Article

Amphetamine-Induced Dopamine Release: Markedly Blunted in Cocaine Dependence and Predictive of the Choice to Self-Administer Cocaine

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Objective: Dopamine is an important mediator of the reinforcing effects of cocaine, and alterations in dopamine function might be involved in cocaine dependence. The goals of the present study were to characterize pre- and postsynaptic dopamine function in recently detoxified cocaine-dependent subjects. Specifically, dopamine response to an acute amphetamine challenge was assessed in striatal subregions in cocaine-dependent and healthy comparison participants using positron emission tomography (PET). Furthermore, the relationship between this dopamine response and the choice to self-administer cocaine in a laboratory model of relapse was investigated.

Method: Twenty-four cocaine-dependent participants and 24 matched healthy subjects underwent [^{11}C]raclopride scans under a baseline condition and following intravenous amphetamine administration (0.3 mg/kg). Cocaine-dependent participants also completed cocaine self-administration sessions in which a priming dose of cocaine was followed by the choice to either self-administer subsequent cocaine doses or receive a monetary reward.

Results: Cocaine dependence was associated with a marked reduction in amphetamine-induced dopamine release in each of the functional subregions of the striatum (limbic striatum: −1.2% in cocaine-dependent participants versus −12.4% in healthy subjects; associative striatum: −2.6% versus −6.7%, respectively; sensorimotor striatum: −4.3% versus −14.1%). Blunted dopamine transmission in the ventral striatum and anterior caudate was predictive of the choice for cocaine over money.

Conclusions: Cocaine dependence is associated with impairment of dopamine function, and this impairment appears to play a critical role in relapse.

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Preclinical models of cocaine dependence have shown that maladaptive changes in dopamine transmission of the striatum play a critical role in this disorder. However, the significance of these changes has yet to be fully understood in humans. Positron emission tomography (PET) and the dopamine type 2 and 3 receptor ($D_{2/3}$) radiolabeled antagonist [^{11}C]raclopride can be used to measure changes in extracellular dopamine in the human brain. The administration of a psychostimulant is associated with an increase in endogenous dopamine and a reduction in the binding of [^{11}C]raclopride. Thus the comparison of pre- and postamphetamine scans provides a measure of in vivo dopamine release (1).

A previous study by Volkow et al. (2) performed in human cocaine-dependent volunteers demonstrated a reduction in methylphenidate-induced dopamine release in the striatum, consistent with a loss of presynaptic dopamine function. This study was performed measuring the striatum as a whole, so the first goal of the present study was to replicate this finding with a high-resolution PET camera that allows investigation of dopamine transmission in limbic, associative, and sensorimotor subdivisions of the striatum.

The clinical significance of this deficit of dopamine transmission was also investigated using a behavioral model of relapse. In animals, a response-independent ("priming") dose of cocaine has been shown to reinstate cocaine self-administration (3–5). Using a similar laboratory model, we can investigate the effect of a priming dose of cocaine on the choice to self-administer cocaine in human participants (6, 7). Thus, the second goal of this study was to investigate the association between deficits in presynaptic dopamine and the choice for cocaine in this model of relapse.

The hypotheses of this study were 1) cocaine dependence would be associated with a reduction in amphetamine-induced dopamine release across the subdivisions of the striatum, and the decrease would be most pronounced in the limbic striatum, and 2) the loss of amphetamine-induced dopamine release in the limbic striatum

This article is discussed in an editorial by Drs. Cohen and Carlezon on p. 543.

would be associated with the choice to self-administer cocaine.

Method

The study was approved by the institutional review board of the New York State Psychiatric Institute. All participants provided written informed consent. The cocaine-dependent participants fulfilled DSM-IV criteria for cocaine dependence with no other axis I diagnosis. Cocaine-dependent participants were not treatment seeking and were admitted to the Irving Center for Clinical Research. PET scans were performed after a minimum of 14 days of abstinence and cocaine self-administration sessions occurred after the PET scans. Healthy comparison participants had no DSM-IV axis I disorder and participated as outpatients. Nicotine dependence was acceptable for both groups.

PET Scan Analysis

[^{11}C]Raclopride was administered as a bolus with constant infusion, and the PET scans were acquired on the ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tenn.) in 3-dimensional mode as eight frames of 5 minutes each (obtained from 40–80 minutes) as previously described (8). All participants underwent two scans with [^{11}C]raclopride: baseline and following intravenous administration of amphetamine (0.3 mg/kg). An MRI (GE 1.5-T Signa Horizon) was acquired for each participant for identification of the regions of interest (8). Four venous samples were analyzed to obtain the plasma concentration of unmetabolized [^{11}C]raclopride (CI/ml) as previously described (8). [^{11}C]Raclopride clearance (liters/hour), free fraction (f_1), and plasma amphetamine levels were measured as previously described (9, 10).

