Brain Reward System Activity in Major Depression and Comorbid Nicotine Dependence

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ABSTRACT

Major depressive disorder (MDD) and nicotine dependence are highly comorbid. MDD patients may use nicotine to ameliorate depressive symptoms. The pathophysiology of the comorbidity of these two disorders is unknown. We hypothesized that a dysfunctional dopaminergic brain reward system (BRS) might be a neurobiological link between MDD and nicotine dependence and that smoking modulates the activity of the BRS by enhancing dopaminergic activity and relieving some depressive symptoms. Eighteen nicotine-dependent, nonmedicated subjects with Diagnostic and Statistical Manual of Mental Disorders (4th edition) diagnosis of MDD and 16 nicotine-dependent, control subjects participated in a double-blind, placebo-controlled, randomized parallel study. A single 30-mg oral dose of d-amphetamine (d-amph) was used to release dopamine and probe the activity of the BRS. The d-amph-mediated physiological and rewarding effects were assessed at baseline and post-treatment using standardized and validated questionnaires. Our results show that d-amph significantly increased blood pressure (p < 0.001). Subjective rewarding d-amph effects increased in both groups. Negative subjective effects were reported while on placebo during nonsmoking sessions. A significant correlation between depression severity (Hamilton depression scale) and d-amph rewarding effects was found in MDD smoker subjects (Addiction Research Center Inventory composite: r = 0.89, p < 0.000; profile of mood states composite: r = 0.71, p < 0.003; and visual analog scales composite: r = 0.78, p < 0.005). These data show that smoking did not modify the response to d-amph in MDD or control subjects, but decreased overall negative mood state during placebo sessions. Severity of depression was significantly correlated with increased rewarding effects of d-amph. Thus, although the BRS may be dysfunctional in MDD subjects, chronic nicotine use does not modify response to d-amph.

Abbreviations: MDD, major depressive disorder; BRS, brain reward system; d-amph, d-amphetamine; HAM-D, Hamilton depression scale; DSM-IV, Diagnostic and Statistical Manual—Version IV; CO, carbon monoxide; ARCI, Addiction Research Center Inventory; AG, amphetamine group; BG, benzodiazepine group; PCAG, pentobarbital chlorpromazine alcohol group; LSD, lysergic acid diethylamide; POMS, profile of mood states; VAS, visual analog scales.
the mesocorticolimbic dopaminergic system, has been extensively studied in the context of perception of pleasure (reward) and the pathogenesis of drug use, abuse, and dependence (Koob, 1992). Recently, it has been proposed that the dopaminergic system could also be involved in incentive learning or the attribution of incentive salience to cues and behaviors associated with administration of addictive drugs (Berridge and Robinson, 1998). Irrespective of its specific mechanism, the BRS plays a primary role in the development of dependence to psychostimulant drugs, including nicotine (Balfour and Ridley, 2000).

Nicotine has central and peripheral neural activity, and nicotinic acetylcholine receptors are likely to be the initial site of action (Dani and Heinemann, 1996). However, the psychopharmacological and rewarding effects of nicotine seem to be dependent on its effects in the BRS (Dani and Heinemann, 1996). Nicotine induces dopamine release, which is associated with a rewarding sensation (Corrigall et al., 1992).

Neurotransmitters interact in a complex regulatory manner, and no single neurotransmitter system can account for all of the symptoms of MDD. Thus, a dysfunctional neurotransmitter system may result in compensatory changes in the other systems as an attempt to achieve homeostasis. Therefore, the various symptoms of MDD may represent dysfunction in different neurobiological systems. The inability to experience pleasure (anhedonia) is one of the most important symptoms in MDD. A dysfunctional BRS may be involved in the pathogenesis of anhedonia (Heinz et al., 1994). During withdrawal from psychoactive drugs, the inability to experience pleasure is consistently experienced (Markou and Koob, 1991). Dopamine is also decreased during some drug withdrawal states (Pulvirenti and Diana, 2001). The nicotine withdrawal syndrome includes symptoms that may be considered motivational in nature and are best described as “negative affective states” (Markou and Koob, 1991; Koob and Le Moal, 1997). Examples of these symptoms include fatigue, depressed mood, and irritability (West and Russell, 1988). During acute nicotine withdrawal, “depressive mood” among other symptoms is a significant predictor for smoking relapse (Kafka, 1994; Killen et al., 1996). Depressed mood (as a nicotine withdrawal symptom) has been correlated with higher rates of smoking relapse (Kafka, 1994; Killen et al., 1996).

