Original Investigation

Denicotinized Versus Average Nicotine Tobacco Cigarette Smoking Differentially Releases Striatal Dopamine

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Abstract

Introduction: Nicotine has long been recognized as a necessary but insufficient component of tobacco cigarettes to maintain a psychophysiological need to smoke. This study examined venous plasma concentrations effects of nicotine in cigarette smoking after overnight abstinence to release striatal dopamine (DA).

Methods: Twenty-two male smokers smoked either denicotinized (denic) or average nicotine (nic) cigarettes under single blind conditions. Each was given [^{11}C]raclopride and scanned in a positron emission tomography (PET) facility.

Results: Smoking either denic or nic cigarettes released striatal DA. Denic cigarette smoking released DA primarily in the right striatum, whereas nic cigarette smoking released DA in both striata, but especially in the left. Increases in venous plasma nicotine concentrations correlated positively with increased DA release in the left caudate nucleus. Smoking denic cigarettes reduced craving as much as smoking nic cigarettes. Craving reduction after nic tobacco smoking correlated with increases in plasma nicotine.

Conclusions: Nonnicotine factors in tobacco smoking produce important right brain effects. Nicotine is a pharmacological factor during tobacco smoking that releases bilateral striatal DA, but more in the left brain.

Introduction

Tobacco dependence and its abstinence involve pharmacological, neurophysiological, and psychological factors. It is well-known that denicotinized (denic) cigarette smoking has very significant mood effects. It reduces craving and withdrawal and increases satisfaction (Butschky, Bailey, Henningfield, & Pickworth, 1995; Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Donny, Houtsmuller, & Stitzer, 2006; Gross, Lee, & Stitzer, 1997; Rose, 2006; Rose, Behm, Westman, Bates, & Salley, 2003; Shahan, Bickel, Madden, & Badger, 1999). It is obvious that the behavioral effects of smoking, including visualizing and lighting the cigarette, seeing the exhaled smoke, feeling its sensations in the throat and lungs, and expectations of set and setting, all contribute to the tobacco smoking experience (Rose & Behm, 1995). Craving to smoke is relieved by using denic tobacco cigarettes that contain very little nicotine, but not by nicotine skin patches. Why is this so? Are the blood levels of nicotine obtained with patches too low or too slow to be reinforcing?

In animal models of nicotine relapse, discrete environmental stimuli reinstate extinguished nicotine seeking (Caggiula et al., 2001; Cohen, Perrault, Griebel, & Soubrie, 2005; Corrigall & Coen, 1991; Goldberg, Spealman, & Goldberg, 1981; LeSage, Burroughs, Dufek, Keyler, & Pentel, 2004; Liu et al., 2003, 2007; Paterson & Markou, 2005). In tobacco smokers, brain response to cigarette cues, as measured by functional magnetic resonance imaging (fMRI), is affected by expectancy to smoke and less by abstinence (McBride, Barrett, Kelly, Aw, & Dagher, 2006). Brody et al. (2004) used [^{11}C]raclopride to measure dopamine (DA) release in smokers and nonsmokers. Tobacco-dependent subjects who smoked immediately outside of the PET scanner had greater release of DA in the left ventral caudate/nucleus accumbens than in those who did not smoke. Barrett, Boileau, Okker, Pihl, and Dagher (2004) found that the hedonic response to tobacco smoking is proportional to DA release in the caudate and posterior putamen but, surprisingly, not in the ventral striatum. Subsequently, Brody, Mandelkern, Olmstead, et al. (2009), using [^{11}C]raclopride compared right plus left ventral striatal DA release in two groups of smokers, one group in response to smoking regular and the other to smoking denicotinized cigarettes. Both groups had reductions in craving and anxiety with smoking, but the regular smoking group had greater improvement in mood. Similarly, after smoking, both groups had reductions

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in ventral striatal [^{11}C]raclopride binding potential nondisplaceable (BP_{ND}), but more in the regular tobacco group. For both groups, the changes in BP_{ND} after smoking correlated inversely with mood, indicating greater DA release. Recently, Brody et al. (2010) reported on the use of [^{11}C]raclopride to measure the ventral caudate/nucleus accumbens BP_{ND} before and after various 8-week treatments for tobacco dependence to smoking a regular cigarette. The small mean smoking induced BP_{ND} reductions were highly correlated with total cigarette puff volumes. Their data indicated that smoking induced DA release is dose dependent. Sharma and Brody (2009) have further summarized the extensive literature on the in vivo human brain effects of nicotine and tobacco smoking.

The purpose of the present study was to determine the effects of venous plasma nicotine concentrations on mood and [^{11}C]raclopride binding using both denicotinized (denic) and regular nicotine (nic) tobacco cigarette smoking in overnight abstinent tobacco smokers. The denic and nic cigarettes were very unique. They had equal amounts of tar and other tobacco smoke constituents. They differed primarily in their nicotine content. Hence, this is a venous plasma nicotine concentration striatal DA effect study.

Methods

Subjects

A total of 24 male tobacco dependent subjects were recruited, of which 17 completed all aspects of this study. The smoker mean age ± *SD* was 25.8 ± 4.6 years. The protocol was approved by the Institutional Review Board, Medicine (IRBMed) at the University of Michigan. Subjects were recruited by newspaper ads as well as hearing from fellow peers about the study. Subjects were monetarily reimbursed for their time and inconvenience as participants in this study. Following a preliminary screening over the telephone, those who appeared eligible were invited for an interview. At the interview, patients signed an informed consent form after being told the details of the study. They also underwent a physical examination.

