Amphetamine-Induced Increases in Extracellular Dopamine, Drug Wanting, and Novelty Seeking: A PET/[¹¹C]Raclopride Study in Healthy Men

Marco Leyton, Isabelle Boileau, Chawki Benkelfat, Mirko Diksic, Glen Baker, and Alain Dagher

Eight healthy men underwent two positron emission tomography (PET) [¹¹C]raclopride scans, one following placebo, the second following d-amphetamine (0.30 mg/kg, p.o.). PET data were analyzed using: (1) brain parametric maps to statistically generate regions of significant change; and (2) a priori identified regions of interest (ROI) manually drawn on each individual's co-registered magnetic resonance (MR) images. Compared with placebo, d-amphetamine decreased [¹¹C]raclopride binding potential (BP) with significant effects in ventral but not dorsal striatum. Change in BP in the statistically generated cluster correlated with self-reported drug-induced 'drug

wanting' (r = 0.83, p = .01) and the personality trait of Novelty Seeking-Exploratory Excitability (r = 0.79, p = .02). The same associations were seen in the manually drawn ROI in ventral striatum but not in dorsal putamen or caudate. Changes in extracellular dopamine (DA) did not correlate with mood. Mesolimbic DA might mediate interest in obtaining reward rather than reward, per se. Individual differences in amphetamine-induced DA release might be related to predispositions to drug and novelty seeking. [Neuropsychopharmacology 27:1027–1035, 2002] © 2002 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

KEY WORDS: Addiction; Reward; Reinforcement; Nucleus accumbens

Preclinical studies indicate that psychostimulant drugs increase extracellular dopamine (DA) levels with preferential effects in ventral striatum (Di Chiara and Imperato 1988). The behavioral significance of in-

creased DA, though, remains a subject of debate. One influential theory suggests that mesolimbic DA mediates rewarding, possibly pleasurable effects of addictive drugs (Wise 1982). Other work suggests that DA signals interest in rewards (Stewart et al. 1984), the expectation that a reward is forthcoming (Schultz 1998), or wanting reward as opposed to liking it (Robinson and Berridge 1993).

Significant individual variability in stimulant drug-induced DA release is apparent. Some evidence suggests that this variability reflects a pre-existing trait. Predictors of the variability include elevated exploratory behavior in novel environments (Hooks et al. 1991), high levels of sugar feeding (Sills and Crawley 1996), and a predisposition to rapidly acquire drug self-administration (Zocchi et al. 1998).

In humans, psychostimulant drugs of abuse elicit a range of behavioral effects, including mood elevation

From the Department of Psychiatry (ML, IB, CB) and Montreal Neurological Institute (IB, CB, MD, AD), McGill University, Montréal, Québec, Canada, and Department of Psychiatry, Mackenzie Centre, University of Alberta, Edmonton, Alberta, Canada (GB).

Address correspondence to: Marco Leyton, Ph.D., Department of Psychiatry, McGill University, 1033 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1. Tel.: (514) 398-5804; Fax: (514) 398-4866; E-mail: marco.leyton@mcgill.ca

Received January 16, 2002; revised April 29, 2002; accepted May 2, 2002.

Online publication: 5/3/02 at www.acnp.org/citations/Npp050302301.

and increased drug wanting (Uhlenhuth et al. 1981; Jaffe et al. 1989; Cousins et al. 2001). Functional neuroimaging studies with labeled D2/D3 benzamide ligands suggest that 0.2 to 0.3 mg/kg of d-amphetamine given intravenously increases extracellular DA levels in human striatum (Laruelle et al. 1995; Breier et al. 1997; Drevets et al. 2001). The magnitude of the drug-induced DA release correlates with self-reported euphoria (Laruelle et al. 1995; Drevets et al. 2001); however, it remains unclear whether the mood-elevation is mediated by DA or instead reflects other effects of the drug. High amphetamine doses increase both catecholamine and serotonin release whereas lower doses primarily increase catecholamines (Kuczenski and Segal 1989). Mood-elevating effects of cocaine are reported to be reduced by lowering serotonin transmission (Aronson et al. 1995). In comparison, stimulant drug-induced mood elevation is not decreased consistently by DA antagonists (Brauer and de Wit 1997).