Following amphetamine administration, vital signs were acquired at baseline and at regular intervals as previously described (11). The area under the curve of the change from baseline was calculated for systolic blood pressure, diastolic blood pressure, and heart rate. The subjective response to amphetamine was evaluated using a simplified version of the Amphetamine Interview Rating Scale, in which euphoria, energy, restlessness, and anxiety were rated on a scale of 1 (least) to 10 (most) as previously described (11).

PET Outcome Measures

$D_{2/3}$ receptor availability was estimated for the pre- and postamphetamine scans using two outcome measures: [^{11}C]raclopride binding potential (ml/g), defined as:

$$BP = V_{T\,ROI} - V_{T\,CER} = f_1 * \frac{B_{MAX}}{K_D'}$$

and the specific-to-nonspecific partition coefficient (V_3'', unitless), defined as:

$$V_3'' = \frac{V_{T\,ROI} - V_{T\,CER}}{V_{T\,CER}} = f_2 * \frac{B_{MAX}}{K_D'}$$

where V_T is the tissue distribution volume for the regions of interest ($V_{T\,ROI}$) and cerebellum ($V_{T\,CER}$), f_2 is the free fraction in the nonspecific distribution volume, B_{max} is the concentration of $D_{2/3}$ receptors, and K'_D is the in vivo equilibrium dissociation constant of the radiotracer in the presence of dopamine (12).

The reduction in D_2 receptor availability following amphetamine ($\Delta V_3''$) was calculated as:

$$\Delta V_3'' = (V_3''baseline - V_3''postamphetamine)/V_3''baseline$$

Region of Interest Analysis

Image analysis was performed in MEDx (Sensor Systems, Inc., Sterling, Va.). The regions of interest were drawn on each subject's MRI, and PET-to-MRI registration was performed as previously described (8). The striatum was divided as previously described (11) into the caudate, putamen, and ventral striatum. The caudate and putamen were further subdivided along their rostral-caudal axis using the anterior commissure to derive the following regions of interest: 1) precommissural dorsal caudate, 2) precommissural dorsal putamen, 3) the postcommissural caudate, and 4) the postcommissural putamen. These regions of interest were then classified into the three following functional subdivisions: 1) *the limbic striatum*, which receives input from limbic structures and includes the nucleus accumbens (also referred to as the ventral striatum); 2) *the associative striatum*, which is largely involved in cognition and includes the precommissural dorsal caudate, precommissural dorsal putamen, and postcommissural caudate; and 3) *the sensorimotor striatum*, which mostly receives input from motor and premotor areas and includes the postcommissural putamen.

The outcome measures for the associative striatum were calculated from the weighted average of the precommissural dorsal caudate, postcommissural caudate, and precommissural dorsal putamen, while the outcome measures for the striatum were calculated as the weighted average of all five regions of interest. Because of limitations in PET camera resolution, the activity measured in a given region of interest includes activity from adjacent regions, which result in error due to partial volume effects. In order to address this error, partial volume effect correction was performed as described previously (13) and in the data supplement that accompanies the online version of this article.

Voxel-Wise Analysis

V_3'' images were formed from the MRI-coregistered PET data and derived from the equation: (mean PET voxel value over scanning period/mean cerebellum activity over scanning period) – 1. The individual MRI images were normalized to the MNI T1 template with nonlinear warping using Statistical Parametric Mapping 1999 (SPM99) (14). The transformation parameters were then applied to the V_3'' images (pre- and postamphetamine) to obtain a set of spatially normalized V_3'' images. $\Delta V_3''$ images were then formed as 1 – (amphetamine condition/control condition). Prior to the statistical analysis, data were smoothed with a 6-mm isotropic Gaussian kernel.

Self-Administration Sessions

The cocaine-dependent participants completed two types of cocaine self-administration sessions: sample sessions and choice sessions. In the sample sessions, the participants self-administered a single dose of smoked cocaine (three sessions of 0, 6, or 12 mg of cocaine) and were asked to rate the subjective effects as previously described (15). Visual analogue scales were used to measure the subjective effects of "good drug effect," "high," and "stimulated" which were grouped into the positive effects cluster (6).

Each cocaine-dependent participant also underwent three cocaine self-administration sessions with 0 mg, 6 mg, and 12 mg doses, as previously described (6, 7). Each session began with a response-independent or "priming" dose of cocaine. Following this dose, participants were given five choices between smoking the same dose of cocaine or receiving a $5.00 merchandise voucher redeemable at local stores and paid upon discharge. The outcome measure for the choice sessions was the number of times a dose of cocaine was chosen over the voucher (range from 0 to 5).