Inclusion/Exclusion Criteria

No women were included in this study because gender issues require a larger number of subjects. Of the 24 male subjects recruited, there were 20 Caucasians, two Blacks, one Hispanic, and one American Indian. These subjects completed almost all aspects of this study. Men between the ages of 18 and 55 years were included only if they were in good health. They smoked between 5 and 30 cigarettes/day with a mean ± *SE* of 18.5 ± 5.75. Hence, the majority were moderate smokers. Subjects were not taking any medications. Those who met criteria for psychoactive substance abuse disorder identified on the SCID IV were excluded as well as those with evidence of recent substance abuse from a urine toxicology screen.

Cigarettes and Smoking Procedure

The nic and denic cigarettes were obtained through the courtesy of Dr. Frank P. Gullotta and Ms. Cynthia S. Hayes of the Philip Morris Research Center, Richmond, VA. The nic cigarettes were made with unextracted tobacco (nicotine 1.01 mg and tar 9.5 mg/cigarette). The denic cigarettes were made with almost 100% extracted tobacco (nicotine 0.08 mg and tar 9.1 mg/cigarette). Both types of cigarettes contained identical filter tips and were made from the same blend of tobacco with no flavors added. It is important to note that the cigarettes used in this study were designed to be as similar as possible to regular cigarettes except for their nicotine content. They differ from denic versus nic cigarettes usually used in other similar studies. Unfortunately, such cigarettes are no longer available.

In order to comply with the University of Michigan Medical Center "No Smoking" policy, special measures were taken to contain tobacco smoke. For the smoking procedure in the scanner, the lit cigarette was confined to a one gallon plastic bottle. The inlet at the bottom of the bottle had 2 one-way valves to allow room air to be drawn into the closed bottle. The cap of the plastic bottle contained a 2.95 cm plastic cigarette holder with the plastic/rubber filter removed (Laden Modern Family Products Factory, Shanghai Youngking Office Produce, China). The cigarette was placed in the plastic cigarette holder and the lit end of the cigarette was placed inside of the closed plastic bottle. Subjects puffed on the lit cigarette contained in the bottle and then exhaled smoke via a facemask through a one-way exhaust valve into a plastic bag, which was then exhausted into the University Hospital anesthesia negative pressure purging system vented to the exterior roof of the building.

Experimental Design

After overnight abstinence, each subject was scanned on separate days in the a.m. verified by exhaled expired-air carbon monoxide (CO) < 10 ppm. The subjects were given [^{11}C]raclopride in a counterbalanced (days) design. Unknown to the smokers, two denic tobacco cigarettes were always smoked first. Two nic cigarettes were smoked about two hr later. The reason two cigarettes were smoked was because of the unusually inefficient method of smoking with a cigarette inside a bottle. Each subject arrived at the PET unit about 7:30 a.m. on two separate days about a week apart. After proper positioning and controls, the radiotracer was given about 8:30 a.m. The first set of scans were with [^{11}C]raclopride and denic tobacco smoking. The second set of scans with [^{11}C]raclopride were with nic tobacco smoking. The experimental timeline is illustrated in Figure 1 with venous plasma nicotine concentrations before and after smoking each type of tobacco cigarette.

Neuroimaging and Image Data Analysis

The detailed imaging methods and data analysis were similar to those described in Scott et al. (2007). PET scans were acquired with a Siemens HR$^+$ scanner in three-dimensional (3D) mode (reconstructed full width at half maximum resolution ~5.5 mm in-plane and 5.0 mm axially) with septa retracted and scatter correction. Participants were positioned in the PET scanner gantry and two intravenous (i.v.) (antecubital) lines placed. A light forehead restraint was used to eliminate intrascan movement.

[^{11}C]Raclopride was synthesized at high specific activity (>2000 Ci/mmol) by the reaction of O-desmethyl raclopride with [^{11}C]methyl triflate. In each of the two scans, 10–15 mCi was administered. The total mass of raclopride was 0.089 ± 0.047 μg/kg per scan. Fifty percent of the radiotracer dose was administered as a bolus and the remaining 50% by continuous infusion for the rest of the study. Images were reconstructed using iterative algorithms (brain mode: FORE/OSEM four iterations; 17 subjects; no smoothing) into a 128 × 128 pixel matrix in a 28.8 cm diameter field of view. Attenuation corrections were performed through a

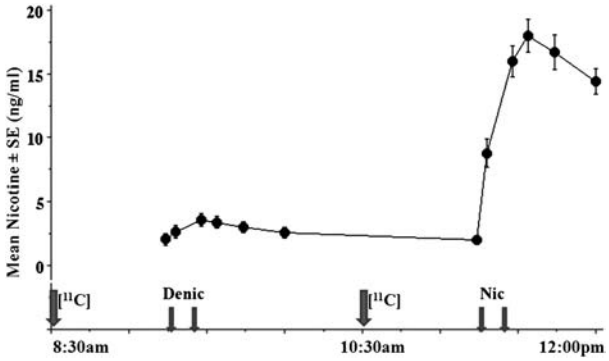

Figure 1. Radioligand dose, tobacco smoking, venous plasma nicotine time line. The first radioligand [^{11}C] dose was given about 8:30 a.m. After its radioactivity decayed, the second dose [^{11}C] was given about 10:30 a.m. Smoking denic tobacco cigarettes produced a minor increase in venous plasma nicotine in contrast to smoking nic cigarettes.