The present study addressed three questions. First, could a relatively low oral dose of d-amphetamine elicit detectable changes in [¹¹C]raclopride binding? Second, would the effect on extracellular DA be larger in ventral than in dorsal striatum? Third, would amphetamine-induced increases in extracellular DA be related to subjective effects of the drug or the personality trait of novelty seeking?

METHODS

Subjects

Eight non-smoking men (Table 1) were recruited using newspaper advertisements. All were healthy, as determined by a physical exam, standard laboratory tests, and an interview using the Structured Clinical Interview for DSM-IV (First et al. 1995). None had a personal or first-degree relative history of axis I psychiatric disorders. On the day of each positron emission tomography (PET) scan, all tested negative on a urine drug screen sensitive to cocaine, opiates, phencyclidine, lysergic acid diethylamide, Δ^9 -tetrahydrocannabinol, and amphetamines (Triage Panel for Drugs of Abuse, Biosite Diagnosis©, San Diego, CA). The study was carried out in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Montreal Neurological Institute. All subjects gave informed written consent.

PET and MRI

Subjects underwent two scans on separate days on a Siemens ECAT HR+ PET camera (approximate resolution 4.2 mm full width half maximum in center of field of view) with lead septa removed. Sixty minutes before tracer injection, a catheter was inserted into the subject's

Table 1. Subject Characteristics

Age	23.8±4.1 (range 19–30)
Current alcohol use (drinks / week)	1.97±1.4 (range 0.25–5)
Lifetime drug use (ever used, mean ± SD)	
Stimulants	5/8, 3.1±5.0 (range, 0–15)
Tranquilizers	0/8
Hallucinogens	5/8, 1.25±1.3 (range, 1–3)
Opiates	1/8, 0.12±0.4 (range, 0–1)
THC	7/8, 13.0±14.0 (range, 0–40)
Novelty Seeking	19.4±4.5 (range, 13–27)
Beck Depression Score	3.0±2.7 (range, 0–8)

antecubital vein, and an oral dose of d-amphetamine was administered (0.0 or 0.3 mg/kg). Immediately before tracer injection, transmission scans were performed using ⁶⁸Ga for attenuation correction. Approximately 10 mCi of [¹¹C]raclopride was injected as an i.v. bolus and data were acquired for 60 min in time frames of progressively longer duration. PET studies were counterbalanced for the order of amphetamine administration and conducted between 2:00 and 5:00 P.M.

High resolution (1 mm) T1-weighted magnetic resonance imaging (MRI) images were obtained for all subjects, co-registered to the summed radioactivity PET images (Evans et al. 1992), and linearly transformed into standardized stereotaxic space (Talairach and Tournoux 1988) using automated algorithms (Collins et al. 1994).

PET images were reconstructed using a 6-mm full width half maximum Hanning filter. Parametric images were generated by calculating [¹¹C]raclopride binding potential (BP = B_{max,free}/K_d) at each voxel using a simplified compartmental model with cerebellar activity as a reference (Gunn et al. 1997). T-Maps were then constructed, representing voxel-by-voxel *t*-tests of change in [¹¹C]raclopride BP between the amphetamine and placebo scans (Aston et al. 2000). Clusters of statistically significant change were identified by thresholding the *t*-maps at a value of *t* > 4.2, which corresponds to *p* < .05 corrected for multiple comparisons (Worsley et al. 1996). BP values for each subject were extracted from the region identified by the *t*-map as well as from regions of interest (ROI) drawn manually on aligned transverse slices from each subject's MRI in stereotaxic space on caudate nucleus, dorsal putamen, and ventral striatum bilaterally. The boundaries for each ROI were labeled well within the gray matter of the structure to reduce potential artifacts due to misalignment or partial volume effects (Figure 1). The rostrocaudal extent of the ROI relative to the anterior commissure was approximately the same for all subjects, *z* = 2 to 15 mm for caudate, *z* = 2 to 10 mm for putamen, and *z* = −4 to −8 mm for ventral striatum, corresponding approximately

Figure 1. One subject's [^{11}C]raclopride binding potential map (right striatum) for the first scan day transformed to Talairach space and overlaid on his MRI in Talairach space. Regions of interest drawn on the same subject's MRI (left striatum) in Talairach space. Red: Ventral Striatum / Nucleus Accumbens ($z = -8$ to -4), Blue: Putamen ($z = 2$ to 10), Green: Caudate ($z = 2$ to 15).

to nucleus accumbens (Talairach and Tournoux 1988). Left and right ROI values were combined. ROI drawn on five consecutive 1-mm slices in cerebellum served as the reference region.