TABLE 1. PET Scan Parameters

	Baseline Scan				Amphetamine Scan			
	Healthy Subjects		Cocaine-Dependent Participants		Healthy Subjects		Cocaine-Dependent Participants	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Injected dose (mCi)	13.6	3.5	12.8	3.9	12.4	3.4	12.8	3.6
Specific activity (Ci/mmol)	1549	701	1579	924	1473	653	1528	630
Clearance (liter/hour)	12.1	3.4	12.8	2.3	11.7	3.3	12.2	2.3
Plasma free fraction (f_1, %)	3.8	0.8	3.5	0.6	3.6	0.9	0.35	0.05
Tissue distribution volume, cerebellum (ml/g)	0.39	0.07	0.39	0.04	0.36	0.07	0.37	0.05
Cerebellum free fraction (f_2, %)	10.0	2.3	8.9	1.6	10.1	2.9	9.3	1.4
Amphetamine level (ng/ml)					49.9	13.6	47.5	15.8

Statistical Analysis

Group demographic comparisons were performed with unpaired t tests. Group differences in pre- and postamphetamine $D_{2/3}$ receptor availability as well as differences in reduction in $D_{2/3}$ receptor availability following amphetamine were analyzed with a repeated measures ANOVA, with the region of interest as the repeated measure and diagnostic group as the cofactor. The use of binding potential for between-group comparisons assumes that f_1 is not significantly different between groups, whereas the use of V_3'' assumes that f_2 is not significantly different between groups (12). For the between-group analyses, f_1, binding potential, and V_3'' were measured to assess the validity of these assumptions. For the within-subject analysis, V_3'' provides a more robust outcome measure (16), so $\Delta V_3''$ was chosen a priori to assess the amphetamine-induced reduction in $D_{2/3}$ receptor availability. For voxelwise analysis, the analysis was restricted to voxels in which $V_3'' \geq 1$ in the baseline condition. Multiple comparison corrections were performed according to the Gaussian random field model employed in the SPM99 software.

Results

Twenty-four cocaine-dependent subjects (19 men and five women, mean age=39 years [SD=3]) and 24 healthy comparison subjects (19 men and five women, mean age=38 years [SD=5]) were enrolled in this study. Seventeen of the subjects from each group were included in a previous study that included only the baseline scan with [^{11}C]raclopride (7). Subjects were matched for ethnicity (healthy group: African-American [N=12], Caucasian [N=7], Hispanic [N=5]; cocaine-dependent group: African-American [N=16], Caucasian [N=4], Hispanic [N=4]) and cigarette smoking (the comparison group smoked on average 12 cigarettes/day [SD=6] and included six nonsmokers and three ex-smokers; the cocaine-dependent group smoked on average 11 cigarettes/day [SD=4] and included four nonsmokers and three ex-smokers). The cocaine-dependent subjects reported smoking crack cocaine an average of 16.1 years (SD=4.4) and were spending $280 weekly (SD=108).

PET Scan Parameters

Table 1 shows the [^{11}C]raclopride scan parameters for the two groups. The volumes of the regions of interest did not differ between the two groups (all $p>0.20$). Although there was no significant difference for cerebellar tissue distribution volume between the two groups before or after amphetamine, there was a small but significant decrease after amphetamine when the data for the two groups was pooled ($p<0.001$, paired t test) with no significant difference in f_2 ($p=0.53$).

Baseline $D_{2/3}$ Receptor Availability

Repeated-measures ANOVA revealed that cocaine dependence was associated with significantly lower baseline [^{11}C]raclopride binding potential (region factor: $p<0.001$; group factor: $p=0.014$; group-by-region interaction: $p=0.009$) and V_3'' (region factor: $p<0.001$; group factor: $p=0.001$; group-by-region interaction: $p=0.0015$), as shown in Table 2. These decreases in baseline binding potential and V_3'' were similar for each of the regions of interest except for the postcommissural caudate. Data corrected for the partial volume effects provided the same results and are presented in the supplement that accompanies the online version of this article.

Amphetamine-Induced Reduction in $D_{2/3}$ Receptor Availability

Repeated-measures ANOVA revealed that cocaine dependence was associated with a blunted effect of amphetamine on [^{11}C]raclopride V_3'' (region factor: $p<0.0001$; group factor: $p=0.0009$; group-by-region interaction: $p<0.0001$ [Table 3]). In the caudate, $\Delta V_3''$ was reduced in the cocaine-dependent participants relative to the comparison subjects, but this difference did not reach significance in either the precommissural dorsal caudate or postcommissural caudate. Similar results were seen following correction for partial volume effects (supplemental data). Post hoc examination showed that dopamine release was blunted to a greater degree in the limbic striatum in cocaine-dependent relative to healthy subjects compared with each of the regions of the associative striatum (all $p<0.04$), but that there was no difference between the ventral striatum and posterior putamen ($p=0.20$).

Cocaine dependence was associated with a lower subjective rating of euphoria in response to amphetamine relative to healthy subjects (1.7 [SD=60.5] versus 38.1 [SD=63.8], respectively; $p<0.04$), with no between-group differences in restlessness, anxiety, or energy. No association was seen between $\Delta V_3''$ and the subjective effects of amphetamine for both the healthy controls and cocaine dependent subjects. As shown in Table 4, no difference in