Published in final edited form as:

Biol Psychiatry. 2009 November 1; 66(9): 898–901. doi:10.1016/j.biopsych.2009.06.011.

Effect of a History of Major Depressive Disorder on Smoking-Induced Dopamine Release

Arthur L. Brody, M.D.^{a,b,c}, Richard E. Olmstead, Ph.D.^b, Anna L. Abrams, B.S.^b, Matthew R. Costello, B.A.^{a,b}, Aliyah Khan, B.A.^{a,b}, Daniel Kozman, B.A.^{a,b}, Sanjaya Saxena, M.D.^d, Judah Farahi, Ph.D.^b, Edythe D. London, Ph.D.^{a,c,e}, and Mark A. Mandelkern, M.D., Ph.D.^{b,f}

^a UCLA Department of Psychiatry and Biobehavioral Sciences

^b Greater Los Angeles VA Healthcare System Positron Emission Tomography Center

^c UCLA Brain Research Institute

^d UCSD Department of Psychiatry

^e UCLA Department of Molecular and Medical Pharmacology

^f UCI Department of Physics

Abstract

Background—Dopamine (DA) system dysfunction is implicated in the pathophysiology of Major Depressive Disorder (MDD). We sought to determine if cigarette smokers with a history of MDD and current mild depressive symptoms have abnormal smoking-induced DA release (measured indirectly as change in ¹¹C-raclopride binding potential [BP_{ND}]).

Methods—Fifty-six cigarette smokers either with (n = 10) or without (n = 46) a history of MDD (MDD+ and MDD–, respectively) underwent bolus-plus-continuous-infusion ¹¹C-raclopride positron emission tomography, during which they smoked a regular cigarette. Pre- to post- smoking changes in ¹¹C-raclopride BP_{ND} were compared between groups. Also, correlations were determined between change in BP_{ND} and depression, anxiety, and withdrawal rating scale scores for the MDD + group.

Results—The MDD+ group had a significantly greater reduction in ¹¹C-raclopride BP_{ND} (–16.3%) than the MDD– group (–8.4%) (ANCOVA, p = 0.03). Significant negative correlations were found between depression/anxiety and change in ¹¹C-raclopride BP_{ND} (r = –0.77, p < 0.01 and r = –0.74, p = 0.01, respectively).

Conclusions—MDD+ smokers have greater smoking-induced DA release than MDD– smokers, and higher depression/anxiety levels are associated with greater smoking-induced DA release. These findings support the theory that MDD+ smokers have DA system dysfunction including heightened smoking-induced DA release.

Corresponding Author: Arthur L. Brody, M.D., UCLA Department of Psychiatry & Biobehavioral Sciences, 300 UCLA Medical Plaza, Suite 2200, Los Angeles, CA 90095, Telephone: 310-268-4778, Fax: 310-206-2802, Email: abrody@ucla.edu.

Financial Disclosures: The authors report no biomedical financial interests or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Tobacco Dependence; Major Depressive Disorder; Dopamine; ^{11}C -Raclopride; Positron Emission Tomography; Ventral Striatum

Background

Brain imaging studies of subjects with Major Depressive Disorder (MDD) suggest that MDD is associated with resting dopamine (DA) system dysfunction and heightened substance-induced DA release in the striatum. These studies have linked MDD with elevated levels of D2 receptor availability (a possible marker for decreased intrasynaptic DA concentration) (1, 2), a heightened reward response to amphetamine administration (3), and elevated monoamine oxidase A activity (which would be expected to lower intrasynaptic DA) (4). Although not all studies agree, low levels of the dopamine transporter have also been demonstrated in MDD (5,6), which could be a compensatory down-regulation in response to low intrasynaptic DA. In addition, a ^{11}C -raclopride positron emission tomography (PET) study found an association between elevated D2 receptor binding potential and motor retardation in MDD (7). Taken together, these findings suggest that subjects with MDD have low resting intrasynaptic DA (though the exact nature of DA dysfunction in MDD is not fully known), and that cigarette smokers with MDD might have greater DA release in response to smoking a cigarette than smokers without MDD.