6-min transmission scan (^{68}Ge source) obtained before the PET study, also with iterative reconstruction of the blank/transmission data followed by segmentation of the attenuation image.

Small head motions were corrected by an automatic computer algorithm for each subject and the images coregistered (Minoshima et al., 1993). Time points were decay corrected during reconstruction of the PET data. Images were transformed on a voxel-by-voxel basis into two sets of parametric maps: (a) a tracer transport measure (K_1 ratio) and (b) a receptor-related measure (distribution volume ratio, DVR). To avoid the need for arterial blood sampling, these measures were calculated using a modified Logan graphical analysis (Logan et al., 1996).

Receptor concentration divided by its affinity for the radiotracer, referred to as the DVR, B_{max}/K_d (or DVR-1), is the "receptor-related" measure (BP, or receptor availability in vivo; B_{max} = concentration of receptors, K_d = receptor affinity for the radiotracer). As changes in B_{max}/K_d cause a change in the slope of the Logan plot, DVR during both the early and late phases of each scan was measured. The slope during the early phase was estimated from 5 to 40 min postinjection, whereas the slope for the second phase was estimated from 45 to 90 min postinjection.

Anatomical MRI scans were acquired before PET scanning on a 1.5 Tesla scanner (Sigma, General Electric, Milwaukee, WI). Acquisition sequences were axial spoiled gradient recalled (SPGR) IR-Prep MR (echo time [TE] = 5.5, repetition time [TR] = 14, T1-weighted [T1] = 300, flip angle = 20°, number of excitations [NEX] = 1, 124 contiguous images, 1.5 mm thickness), followed by axial T2 and proton density images (TE = 20 and 100, respectively; TR = 4000, NEX = 1, 62 contiguous images, 3 mm thickness). K_1 and DVR images for each experimental period and the MR images were coregistered to each other and to the International Consortium for Brain Mapping (ICBM) stereotactic atlas orientation. Statistical parametric maps of differences between conditions (denicotinized vs. nicotine) were generated by anatomically standardizing the T1-SPGR MRI of each subject to the ICBM stereotactic atlas coordinates.

Differences within subjects and between conditions (effects of nicotine) were mapped into stereotactic space using z maps of statistical significance with SPM5 and Matlab software, with a general linear model and correction for multiple comparisons. No global normalization was applied to the data, and therefore, the calculations presented are based on absolute B_{max}/K_d estimates. Increased (reduction in BP_{ND}) and decreased (increases in BP_{ND}) DA neurotransmitter release was assumed from the BP_{ND} change.

Seventeen of the 24 smokers had at least 10 ng/ml venous plasma nicotine increases above baseline (boost) following nic cigarette smoking. SPM5 was used to determine voxel differences. More than 10 ng/ml nicotine minimum is justified as per the literature described in the Discussion. T1 weighted SPGR MRI utilized the ICBM standard atlas coordinates for anatomical normalization (Mazziotta et al., 2001). Activation of the DA transmitter system was calculated as the differences between the denic cigarette and nic cigarette conditions for correlation coefficients with striatal BP_{ND}. To account for potential mass and age effects, the mean internal dose and mean age were calculated. The mean ± *SD* internal dose of radiation from the [^{11}C]raclopride was 0.04 ± 0.04 nmol/kg, with the highest dose being 0.23 nmol/kg. This is well under the 1.5 nmol/kg threshold for a tracer dose without any mass effect, as established by multiple studies (Kung & Kung, 2005; Opacka-Juffry et al., 1998; Yoder et al., 2008). When stratified by age groups, our subjects were not significantly different. The average age of our subjects was clustered around a mean and *SD* of 25.8 ± 4.6. Since the age-related decline of D_2/D_3 receptors is slow (~7.9% per decade), one can be confident that there was no significant age effect (Antonini et al., 1993; Volkow et al., 1996).

Nicotine Blood Sampling

Venous blood samples were drawn at baseline prior to smoking and also at five time points after initiation of smoking (4, 14, 20, 30, and 50 min). Maximum nicotine venous plasma levels postsmoking were used for correlations with other measures. Samples were analyzed for nicotine by Med Tox Laboratories (St. Paul, MN).

Subjective Measures

Visual analog scales (VAS) were administered before and after smoking. Subjects were asked to rate how they felt at that moment with regard to craving for cigarettes, relaxed, sickness, wakefulness, and nervousness. They were asked to rate these items on a scale from 1 to 10, where 1 was "*not at all*" and 10 was "*most ever*."

Data Analysis

The VAS data were analyzed using one-way analysis of variance (ANOVA) with repeated measure (INSTAT 2.0 for MacIntosh, 1993) followed by the Bonferroni post hoc test when a significant *F* ratio was obtained. An alpha level (*p* value) of .05 was used as the level of significance for all tests. A correlation coefficient analysis was conducted to find the relationship between plasma nicotine level and the craving score change.

Results

Effects of Tobacco Smoking on Mood and Nicotine Plasma Levels

As illustrated in Figure 2, smoking both types of nicotine/tobacco cigarettes had significant effects on craving and wakefulness.