Acknowledging that many neurotransmitters are involved in the pathophysiology of MDD, we hypothesized that a dysfunctional dopaminergic BRS may be a common neurobiological substrate in nicotine dependence and comorbid MDD. Hence, smoking may modulate the activity of the human BRS by enhancing dopaminergic activity and relieving some of the symptoms of MDD (e.g., anxiety, decreased concentration, and lack of pleasure).

In this study, the activity of the BRS was assessed in nondepressed and depressed cigarette smoker subjects by measuring the rewarding effects of a dopamine-releasing probe. The probe consisted of the single oral administration of 30 mg of d-amph. The objectives of this study were to 1) determine whether smoking modified the response to d-amph in MDD subjects, and 2) determine whether the rewarding effects of d-amph are different during smoking and smoking-abstinent conditions.

Subjects

Subjects of either gender, aged 18 to 65, were recruited through advertisement, word of mouth, and by using a network of psychiatrists from several hospitals in Toronto (ON, Canada). A trained researcher initially contacted and systematically screened potential subjects by telephone to determine study suitability. The present study is part of a larger study including four different groups with the following characteristics: depressed smokers, depressed nonsmokers, control smokers, and control nonsmokers. Characteristics and results of the combined smoker and nonsmoker groups have been described elsewhere (Tremblay et al., 2002). For the purposes of this article, only data obtained from smoker groups (depressed and nondepressed) are shown. The 21-item Hamilton depression scale (HAM-D) was used to assess severity of depression during telephone screening (Hamilton, 1960). An HAM-D score of <15 in the depressed groups or >6 in the control groups precluded the participation of subjects. All depressed subjects met current criteria for MDD according to DSM-IV criteria and were either assessed by a trained researcher using the Structured Clinical Interview for the DSM-IV and/or were diagnosed by a psychiatrist. Depressed subjects were not currently taking antidepressant medication for at least 2 weeks (5 weeks for fluoxetine), had no history of comorbid psychiatric disorders or substance abuse (other than nicotine), and had no suicidal ideation posing an immediate threat to the subject’s life. A Fagerström test score of at least 3 was required for the inclusion of smokers in the study ( Heatherton et al., 1991). Suitable subjects were scheduled to attend an assessment. During the assessment, the study was explained to the subjects and both the HAM-D and the Beck depression inventory (Kendall et al., 1987) were used to assess severity of depression. Subjects who were willing to participate signed a Consent Form approved by the Ethics board at the University of Toronto. All participating subjects were healthy according to medical examination, blood chemistries, and electrocardiogram. Subjects were not currently using/abusing psychoactive drugs (other than alcohol use and nicotine abuse) as determined by questioning and urine drug screen results. All subjects who participated in the study signed an Informed Consent and received compensation for their time ($100 Canadian).

Drugs

d-Amphetamine sulfate (Dexedrine) and placebo were prepared at the pharmacy into 10-mg identical capsules filled with drug and/or dextrose powder. The d-amph dose we selected for this study (30 mg) is safe and within therapeutic range (CPS, 1998) and, in previous studies, has been shown to produce the intended behavioral effects (De Wit et al., 1987).

Experimental Design

This was a between-subject, double-blind, placebo-controlled randomized study. Depressed smoker subjects participated in a single study session that lasted approximately 5 h. Due to ethical issues and to avoid postponing the initiation of antidepressant treatment, the time to test our MDD subjects was restricted to only 1 day after the diagnosis was made. Thus, MDD smokers were only assessed under regular smoking conditions (to avoid nicotine withdrawal symptoms that could hinder study results). To determine whether nicotine modified the rewarding effects of d-amph and to measure nicotine withdrawal symptoms, control smokers participated in an additional session separated by at least 72 h (during smoking and smoking-abstinent conditions). During smoking sessions, subjects were allowed to smoke from four up to eight cigarettes. In the nonsmoking session, control subjects were requested to abstain from smoking for 12 h before and during the study session. All subjects were instructed not to ingest any food or products containing caffeine 12 h before and during the study session. Subjects were requested to

Materials and Methods
smoke a single cigarette in the morning before attending the smoking session.