For the present study, we hypothesized that cigarette smokers with a history of MDD and current mild depressive symptoms would have greater decreases in ^{11}C -raclopride binding potential (BP_{ND}) (an indirect marker of DA release) in response to smoking a cigarette than smokers with no history of MDD. Subjects with a history of (rather than a current episode of) MDD were studied here based on the desire to study subjects who were comparable to those with full MDD, but who were in a relatively stable mood state (where, for example, medication changes would not confound brain imaging results). We also sought to determine if these smokers with a history of MDD had associations between ^{11}C -raclopride BP_{ND} change and baseline depression/anxiety and/or withdrawal symptom improvement with smoking, as has been observed in non-depressed smokers (8–10).

Methods and Materials

Fifty-six otherwise healthy adult (21 to 65 years old) cigarette smokers either with ($n = 10$) or without ($n = 46$) a history of Major Depressive Disorder (MDD+ and MDD–, respectively) completed the study. Findings from the MDD– smokers were published recently (10), and inclusion/exclusion criteria, screening procedures, rating scales, and all PET and magnetic resonance imaging (MRI) scanning methodology were the same here as in our previous reports (8,10), except that one study group here consisted of a preliminary sample of MDD+ subjects who had not had an acute episode of MDD meeting DSM-IV criteria (11) for at least six months prior to study participation.

Participants underwent bolus-plus-continuous-infusion ^{11}C -raclopride PET scanning for 90 mins, during which they smoked a regular cigarette (favorite brand) outside the scanner between minutes 50 and 60. Demographic and other clinical variables were collected before scanning, and symptoms of tobacco withdrawal and smoking characteristics (Clinical Research Support System device, Plowshare, Baltimore, MD) were monitored during scanning. A structural MRI scan was obtained within one week of PET scanning to aid in brain region localization. Each participant received a description of the study, and gave written informed consent, using forms approved by the local IRB, before scanning.

While no MDD+ subjects met DSM-IV criteria for an acute depressive episode, these subjects did report between mild depressive symptoms (range = 1 to 4) at the time of PET scanning. Four subjects were taking antidepressants (stable dose > 2 months; 2 taking serotonin reuptake inhibitors, 1 taking venlafaxine, and 1 taking bupropion).

To verify similarities in demographic and rating scale variables between groups at baseline, unpaired Student t-tests and a Chi-Square test (for gender) were performed. To compare groups in clinical responses to smoking during scanning, unpaired Student t-tests were performed for changes in withdrawal symptoms from before to after smoking.

For PET data, changes in ^{11}C -raclopride binding potential (BP_{ND}) from before to after smoking were compared between groups with an ANCOVA, with BP_{ND} percent change as the dependent measure, group (MDD+ vs. MDD-) as the between-subject factor, and age, gender, and total cigarette puff volume as covariates. Even though the groups did differ significantly in these covariates (see results below), these variables were included in the analysis, because of prior reports linking them with differences in DA system function (see (10) for review information). Because of concern that taking an antidepressant might affect smoking-induced DA release, an ANCOVA with the same design as above was also run excluding those MDD+ subjects who were taking an antidepressant at the time of scanning.

For the MDD+ group, Pearson Product Moment Correlation Coefficients were determined between BP_{ND} percent change and pre-smoking Hamilton Depression and Anxiety (HAM-D and HAM-A) Scale scores, to establish if baseline depression and anxiety levels were associated with smoking-induced DA concentration change. Correlation coefficients were also determined between BP_{ND} percent change and percent change in craving (Urge to Smoke [UTS] scale), state anxiety (Spielberger State Trait Anxiety Index [STAI]), and mood analog scores with smoking, to determine relationships between DA concentration change and withdrawal alleviation. Statistical tests were performed with SPSS version 16.0 (SPSS; Chicago, IL).

Results

Clinical Results

The MDD+ and MDD- groups did not differ significantly in demographic variables (Table 1); however, they did differ in HAM-D and HAM-A scores at baseline, with the MDD+ group having mild depressive and anxiety symptoms and the MDD- group having very few depressive and anxiety symptoms (Table 1). The groups also differed in response to smoking a cigarette on the mood analog scale, with the MDD+ group having a small mean worsening and the MDD- group having improvement in mood (Table 1).