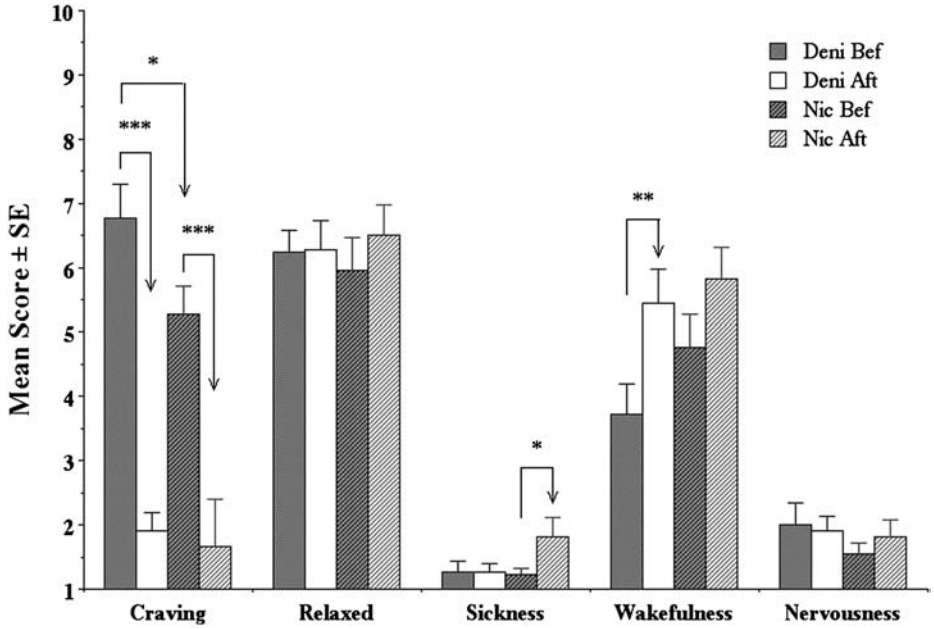

Figure 2. Mood effects of smoking denicotinized and nicotine tobacco cigarettes. Smoking either type of cigarette markedly reduced craving. Sickness was increased after nic tobacco smoking. Wakefulness was increased following denic tobacco smoking and maintained. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Only nic cigarettes had a significant effect on sickness, but neither type had an effect on relaxation or nervousness. A one-way ANOVA with repeated measures indicated that craving was decreased, $F(3, 43) = 103.63$, $p < .0001$, and wakefulness, $F(3, 43) = 42.404$, $p < .0001$, and some sickness ($p < .05$) increased with smoking the different types of cigarettes.

Craving before smoking denic cigarettes gave a mean ± *SE* of 6.7 ± 0.52 and after smoking 1.91 ± 0.28. Craving before smoking nic cigarettes gave a mean ± *SE* of 5.27 ± 0.44 and after smoking 1.67 ± 0.72. When normalized, the mean percentage decrease in craving from before to after smoking denic cigarettes was 71.2% and 68.3% for smoking nic cigarettes.

After smoking the denic cigarettes, subjects' venous plasma nicotine levels remained very low, whereas after smoking nic cigarettes, plasma nicotine levels increased. The mean ± *SE* data are shown in Figure 1.

The correlation coefficients between mood and venous plasma nicotine before and after smoking were determined for all of the volunteers. The minor increases in plasma nicotine with denic smoking (before and after) and craving gave a nonsignificant correlation coefficient $r = -.282$. The larger increase in plasma nicotine with nic smoking (before and after) and craving change gave a significantly larger correlation coefficient $r = -.641$ ($p < .01$). There was no correlation between plasma nicotine levels and wakefulness, ranging from $r = .107$ (*ns*) for denic, $r = .071$ (*ns*) for nic, and $r = .074$ (*ns*) for combined cigarette smoking.

Striatal Dopamine Release Following Denic Cigarette Smoking

When using an uncorrected statistical threshold, smoking denic cigarettes reduced the BP_{ND} of [^{11}C]raclopride primarily in the right striatum, as illustrated in Figure 3 ($p_{(unc)} = .001$, extent threshold $k = 0$ voxel). Note that the right side of the volunteers' coronal images is on the left. The reduced BP_{ND} included the right caudate (x, y, z coordinates, in mm 8, 8, 10; cluster size = 24 mm^3) and the right lentiform nucleus of the putamen (30, −16, 8; cluster size = 16 mm^3). The coordinates indicate the region was very close to the right insula, as illustrated in the lower right coronal section of Figure 3. In contrast, there was no effect in the left hemisphere.

Striatal Dopamine Release Following Nic Cigarette Smoking

Smoking nic cigarettes reduced the BP_{ND} of [^{11}C]raclopride in both left and right striatum, as illustrated in Figure 4 ($P_{\text{false discovery rate (FDR)}} = .04$, extent threshold $k = 32$ voxels) with a very strict statistical criterion. This included the left hemisphere, the caudate (−14, 12, 14; cluster size = 4,616 mm^3; −16, −2, 20; cluster size = 3,504 mm^3), putamen (−16, 10, −6; −22 0, −6; cluster 4,616 mm^3), and nucleus accumbens (−13.6, 9.8, −8; −12.7, 11.6, −8; cluster size = 368 mm^3). In the right hemisphere, nic tobacco smoking reduced the BP_{ND} in the right putamen (20, 20, 0; 28, 6, −4; cluster size = 3,504 mm^3), and claustrum (32, 4, 8; cluster size = 3,504 mm^3). Maximum venous plasma nicotine levels after smoking nic cigarettes had a negative correlation with [^{11}C]raclopride binding only in the left caudate nucleus (−16, −2, 20; $r = -.543$, $p < .05$). Note that nic tobacco smoking had a lower BP_{ND} in the left than the right hemisphere, as illustrated in the bar graph in Figure 5.