Subjective Effects of Amphetamine

Subjective effects induced by d-amphetamine were measured with the Addiction Research Center Inventory (ARCI) Benzedrine scale (Hill et al. 1963), and 10 visual analog scales (VAS) labeled Want Drug, Like Drug, Euphoria, Mind Racing, Alert, Energetic, Excited, Rush, Anxiety, and High (Bond and Lader 1974). The VAS were administered at five time points, immediately before drug (or placebo), and at 30, 60, 90 and 120 min afterward. Changes in VAS measures were analyzed as the peak change from pre-drug administration to the end of the test session. The ARCI was administered only once per test session, 120 min post-drug.

Tridimensional Personality Questionnaire

All subjects completed the Tridimensional Personality Questionnaire (TPQ; Cloninger 1987; Cloninger et al. 1991). The TPQ measures four dimensions, Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence. Cloninger has proposed that TPQ traits of Novelty Seeking, Harm Avoidance, and Reward Dependence might be related, in significant part, to DA,

serotonin, and norepinephrine neurotransmission, respectively.

Plasma Amphetamine

Blood samples were drawn immediately before d-amphetamine administration and 90 min later, which corresponded to the mid-point of the 60-min PET scan. Plasma concentrations of amphetamine were analyzed with electron-capture gas chromatography after extraction and derivatization of amphetamine (Paetsch et al. 1992). Plasma samples from one subject were lost.

Statistics

Plasma d-amphetamine concentrations, self-report questionnaire data, and [^{11}C]raclopride ROI BP values were analyzed by within groups ANOVA and, when appropriate, Newman-Keuls post hoc tests. Correlations were assessed with Pearson's correlation coefficient.

RESULTS

On the day that subjects received active drug, plasma d-amphetamine levels increased from 0.0 ± 0.0 ng/ml before drug administration to 10.5 ± 8.2 ng/ml 90 min later ($p = .001$). d-Amphetamine was not detected on the placebo test day.

Compared with placebo, d-amphetamine significantly increased ARCI scores ($F_{1,7} = 10.34$, $p = .02$), and the magnitude of this effect was non-significantly associated with plasma d-amphetamine levels ($r^2 = 0.46$, $p = .09$). d-Amphetamine, compared with placebo, also led to greater peak changes on VAS labeled 'Alert' ($F_{1,7} = 23.20$, $p = .002$), 'Mind Racing' ($F_{1,7} = 19.64$, $p = .003$), 'Energetic' ($F_{1,7} = 11.06$, $p = .01$), and 'Excited' ($F_{1,7} = 7.32$, $p = .03$) (Table 2). Peak changes on the VAS labeled 'Like Drug' correlated with plasma concentrations of d-amphetamine ($r^2 = 0.61$, $p = .04$).

A Drug X Region ANOVA yielded significant main effects of Drug ($F_{1,7} = 55.6$, $p < .001$) and Region ($F_{2,14} = 31.2$, $p < .0001$), and a significant Drug X Region interaction ($F_{2,14} = 8.96$, $p = .003$). [^{11}C]Raclopride BP values were significantly lower in ventral striatum, compared with caudate and putamen ($p < .001$) on both the placebo and amphetamine scans ($p < .001$) (Table 3), consistent with previous post-mortem and PET studies (Hall et al. 1994; Mawlawi et al. 2001).

d-Amphetamine, compared with placebo, significantly decreased [^{11}C]raclopride BP in ventral striatum only ($p = .05$); d-amphetamine did not decrease [^{11}C]raclopride BP in caudate ($p = .68$) or putamen ($p = .96$) (Table 3). The percent change in BP also varied with ROI ($F_{2,14} = 6.01$, $p = .01$), and the effect of d-amphetamine was significantly greater in ventral striatum ($-10.7 \pm 9.5\%$) than in dorsal putamen ($0.4 \pm 9.0\%$, $p = .02$) or caudate ($-1.5 \pm 9.3\%$, $p = .02$). Parametric mapping analyses yielded the same results. Compared with placebo, a significant effect of d-amphetamine on [^{11}C]raclopride BP was restricted to bilateral ventral striatum (peak effect: coordinates = 32, -3, -6, $t = 7.34$) (Figure 2). In the t -map identified cluster there was a mean $8.4 \pm 19.6\%$ decrease in [^{11}C]raclopride BP.