During the study session, all subjects received an identical light breakfast to control for differences in the absorption of the drug. Subjects were randomized to d-amph or placebo. Physiological (blood pressure, heart rate, and body temperature) and rewarding effects of d-amphetamine (see below) were assessed at 0 (baseline), 30, 60, 120, 180, and 240 min postdrug. A 10-ml blood sample was taken at baseline and at 120 min (expected peak effect) to analyze d-amph and homovanillic acid plasma concentrations. Because CYP2A6 heterogeneity has been linked with differential smoking patterns (Pi-anezza et al., 1998), another blood sample was collected to determine CYP2A6 genotype. A carbon monoxide meter (Micro Smokerlyzer; Bedfont Instruments) was used to determine smoking abstinence compliance in control smokers before initiating the smoking-abstinence session. A carbon monoxide (CO) reading ≥10 ppm precluded participation during nonsmoking sessions. Also, CO was measured to assess within-session variability in smoking patterns.

Subjective Measures

The following measures were used to assess the effects of d-amph/ placebo.

Addiction Research Center Inventory (ARCI/ARCI Cole).

This questionnaire measures drug-specific subjective effects (Jasinski and Henningfield, 1989). It is a true-false questionnaire with empirically derived scales sensitive to various classes of psychoactive substances: sedation-mental, sedation-motor, stimulation-motor, stimulation-mental, unpleasantness-dysphoria, unpleasantness-physical, abuse-potential, amphetamine group (AG), morphine-benzodrine group (MBG), benzodrine group, pentobarbital chlorpromazine alcohol group (PCAG), and LSD group. For example, scales such as AG and PCAG measure stimulation and sedation, respectively, characteristic of these drugs.

Profile of Mood States (POMS). This is a questionnaire commonly used to assess time-sensitive, drug-induced changes in mood (Foltin and Fischman, 1991). Subjects indicate how they feel with respect to a series of adjectives using a 5-point scale from “not at all” to “extremely”. The adjective checklist yields 10 empirically defined scales: tension-anxiety, anger-hostility, fatigue, confusion, depression-dejection, vigor, elation, friendliness, arousal, and positive mood.

Visual Analog Scales (VAS). These scales are often used to assess momentary changes in affect (Fischman and Foltin, 1991). They consist of a selection of visual analog rating scales (100-mm lines) anchored at either end by opposing adjectives to evaluate drug effects (e.g., like versus dislike). Subjects rate how they feel by making a mark along the line. VAS were administered to assess the following drug effects: high, anxiety, irritability, alert, restlessness, energy, thought, drug effects, liking, bad effects, and good effects.

Data Analysis

For the self-report values, the peak d-amph behavioral effect (the highest value between 1 and 3 h postdrug) was calculated, and the corresponding baseline value was subtracted. The major dependent variable, was termed “ARCI positive effects composite” and consisted of an amalgamation of the baseline corrected peak scores of the scales that measure positive reinforcing effects (AG, morphine-benzodrine group, abuse-potential, and stimulation-euphoria). An ARCI negative effect composite (sedation-mental, unpleasantness-dyspho-

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* Mean ± S.D. |
CYP2A6 Genotypes

Samples for all smoking subjects were successfully genotyped for the *a2 point mutation, the *a4 gene deletion, and the duplication variant. All subjects in the control smoker group expressed the *a1/*a1 CYP2A6 wild-type deletion except for two subjects (one expressed the *a1/*a2 genotype, and the other expressed the *a1/*a4 genotype). All subjects in the depressed smoker group expressed the CYP2A6 wild-type genotype.