The effects of nicotine on [^{11}C]raclopride binding were determined from the data after denic minus after nic smoking. The effects of denic were determined from before denic minus after denic, which is before nic smoking. In both cases, only the striatal brain areas that showed statistically significant changes in [^{11}C]raclopride binding were used. The percent change from

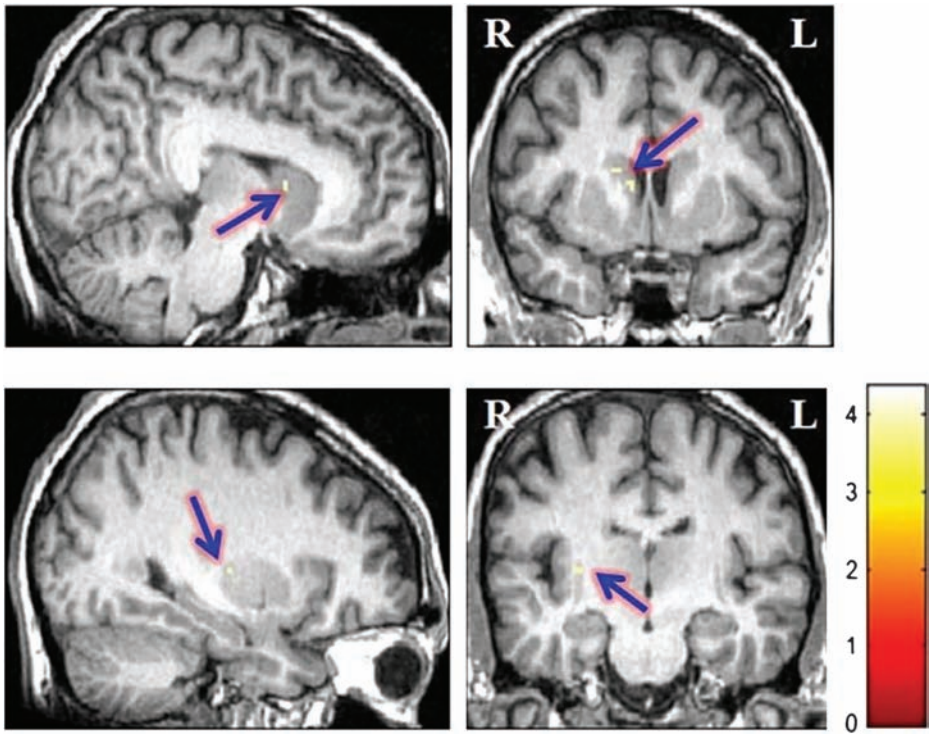

Figure 3. Smoking denicotinized cigarettes increases brain striatal dopamine release. Smoking denic cigarettes significantly reduced the BP_{ND} of [^{11}C]raclopride only in the right striatum ([−8, 8, 10], [−30, −16, 8] radiological convention). $T = 4.35–3.80$, $p_{(unc)} = .001$. Extent threshold $k = 0$ voxels. In this figure, the arrows highlight the significant brain sites because the statistically significant brain areas are difficult to see. The colored bar in this and Figure 4 represents the level of each t value. The arrows point to the hot colors that indicate significant brain sites. Note: It is assumed that a decrease in [^{11}C]raclopride BP_{ND} represents an increase in DA release in both figures as described throughout the manuscript.

baseline to after smoking was also calculated. After nic tobacco smoking, binding potentials decreased in both striata from 4.86% to 6.95%. On the other hand, smoking denic cigarettes decreased [^{11}C]raclopride binding from 0.66% to 4.06%.

Discussion

In the present study, the quantitative changes in plasma nicotine were compared with craving for tobacco cigarettes. Both denic or nic tobacco smoke inhalation rapidly decreased the subjects' craving for smoking. When all of the data were combined, there was a barely significant negative correlation ($r = −.483$, $p < .05$) that increased venous plasma nicotine levels reduced craving. The issue of denicotinized cigarettes, as well as nicotine, in relieving craving has been mixed. For example, many years ago, Lucchesi et al. (1967) and later Benowitz and Jacob (1990) found that i.v. infusions of nicotine in smokers partially decreased their urge to smoke. However, Kumar et al. (1977) could not confirm that i.v. nicotine reduced smoking, but later Russell (1985) did. Jarvik et al. (2000) found a significant negative correlation between nicotine blood levels (venous plasma) and craving scores in tobacco smokers. Subsequently, Rose, Behm, Westman, Mathew, et al. (2003) reported a small suppression by i.v. nicotine on *ad libitum* smoking behavior. Denicotinized smoking produced a larger reduction but only the combination was equivalent to smoking usual nicotine containing cigarettes. Later, Guthrie, Ni, Zubieta, Teter, and Domino (2004) found that craving for a cigarette was reduced by smoking nic tobacco cigarettes that correlated with the area under the curve of arterial plasma nicotine concentrations but not well ($r = −.57$, $p < .01$). In the same experiment, subsequent smoking a nic cigarette also reduced craving from an already lower baseline.