The groups did not significantly differ in smoking characteristics. For the MDD+ and MDD- groups, total puff volume (1022.8 ± 63.5 vs. 886.4 ± 44.0 mL, respectively), number of puffs (19.0 ± 1.8 vs. 17.3 ± 1.2 , respectively), and average puff volume (59.5 ± 5.3 vs. 57.3 ± 2.7 mL, respectively) were similar (unpaired Student t-tests, non-significant).

PET Results

The MDD+ group had a significantly greater mean reduction in ^{11}C -raclopride BP_{ND} ($-16.3 [\pm 2.3]\%$) than the MDD- group ($-8.4 [\pm 1.5]\%$) (ANCOVA, $df = 1, 51$, $F = 5.0$, $p = 0.03$) (Figure 1), indicating that smokers with a history of MDD have greater smoking-induced DA release than those without such a history. This result was still significant when the MDD+ subjects who were taking an antidepressant at the time of scanning were excluded (mean BP_{ND} change for this subgroup was $2.06 [\pm 0.19]$ to $1.70 [\pm 0.19]$ or $-17.6 [\pm 3.42]\%$; ANCOVA, $df = 1, 47$, $F = 4.0$, $p = 0.05$). Baseline raclopride BP_{ND} did not differ between

study groups (2.17 ± 0.16 for the MDD+ group versus 2.26 ± 0.07 for the MDD- group; Student's t-test, n.s.).

For the MDD+ group, there were significant negative correlations between smoking-induced change in ^{11}C -raclopride BP_{ND} and baseline HAM-D and HAM-A scores (correlation coefficients, $r = -0.77$, $p < 0.01$ and $r = -0.74$, $p = 0.01$, respectively), indicating that greater smoking-induced DA release was associated with greater pre-scan depression/anxiety levels. There were no significant correlations between ^{11}C -raclopride BP_{ND} change and UTS, STAI, or analog mood scale change scores.

Discussion

Smokers with a history of MDD have greater smoking-induced displacement of ^{11}C -raclopride (an indirect marker for DA release) than smokers without such a history, and this relationship was significant even after controlling for factors that could potentially affect DA release (such as age, gender, amount of a cigarette smoked, and antidepressant treatment). The 16.3% ^{11}C -raclopride displacement found here with smoking a cigarette in MDD+ smokers is more than the 8–10% seen with cigarette smoking in prior studies (8,10,12) and less than the 20–31% decrease found with cocaine (13,14) or amphetamine (15,16) administration in studies using similar methodology.

This central finding supports the theory that MDD+ smokers have striatal dopaminergic dysfunction and heightened smoking-induced DA release. While subjects here did not meet full criteria for an episode of MDD, all MDD+ subjects had depressive symptoms and a history of at least one full episode of MDD, indicating some comparability of these subjects to those who participated in prior studies of MDD. As noted above, prior brain imaging studies indicate that subjects with MDD have dopaminergic dysfunction, and our prior research indicates that MDD- smokers who are genetically predisposed to having low resting intrasynaptic DA have heightened smoking-induced DA release (8). Thus, the current study extends prior reports to include responses to cigarette smoking and DA release in MDD+ smokers.

The correlations here linking greater depression and anxiety with heightened smoking-induced DA release also support this theory, as does other research indicating that low resting DA tone is associated with high phasic DA release (17). Furthermore, these findings may be specific to cigarettes (or to a drug to which one is already addicted), since one prior study did not demonstrate abnormalities in amphetamine-induced DA release in subjects with MDD who were not amphetamine-dependent (18). Given the rewarding property of DA release, the combination of low resting DA tone and heightened smoking-induced DA release may help explain why MDD+ smokers have more difficulty quitting than non-depressed smokers (19, 20).

Acknowledgments

Supported by a National Alliance for Research on Schizophrenia and Depression Independent Investigator Award (A.L.B.), the Tobacco-Related Disease Research Program (A.L.B. [11RT-0024 and 16RT-0098], the National Institute on Drug Abuse (A.L.B. [R01s DA15059 and DA20872]), a Veterans Administration Merit Review Type I Award (A.L.B.), the National Institute of Mental Health (S.S. [R01 MH69433]), and the Office of National Drug Control Policy (E.D.L. [DABT63-00-C-1003]). The authors thank Josephine Ribe and Michael Clark for technical support in performing positron emission tomography and magnetic resonance imaging scans, respectively.

