Tiffany scale, with increases in urges to smoke at the 0.8- and 1.6-mg doses and no effect at the 3.2-mg dose. A probable explanation for these results is that subjects may only become aware of alterations in craving and fatigue when withdrawal distress becomes less intense. For example, with the 1.6-mg dose, scores on the Tiffany scale and "feeling tired" started to increase when the CINA scores declined at the 20-minute observation point (Figure, A and B). Conversely, following administration of the 3.2-mg dose, CINA scores were still elevated at the 60-minute time point, and increases in craving and fatigue may have appeared later when withdrawal symptoms decreased.

While we did not assess smoking behavior in our paradigm, other investigators have shown reductions[23,24] and no effect[25] on the number of cigarettes smoked and no effect on tobacco withdrawal[23] following naloxone administration. These inconsistencies may be due to methodological factors, such as differences in doses of naloxone used, smoking deprivation time, and assessments used to evaluate withdrawal.

It has been previously suggested that naloxone may disinhibit the inhibitory effects of endogenous opioids on the hypothalamic corticotropin-releasing factor neurons, resulting in activation of the HPA axis and increased levels of cortisol, which may play a role in development of withdrawal distress.[26,27] This effect would be directly dependent on the level of opioid activity at the hypothalamus; therefore, any behavior that alters opioid activity should alter responsivity to naloxone. For example, a link between alcohol dependence and abnormalities in the HPA axis[28,29] and endogenous opioid activity[30,31] has been established and Kemper et al[32] have documented diminished cortisol release following a large naloxone dose in alcohol-dependent individuals. Recently Wand et al[33] have demonstrated that individuals with a family history of alcoholism but who are not alcohol dependent themselves have diminished cortisol responses to naloxone, suggesting that abnormalities in opioid tone may mediate higher rates of alcohol-seeking behavior in these individuals.

Our data demonstrate that nicotine-dependent individuals may also have similar alterations in responsivity of the endogenous opioid system. Smokers experienced naloxone dose–dependent increases in cortisol levels that were significantly less in magnitude than in nonsmokers. Interestingly, naloxone-induced cortisol increases were uncorrelated with increases in CINA scores, suggesting that activation of the HPA axis may not directly mediate naloxone's ability to precipitate opiate-like withdrawal symptoms in smokers. The diminished responsiveness of the HPA axis to naloxone may be the result of altered opioid tone and/or altered pituitary or adrenal responsiveness, as a result of either long-term nicotine exposure or acute nicotine withdrawal. Kirschbaum et al[34] have reported similar decreases in cortisol responses following a psychological stressor in mildly deprived smokers compared with nonsmokers. Our data also indicate that cortisol levels may be suppressed during nicotine withdrawal in dependent smokers, as evidenced by decreased early morning levels of cortisol following approximately 10 hours of nicotine deprivation. While it is well established that the HPA axis is activated by acute administration of nicotine,[35] the status of this axis during nicotine withdrawal is controversial and there are studies documenting both decreases[36,37] and no alteration[38,39] in cortisol levels.

One limitation of this study is the small sample size and the short observation period. Observation of subjects for longer than 1 hour may have accentuated naloxone-induced responses and eliminated the irregularity in the dose-response effect. Nevertheless, these findings of HPA axis perturbations and opioid antagonist–precipitated withdrawal in smokers have significant implications for similar studies conducted in other substance-abusing and psychiatric populations. High rates of smoking have been documented in individuals with schizophrenia and other psychiatric disorders[40-42] as well as those who use other substances such as alcohol, cocaine, and opiates.[43-47] However, studies of withdrawal and HPA axis functioning in these populations rarely report or control for concurrent nicotine dependence. Therefore, abnormalities associated with these disorders may be related to nicotine use in these populations. Future studies should take into account the smoking status of these clinical populations and healthy controls in the design as well as in the interpretation of results.

In summary, these results provide preliminary pharmacological evidence of alterations in the responsivity of the endogenous opioid system produced by long-term nicotine use, which may mediate not only the physical but also the motivational aspects of withdrawal from nicotine.

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