Russell et al. (1995) reviewed the data about the precision of regulation of nicotine intake in tobacco smokers. The plasma nicotine profile of a typical 1 cigarette/hr smoker consists of hourly rapid spikes of about 20 ng/ml boost and fall with each smoke inhalation. In contrast, in very heavy smokers, the plasma nicotine spikes are about 5–10 ng/ml or less per smoke inhalation with a steady mean increase after 3 hr of smoking for the rest of the day. Russell et al. suggested that the relative reduction of plasma nicotine spikes in heavy smokers is to avoid any drop in nicotine, which will cause discomfort or other negative effects. In contrast, the rapid peaks (boosts) in nicotine in regular smokers are positively reinforcing. They also concluded that a venous blood nicotine boost of 10 ng/ml per tobacco cigarette is sufficient for positive subjective effects. A similar boost in venous plasma nicotine produces electroencephalographic changes consistent with increased arousal (Kadoya, Domino, & Matsuoka, 1994). Such a nicotine boost can also be obtained from oral and nasal snuff or nasal spray but as rapidly as other forms, such as nicotine gum and patches. Russell et al. (1980) suggested in very heavy smokers reinforcement through withdrawal relief, in contrast to light smokers where positive reinforcement to nicotine boost occurs. In light tobacco smokers, there is a positive correlation between the number of cigarettes smoked and plasma nicotine, whereas there is little correlation in heavy tobacco smokers. Similar findings were reported by Gori and Lynch (1985) using a much larger sample.

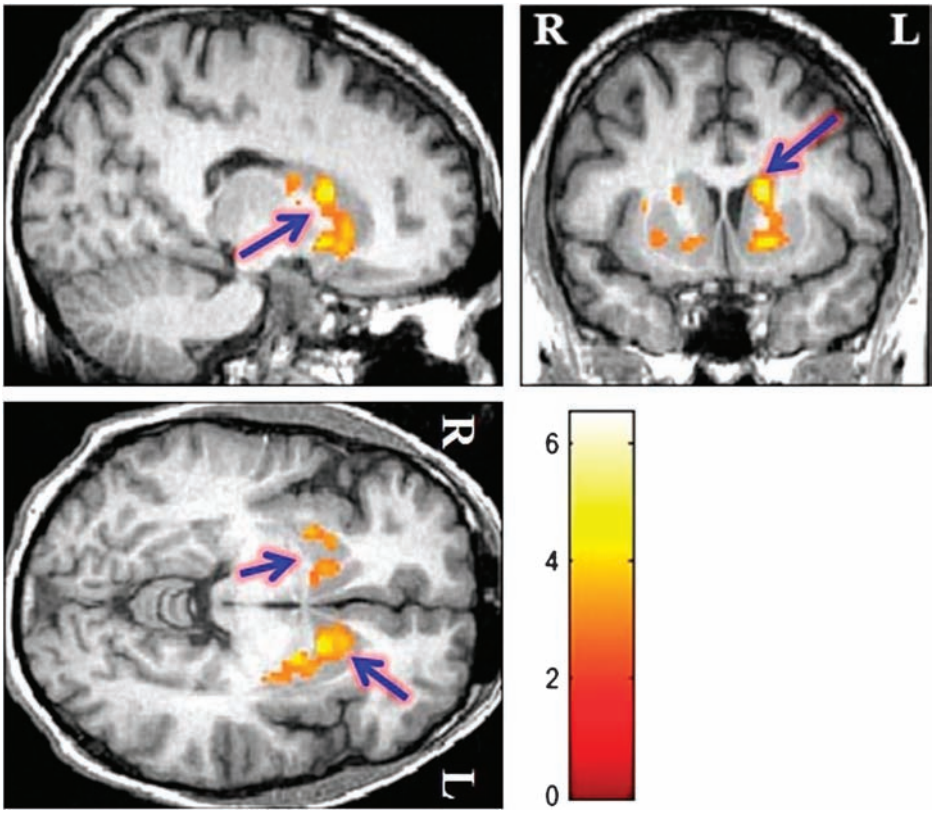

Figure 4. Smoking nicotine cigarettes reduced the BP_{ND} of [^{11}C]raclopride more in the left but also the right striatum ([16, 10, −6], [−20, 20, 0], radiological convention). (AftDenic-AftNic). $T = 6.51\text{-}3.01$, $P_{(\text{false discovery rate})} = .023–.044$. Extent threshold $k = 32$ voxel.

Besides nicotine, the major pharmacologically active ingredient, there are many other chemicals in tobacco smoke (Bernhard, 2011; Layten-Davis & Nielson, 1999; Rodgman & Perfetti, 2008; Schmeltz, 1995). Fowler, Volkow, Wang, Pappas, Logan, MacGregor, et al. (1996) and Fowler, Volkow, Wang, Pappas, Logan, Shea, et al. (1996) reported that tobacco smoke inhibits brain monoamine oxidase A and B, but exactly what chemical is responsible is still unclear. Clemens et al. (2009) found five