Reference List

1. D'haenen HA, Bossuyt A. Dopamine D2 receptors in depression measured with single photon emission computed tomography. *Biol Psychiatry* 1994;35:128–132. [PubMed: 8167208]

2. Shah PJ, Ogilvie AD, Goodwin GM, Ebmeier KP. Clinical and psychometric correlates of dopamine D2 binding in depression. *Psychol Med* 1997;27:1247–1256. [PubMed: 9403896]
3. Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE. Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. *Arch Gen Psychiatry* 2002;59:409–416. [PubMed: 11982444]
4. Meyer JH, Ginovart N, Boovariwala A, Sagrati S, Hussey D, Garcia A, et al. Elevated monoamine oxidase A levels in the brain: an explanation for the monoamine imbalance of major depression. *Arch Gen Psychiatry* 2006;63:1209–1216. [PubMed: 17088501]
5. Meyer JH, Kruger S, Wilson AA, Christensen BK, Goulding VS, Schaffer A, et al. Lower dopamine transporter binding potential in striatum during depression. *Neuroreport* 2001;12:4121–4125. [PubMed: 11742250]
6. Sarchiapone M, Carli V, Camardese G, Cuomo C, Di GD, Calcagni ML, et al. Dopamine transporter binding in depressed patients with anhedonia. *Psychiatry Res* 2006;147:243–248. [PubMed: 16952448]
7. Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP, et al. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [¹¹C]raclopride positron emission tomography study. *Am J Psychiatry* 2006;163:1594–1602. [PubMed: 16946186]
8. Brody AL, Mandelkern MA, Olmstead RE, Scheibal D, Hahn E, Shiraga S, et al. Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Arch Gen Psychiatry* 2006;63:808–816. [PubMed: 16818870]
9. Montgomery AJ, Lingford-Hughes AR, Egerton A, Nutt DJ, Grasby PM. The effect of nicotine on striatal dopamine release in man: A [¹¹C]raclopride PET study. *Synapse* 2007;61:637–645. [PubMed: 17492764]
10. Brody AL, Mandelkern MA, Olmstead RE, Allen-Martinez Z, Scheibal D, Abrams AL, et al. Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology* 2009;34:282–289. [PubMed: 18563061]
11. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition (SCID-I/P, version 2.0). 1995
12. Scott DJ, Domino EF, Heitzeg MM, Koeppe RA, Ni L, Guthrie S, et al. Smoking modulation of mu-opioid and dopamine D2 receptor-mediated neurotransmission in humans. *Neuropsychopharmacology* 2007;32:450–457. [PubMed: 17091130]
13. Park MH, Park EH. Synaptic concentration of dopamine in rat striatal slices in relationship to [³H] raclopride binding to the dopamine D2 receptor. *Arch Pharm Res* 2000;23:360–366. [PubMed: 10976584]
14. Volkow ND, Fowler JS, Gatley SJ, Dewey SL, Wang GJ, Logan J, et al. Comparable changes in synaptic dopamine induced by methylphenidate and by cocaine in the baboon brain. *Synapse* 1999;31:59–66. [PubMed: 10025684]
15. Drevets WC, Price JC, Kupfer DJ, Kinahan PE, Lopresti B, Holt D, et al. PET measures of amphetamine-induced dopamine release in ventral versus dorsal striatum. *Neuropsychopharmacology* 1999;21:694–709. [PubMed: 10633475]
16. Carson RE, Breier A, de Bartolomeis A, Saunders RC, Su TP, Schmall B, et al. Quantification of amphetamine-induced changes in [¹¹C]raclopride binding with continuous infusion. *J Cereb Blood Flow Metab* 1997;17:437–447. [PubMed: 9143226]
17. Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-o-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology* 2004;29:1943–1961. [PubMed: 15305167]
18. Parsey RV, Oquendo MA, Zea-Ponce Y, Rodenhiser J, Kegeles LS, Pratap M, et al. Dopamine D(2) receptor availability and amphetamine-induced dopamine release in unipolar depression. *Biol Psychiatry* 2001;50:313–322. [PubMed: 11543733]
19. Agrawal A, Sartor C, Pergadia ML, Huizink AC, Lynskey MT. Correlates of smoking cessation in a nationally representative sample of U.S. adults. *Addict Behav* 2008;33:1223–1226. [PubMed: 18501526]
20. Berlin I, Covey LS. Pre-cessation depressive mood predicts failure to quit smoking: the role of coping and personality traits. *Addiction* 2006;101:1814–1821. [PubMed: 17156181]

Figure 1.