CO Levels

Readings of CO were obtained from only 22 subjects (MDD, n = 8; control, n = 14). Missing measurements from other subjects are due to the CO meter unavailability. There were no significant differences in CO levels between MDD and control subjects at any time when measured during study sessions. The mean CO measure at baseline was 15.2 ± 5.5 and 14.6 ± 7.3 ppm for MDD and controls, respectively (p < 0.05). The mean CO levels measured at the end of the study session were 30.6 ± 13.6 and 18 ± 7 ppm for MDD and control subjects, respectively (p < 0.06). The baseline-corrected peak for CO levels was 11.1 ± 11 and 7.7 ± 7.5 ppm for MDD and controls, respectively (p < 0.41).

d-Amphetamine versus Placebo Effect

Physiological Effects. As expected, analysis of variance values revealed significantly higher d-amph effects in cardiovascular parameters than placebo in both MDD and control groups as reflected by baseline-corrected peak scores (systolic blood pressure, p < 0.000; diastolic blood pressure, p < 0.000; and heart rate, p < 0.02).

Subjective Effects of d-Amphetamine. Large interindividual variations on the subjective response to d-amph and placebo were found (baseline-corrected peak response means). Using data obtained from MDD and control smokers, analysis of variance revealed that d-amph was associated with significant increases in some positive effects such as stimulation-motor (p < 0.05), alertness (p < 0.04), and drug effects (p < 0.01). The only negative scale that was found to be significantly decreased was the arched rating of sedation as measured by the ARCI PCAG variable (p < 0.05). When drug effects where analyzed by group, d-amph effects in control smokers were associated with significant increases in vigor (p < 0.003), arousal (p < 0.005), positive mood (p < 0.007), high (p < 0.002), drug effects (p < 0.006), liking (p < 0.000), and good drug effects (p < 0.02). In the MDD group, d-amph effects were associated with increases in arousal (p < 0.03), alert (p < 0.01), energy (p < 0.01), drug effect (p < 0.03), and good drug effects (p < 0.04). In addition, in the MDD group there were significant decreases in sedation-motor (p < 0.04), unpleasantness-physical (p < 0.01), and PCAG (p < 0.02).

d-Amphetamine Response Differences between Depressed and Control Smokers

High interindividual variability was found in the response to the positive effects of d-amph in the MDD and control groups, resulting in large standard deviations and results that are not significant. However, by observing the means, a trend of MDD subjects who report higher positive effects of d-amph than control subjects is noticeable (Fig. 1).

Interestingly, significant drug × group interactions were found on the report of d-amph effects on negative symptoms (Fig. 2). Depressed subjects showed a significant decrease in the report of negative symptoms (e.g., dysphoria and depression) when receiving d-amph, whereas control subjects had minimal response. Linear regression analysis demonstrated that age and gender did not contribute to the variability in the response.

Correlation between Severity of Depression and Composite Scales Measuring Subjective Effects

Several variables such as gender, age, and baseline were used as covariates to explain the high variability in the response to the positive rewarding subjective effects to d-amph found in MDD subjects. Depression severity (assessed by using the HAM-D) was the only variable that showed a significant effect on the response to the drug. Correlation analysis demonstrated a highly significant interaction between HAM-D scores and baseline-corrected peak response to the rewarding effects of d-amph (assessed by the composites) in MDD subjects. The significance of the correlation analysis is as follows: ARCI positive effects composite (r = 0.90; p = 0.000), ARCI negative effects composite (r = 0.61; p = 0.04), POMS positive effects composite (r = 0.71; p = 0.01), POMS negative effects composite (r = 0.64; p = 0.03), and VAS positive effects composite (r = 0.78; p = 0.005). Thus, more severely depressed individuals had a higher response to the rewarding effects of d-amph. There were significant differences in mean baseline scores between control and MDD groups. Thus, to control for possible baseline effects, partial
correlation analysis was performed. After controlling for baseline, results from several composites remained significant, including ARCI positive effects composite ($r = 0.89; p < 0.001$), POMS positive composite ($r = 0.80; p < 0.005$), and VAS positive effects composite ($r = 0.77; p < 0.008$). None of the composites measuring negative subjective effects remained significant. Interestingly, in MDD subjects receiving placebo, severity of depression was also correlated with an increased report of subjective effects in some composites. After controlling for baseline effects, the POMS positive effects composite ($r = 0.88; p < 0.02$) and VAS negative effects composite ($r = 0.84; p < 0.03$) remained significant. Therefore, MDD subjects tended to have a higher subjective response than controls irrespective of whether they received d-amph or placebo.

**Effects of Cigarette Smoking in Control Subjects**

**Subjects Receiving d-Amphetamine.** $t$ tests demonstrated that physiological measures were different in control smoker subjects receiving d-amph during smoking and nonsmoking sessions.