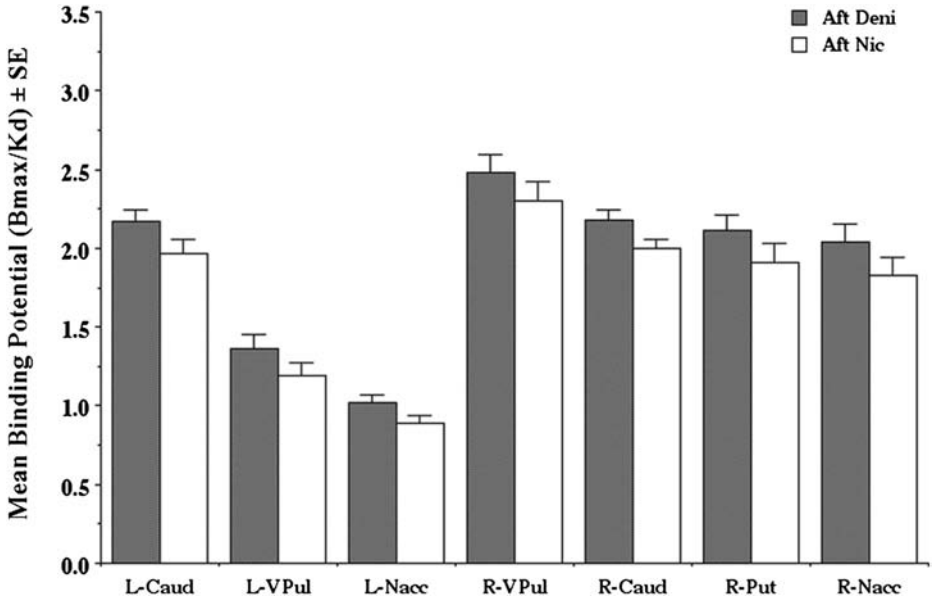

Figure 5. Lower binding potential nondisplaceable in regional striatal [^{11}C]raclopride binding in the left than the right brain hemisphere pre- and post- after nicotine than denicotinized tobacco smoking. More DA is released with nic than denic tobacco smoking in the left striatum. Abbreviations: Aft = after; L = left; R = right; Caud = dorsal caudate; VPut = ventral putamen; Put = dorsal putamen; Nacc = nucleus accumbens.

minor tobacco alkaloids that increase rat nicotine locomotor activity and nicotine self-administration. Rodd-Henricks et al. (2002) described the reinforcing effects of acetaldehyde (also in tobacco smoke) in the posterior tegmental area of alcohol preferring rats. Presumably, all of these substances are present equally in the smoke of the denic as well as nic cigarettes used and could be one explanation of the effects of denic tobacco smoking. Another could be the psychological cues surrounding cigarettes and other addictive substances that acquire value. This is central to many theories of addiction, most notably the incentive sensitization theory of addiction of Robinson and Berridge (1993). In real world situations, there are cues that surround and pervade the life of smokers such as time breaks, advertisements, etc. Cues are strongly linked to the maladaptive behavior of addicts to many different substances including tobacco (Berridge, 2000, 2007; Flagel, Akil, & Robinson, 2009; Jansen, 1998). Environmental cues have been shown to have the ability to motivate behavior and result in reward-seeking behaviors, including maintaining and reinstating nicotine or cocaine seeking behaviors in animal models of self-administration (Caggiula et al., 2001, 2002; De Wit & Stewart, 1981).

The results obtained with [^{11}C]raclopride binding confirm other reports in the literature but there were some surprises. Smoking denic cigarettes reduced [^{11}C]raclopride binding in the striatum as expected because of its cue-related smoking effects. One possibility is that the many chemicals in tobacco smoke with very small amounts of nicotine are important salience cues. Only some regions of the right hemisphere showed a significant increase in DA release with denic smoking when an uncorrected $p < .001$ was used. However, with a strict statistical criterion using a p_{FDR} corrected to $p < .02$, smoking nic cigarettes increased striatal DA release but more on the left, consistent with previous research (Brody et al., 2004). In the present study, only one region in the left caudate showed a weak ($p < .05$) correlation between an increase in plasma nicotine and increased DA release. Berridge, Espana, and Stalnaker (2004) described the brain asymmetry of DA efferents within the prefrontal cortex in regard to coping and stress in rodents. They suggested in humans that DA in the right hemisphere may play a unique role in affective and cognitive processes. Furthermore, right hemisphere damage in humans produces unique disorders of communication and cognition (Myers, 1999). In one word, the right brain is concerned with "gestalt."

The fact that nic smoking had marked bilateral striatal release effects, of which release DA in one area correlated with increased venous plasma nicotine, is further evidence of a pharmacological role of nicotine. Marti et al. (2011) found that tobacco smoke extracts that contain nicotine, as well as nicotine alone, enhance triggered DA ventral tegmental area neurons in anesthetized wild type (WT) mice, but weak and inhibitory firing occurred with tobacco extracts. In β2−/− knockout mice, nicotine or tobacco smoke had no effect on the firing patterns of DA neurons. However, the differences between DA neuron firing produced by tobacco extract/tobacco smoke or nicotine alone observed in the WT animals persisted in the α6−/− mice but not in the α4−/− mice. Marti et al. (2011) concluded that tobacco smoke or nicotine alone act through $\alpha_4\beta_2$ nicotinic cholinergic receptors (nAChRs) and that tobacco extract may contain unknown chemicals that antagonize the effects of nicotine. Whether denic cigarette smoke contains substances that affect α6−/− nAChRs needs further research.