Representative ¹¹C-raclopride positron emission tomography (PET) scans from four study subjects showing mean radioactivity before and after smoking a single cigarette (favorite brand) for cigarette smokers with or without a history of Major Depressive Disorder (MDD+ and MDD-, respectively). MDD+ smokers had greater mean displacement of ¹¹C-raclopride (an indirect marker for dopamine release) than MDD- smokers.

Table 1
Demographic, Rating Scale, and Positron Emission Tomography Data

Variable	Total Group (n = 56)	MDD+ (n = 10)	MDD- (n = 46)	P Value (MDD+ vs. MDD-)
Age, years	41.0 ($\pm$ 1.5)	38.4 ($\pm$ 3.1)	41.6 ($\pm$ 1.7)	n.s.
% female	33.9%	30.0%	34.8%	n.s.
Cigarettes/day	24.7 ($\pm$ 0.9)	23.9 ($\pm$ 2.0)	24.9 ($\pm$ 1.0)	n.s.
Years smoking	22.6 ($\pm$ 1.5)	18.8 ($\pm$ 3.2)	23.5 ($\pm$ 1.7)	n.s.
Education (yrs)	13.7 ($\pm$ 0.3)	13.4 ($\pm$ 0.5)	13.8 ($\pm$ 0.3)	n.s.
FTND	6.5 ($\pm$ 0.3)	7.0 ($\pm$ 0.6)	6.4 ($\pm$ 0.3)	n.s.
HAM-D	2.3 ($\pm$ 0.4)	6.3 ($\pm$ 1.3)	1.5 ($\pm$ 0.3)	< 0.0001
HAM-A	2.6 ($\pm$ 0.4)	6.9 ($\pm$ 1.5)	1.7 ($\pm$ 0.3)	< 0.0001
Exhaled CO (ppm)	18.3 ($\pm$ 1.4)	22.0 ($\pm$ 3.7)	17.5 ($\pm$ 1.5)	n.s.
Total Puff Volume (mL)	910.8 ($\pm$ 38.3)	886.4 ($\pm$ 44.0)	1022.8 ($\pm$ 62.5)	n.s.
% Change UTS with Smoking	-74.5 ($\pm$ 3.5)	-67.7 ($\pm$ 11.5)	-76.0 ($\pm$ 3.5)	n.s.
% Change STAI with Smoking	-20.6 ($\pm$ 16.4)	4.8 ($\pm$ 20.1)	-26.1 ($\pm$ 19.5)	n.s.
% Change Mood with Smoking	10.7 ($\pm$ 5.1)	-9.8 ($\pm$ 4.2)	15.2 ($\pm$ 6.0)	0.05
Binding Potential (BP _{ND}) Pre-Smoking	2.2 ($\pm$ 0.1)	2.2 ($\pm$ 0.2)	2.3 ($\pm$ 0.1)	n.s.
BP _{ND} Post-Smoking	2.0 ($\pm$ 0.1)	1.8 ($\pm$ 0.2)	2.1 ($\pm$ 0.1)	n.s.
% Change in BP _{ND}	-9.8 ($\pm$ 1.3)	-16.3 ($\pm$ 2.3)	-8.4 ($\pm$ 1.5)	<0.05

Values are stated as mean ($\pm$ standard error of the mean); P values are for unpaired Student t-tests between the groups with (MDD+) and without (MDD-) a history of Major Depressive Disorder; n.s. = non-significant; yrs = years; FTND = Fagerström Test for Nicotine Dependence; HAM-D = Hamilton Depression Rating Scale (17-item); HAM-A = Hamilton Anxiety Rating Scale; CO = exhaled carbon monoxide; ppm = parts per million; UTS = Urge to Smoke Scale; STAI = Spielberger State-Trait Anxiety Index state anxiety questions total score; Mood = mood analog rating scale score.