Baseline-corrected peak d-amph effects on VAS such as high and drug effect were significantly increased in control subjects during the smoking session ($p < 0.02$ and $p < 0.05$ for high and drug effect, respectively). However, smoking did not seem to modify the report of any other subjective effects of d-amph. No significant between-session differences were found at baseline, peak, or peak/baseline in control smoker subjects.

No between-session differences were found when comparing the results obtained from composites in control subjects receiving d-amph in baseline, peak, or peak-baseline scores.

**Subjects Receiving Placebo.** Physiological parameters in control smoker subjects receiving placebo were not statistically different during smoking and nonsmoking sessions. Despite not reaching statistical significance, there was a trend of decreased heart rate during the nonsmoking session ($p < 0.06$).

In contrast, results from several subjective scales were statistically significant when comparing the effects of placebo between smoking and nonsmoking sessions. Important decreases in the reports of baseline-corrected peak effects were found in the following scales: sedation-motor ($p < 0.004$), unpleasantness-physical ($p < 0.02$), PCAG ($p < 0.03$), LSD ($p < 0.04$), anger-hostility ($p < 0.03$), fatigue ($p < 0.000$), and confusion ($p < 0.02$). No significant differences were found in the report of scales associated with the rewarding effects of drugs.

Paired samples $t$ test analyses demonstrated statistically significant baseline differences between smoking and nonsmoking sessions in the ARCI positive composite ($p < 0.04$), POMS positive composite ($p < 0.01$), and VAS negative composite ($p < 0.04$). Nonsmoking sessions were associated with lower baseline scores for positive subjective effects and higher baselines for negative effects. No other differences were found between smoking and nonsmoking sessions.

**Comparison between Smokers and Nonsmokers**

The present study is part of a larger study including smokers and nonsmokers that has been published elsewhere (Tremblay et al., 2002). By comparing baseline-corrected peak d-amph effects between smokers and nonsmokers, we found that there were no significant differences dependent on smoking status in any individual scales or composites. Thus, response to d-amph was no different between smokers and nonsmokers either control or depressed. However, there were significant differences in the response to d-amph between control and MDD subjects. Severity of depression was also highly correlated with subjective response to d-amph in nonsmoker MDD subjects (Tremblay et al., 2002).

**Safety Issues.** d-Amphetamine was generally well tolerated and most subjects did not report any side effects. Reported side effects were mild and short-lived (e.g., headache, anxiety, and insomnia on the night after the study).

**Discussion**

This is the first human study evaluating the activity of the BRS as a possible common neurobiological substrate between MDD and nicotine dependence. d-Amphetamine was used as a probe of the BRS due to its ability to effectively release dopamine in the brain (Price et al., 2001). The results of this study showed the following. 1) d-Amph produced expected and reliable physiological and subjective reinforcing effects in both MDD and control subjects. 2) Severely depressed smokers showed significantly higher responses to d-amph than moderately depressed ones. 3) Chronic cigarette smoking did not change the response to d-amph in moderately to severely nicotine-dependent subjects. Furthermore, the reports of d-amph subjective effects in control subjects remained similar under smoking and nonsmoking sessions. 4) Nicotine withdrawal symptoms are likely responsible for the increased report of negative subjective effects in control subjects receiving placebo during the nonsmoking session. This suggests that the BRS may be dysfunctional in MDD, where depressed subjects are more sensitive to BRS activation. Smoking, however, did not modify the response to d-amph.

Nicotine dependence is often comorbid with psychiatric disorders. Various behavioral models that have been proposed to describe the etiology of comorbid disorders (Merikangas and Stevens, 1998). Several neurotransmitter systems are likely involved in the neuropathology of MDD, and they may mediate different symptoms (e.g., cognitive, mood, and anhedonia). Nicotine has been postulated to modulate some of these psychiatric symptoms. Thus, cigarette smoking may be a form of self-medication. For example, nicotine activity in the cholinergic system has been linked to enhanced cognitive performance (Picciotto et al., 2000).