Another important issue is whether the very low venous plasma nicotine levels after smoking denic cigarettes are sufficient to cause any brain effects. Brody et al. (2006) used the ^{18}F derivative of A-85380, a selective PET $\alpha_4\beta_2$ nicotine cholinergic ligand, to demonstrate the effects of tobacco smoking on brain nAChRs. Smoking just one regular tobacco cigarette produced more than 88% receptor occupancy. A venous plasma nicotine concentration of only 0.87 ng/ml produced 50% occupancy of $\alpha_4\beta_2$* (labeled) nAChR. Subsequently, Brody, Mandelkern, Costello, et al. (2009) reported in detail additional results that a denicotinized cigarette (0.05 mg) produced a 26% brain $\alpha_4\beta_2$ nAChR occupancy. By U.S. Food and Drug Administration regulations, radioactive ligands used in PET research cannot have a pharmacological effect. Since in our study the denic cigarettes produced venous plasma levels of 1–3 ng/ml, it is obvious that well more than 50% of the labeled nAChR receptors were occupied. Whether this percentage of radiolabeled nAChR produces a pharmacological effect is not known but is a possibility. It remains for experts with knowledge of AChR receptor states, such as high affinity, low affinity, overexpression, reserve, etc., and their relationship to intrinsic pharmacological activity to solve the conundrum Brody et al. have given us. Although the pharmacological effects of many drugs including nicotine are dose or concentration dependent, the effects are not linearly proportional to receptor occupancy. Some high affinity nAChRs may be occupied by nicotine but not sufficient to produce an effect. One must be cautious and not make assumptions concerning a response to nicotine based on its receptor binding. Hence, the very small amounts of nicotine present after denic cigarette smoking may bind some nAChRs but do not produce any release of DA as measured by ^{11}C-raclopride in contrast to nic tobacco smoking.

The use of [^{11}C]raclopride only provides information about the striatum, of which in humans, nucleus accumbens is not as prominent as in rodents. Small percent changes in the BP_{ND} of nucleus accumbens were observed, but the largest changes were in the dorsal striatum. Either very little DA was released or that [^{11}C]raclopride is a relatively insensitive radioligand. Although both denic and nic cigarette smoking reduced BP_{ND} in both right and left striata, the effects of denic were primarily on the right and those of nic were bilateral but more on the left. Neural responses (fMRI) to smoking cues vary as a function of both craving and expectancy and include more of the left than right hemisphere (McBride et al., 2006). Barrett et al. (2004) found the hedonic response to cigarette smoking was related to DA release using [^{11}C]raclopride in the left caudate and putamen but not in the ventral striatum. Brody, Mandelkern, Costello, et al. (2009) and Brody et al. (2010) found craving, anxiety, and mood improvements from smoking regular or denic cigarettes are correlated with right and left ventral striatal DA release. The present study only used the $DA_{2/3}$ radioligand [^{11}C] raclopride. Yasuno et al. (2007) used both [^{15}O] and [^{11}C] SCH 23390, the former to measure cerebral blood flow and the latter to measure D_1 receptor binding in cigarette craving. Cue activation was observed in the left ventral striatum. D_1 receptor binding in this region had a negative relationship (more DA release) with cue induced craving and rCBF.

A major limitation to the present study is the fact that only male smokers were studied. Perkins et al. (2006) found that

smoking behavior of women is more responsive to nonpharmacological factors than men. Both groups smoked denic as well as nic cigarettes. The authors found in women but not in men that accurate verbal information about the dose of nicotine in the two different cigarettes they smoked enhanced smoking reward and reinforcement. McClernon, Kozink, and Rose (2008) found in an fMRI study that women had greater cue reactivity than men in the cuneus (visual cortex) and left superior temporal gyrus. Craving was negatively correlated with cue reactivity in the left ventral striatum. Barrett (2010) found that smoking denic cigarettes induced more craving relief in females than male smokers. A sex difference in the genetics of the DA_2 receptor indicates that Black women are less likely to quit smoking than Black men if they possess a GTG haplotype (David et al., 2010). An additional limitation to the present research is the fact that denic tobacco cigarettes were smoked first. Relative novelty/familiarity in the scanner environment and smoking procedures could have influenced the results. A crossover, balanced experimental design of tobacco smoking would have been preferable. This was not done because it was postulated that denic smoking would result in a minor increase in plasma nicotine and that its brain effects would return quickly to the nicotine overnight abstinent state. This turned out not to be true because craving to smoke did not increase completely to its presmoking controls as hypothesized. Another limitation is that initial novelty in the scanner environment plus denic cigarette smoking first makes it problematic to determine which is more important for striatal DA release. First day exposure to the PET scanner produces slightly greater increases in plasma cortisol levels than on second day exposure (Xue et al., 2010). Furthermore, besides plasma nicotine, there are additional variables such as number of puffs or delta CO that reflect smoke inhalation that should be correlated with striatal DA release that were not done. Another issue that needs further study is that depending on the camera used, the test–retest of [^{11}C]raclopride varies and may be greater than the denic DA release. Finally, the present study involves a relatively small number of smokers. It needs replication with independent samples and a better experimental design.

The most important new finding of the present study is that denic cigarette smoking produced a significant release of DA in the striatum of the right hemisphere. This emphasizes that psychological or other nonnicotine pharmacological factors have important brain effects. Smoking nic cigarettes produced marked bilateral striatal DA release, but more in the left hemisphere. Maximum increases in venous plasma nicotine after smoking showed a concentration brain DA release relationship but only in the left caudate nucleus and, surprisingly, not in the ventral striatum/nucleus accumbens.

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Declaration of Interests

None declared.

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