Although it has been suggested that MDD and nicotine dependence may share some neural substrates (Quattrocchi et al., 2000), there is lack of studies evaluating the effects of nicotine on depressive symptoms. Nicotine has been shown to indirectly enhance dopamine release in the brain (Corrigall et al., 1992; Di Chiara, 2000), which may modulate depressive mood. The idea of using nicotine as a treatment adjuvant in MDD has already been evaluated in one study (Salin-Pascual et al., 1996) where 12 nonmedicated nonsmoker MDD patients wore the transdermal nicotine patch for 4 days. The use of the nicotine patch was associated with decreased depressive symptoms. Results from this study should be interpreted with caution due to methodology limitations.

Nicotine acts as a synergist when coadministered with cocaine, producing increased subjective effect (Jones et al.,
Thus, an enhanced subjective response to d-amph was hypothesized in both MDD and control smokers compared with nonsmokers from the larger study (Tremblay et al., 2001). However, cigarette smoking in moderately and severely nicotine-dependent control subjects did not modify the effects of d-amph. Furthermore, when smokers both MDD and control were compared with nonsmokers, smoking status did not modify d-amph or placebo response. Thus, it is possible that the effect of nicotine on dopamine release in chronic smokers is too mild and transient to be differentiated from the subjective response to d-amph. Tolerance to nicotine may also account for the observed lack of synergistic effects. Our observations agree with results from two recent PET studies. In one study in monkeys (Tsudaka and Domino, 2001), i.v. nicotine (administered in tobacco smoking-related doses) did not release sufficient brain dopamine to displace $[^{1}C]$raclopride from D$_2$ receptors, in contrast to methamphetamine. In another study in nicotine-deprived control healthy smokers (Barret et al., 2001), despite an increased report of head rush and decreased level of craving, smoking did not modify $[^{1}C]$raclopride binding in striatum. Thus, either a minimal dopaminergic response to tobacco smoking or tolerance arising from repeated nicotine administration may occur and explain these results.

Results obtained from the comparisons between d-amph and placebo response in MDD and control subjects, irrespective of whether they were smokers or nonsmokers, have been reported by our group previously (Tremblay et al., 2002). It is possible that the instruments used for assessing the subjective effects of nicotine when coadministered with d-amph are not sensitive enough to adequately assess cigarette-smoking effects. However, in control smokers, several variables associated with negative mood (measured at baseline) were significantly lower during nonsmoking sessions compared with smoking sessions. Although the instruments used in this study are not specific to assess smoking effects, independent variables such as anxiety, restlessness, and dysphoria are associated with the nicotine withdrawal syndrome. Thus, our instruments seem sensitive to assess nicotine effects, or at least, changes in nicotine withdrawal symptoms.

Interindividual variation in cigarette smoking patterns (e.g., number of cigarettes smoked and strength of inhalation) and nicotine metabolism may influence the subjective experience of smoking. Several of these factors were assessed to minimize differences between participating individuals. All subjects were moderately to severely dependent on nicotine according to DSM-IV criteria and the Fagerström test of nicotine dependence. Nicotine is metabolized through the polymorphic hepatic enzyme CYP2A6. Individuals expressing the fully active enzyme (wild type) have shown to smoke more cigarettes than those who express the heterozygote or the null allele variant (Tyndale et al., 1999). All of our subjects expressed at least one CYP2A6 wild-type allele. The measurement of CO is sensitive to number of cigarettes smoked and inhalation strength. Differences in the mean levels of CO, measured during the study sessions, were not statistically significant between MDD smokers and controls. Therefore, it is unlikely that interindividual subjective response variability could be attributed to differential nicotine metabolism or smoking patterns.

In summary, results from this study suggest that despite the fact that nicotine did not modify the response to d-amph, the BRS may be dysfunctional in MDD subjects, smokers or nonsmokers. Also, the severity of depression was significantly correlated with increased rewarding subjective effects of d-amph. It is possible that the comorbidity between nicotine dependence and MDD relies on a neurotransmitter system other than the dopaminergic system in the brain (e.g., cholinergic). The availability of neuroimaging techniques such as PET and fMRI may allow us to more directly assess the role of the dopaminergic BRS in MDD and comorbid nicotine dependence. Understanding the underlying neurobiological mechanisms/substrates between MDD and nicotine dependence may have important implications in the development of new treatments for both disorders and warrants further study.

References


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