Changes in [^{11}C]raclopride BP in the t -map identified cluster and the manually drawn ventral striatum were

Table 2. Effect of d-amphetamine (0.0, 0.3 mg/kg, p.o.) on Addiction Research Center Inventory (ARCI) Scores and Visual Analog Scales (Δ max). Effects Assessed with 2-Tailed Repeated Measures t -tests.

	Placebo (mean $\pm$ SD)	Amphetamine (mean $\pm$ SD)	p -value
ARCI	4.6 $\pm$ 4.2	11.8 $\pm$ 10.2	.02
Visual Analog Scale			
Alert	-1.5 $\pm$ 1.9	1.8 $\pm$ 2.2	.002
Mind Racing	0.25 $\pm$ 1.2	2.4 $\pm$ 2.0	.003
Energetic	-1.2 $\pm$ 1.5	2.0 $\pm$ 1.7	.01
Excited	0.0 $\pm$ 0.9	1.9 $\pm$ 1.7	.03
Euphoria	0.0 $\pm$ 0.8	1.4 $\pm$ 1.8	.09
Rush	-0.1 $\pm$ 0.6	1.6 $\pm$ 2.6	.13
Like Drug	-0.2 $\pm$ 1.8	1.4 $\pm$ 3.0	.17
High	0.2 $\pm$ 1.6	1.2 $\pm$ 2.1	.41
Want Drug	0.6 $\pm$ 1.1	1.4 $\pm$ 2.5	.46
Anxiety	0.2 $\pm$ 1.0	0.6 $\pm$ 1.4	.53

Table 3. [^{11}C]Raclopride binding potential values on test days with placebo or d-amphetamine (0.3 mg/kg, p.o.). Newman-Keuls *post hoc* tests.

Test Day	Ventral Striatum	Caudate	Putamen
Placebo	1.44 $\pm$ 0.5 [†]	1.97 $\pm$ 0.2*	2.45 $\pm$ 0.3* [†]
d-Amphetamine	1.26 $\pm$ 0.4 ^{##}	1.94 $\pm$ 0.2*	2.45 $\pm$ 0.3* [†]

[†]Different from placebo, $p = .05$.

* Different from ventral striatum, $p < .001$.

[‡] Different from caudate, $p < .001$.

significantly correlated ($r^2 = 0.67$, $p = .01$) supporting the proposition that both methods of analysis identified the same changes in tracer binding. In comparison, changes in [^{11}C]raclopride BP in caudate and putamen correlated with each other ($r^2 = 0.88$, $p < .001$) but not with changes in ventral striatum or the t -map ($p > .70$).

d-Amphetamine-induced changes in [^{11}C]raclopride BP in the ventral striatum correlated significantly with two TPQ items, overall Novelty Seeking ($r^2 = 0.56$, $p = .03$) and the Novelty Seeking subscale, Exploratory Excitability ($r^2 = 0.55$, $p = .05$). Similar correlations were also observed in the t -map identified region (Table 4 and Figure 3). Change in [^{11}C]raclopride BP did not correlate significantly with any other TPQ scale or subscale ($p > .10$).

d-Amphetamine-induced increases in extracellular DA in the ventral striatum correlated significantly with only one reported effect of the drug, 'Want Drug' on the d-amphetamine test day (t -Map: $r^2 = 0.69$, $p = .01$; ROI: $r^2 = 0.38$, $p = .10$) (Table 4 and Figure 4). Self-reported 'Want Drug' on the d-amphetamine test day also correlated with the TPQ Novelty Seeking trait, Exploratory Excitability ($r^2 = 0.74$, $p = .006$); this association was not seen on the placebo test ($r^2 = 0.004$, $p = .89$).

Drug-induced change in extracellular DA in dorsal caudate and putamen correlated negatively with one reported effect of the drug, 'Mind Racing' (caudate: $r^2 = -0.70$, $p = .009$; putamen: $r^2 = -0.55$, $p = .03$); however, these negative correlations, not expected a priori, were driven by a single outlier, and the associations were no longer significant when this subject was removed (caudate: $p > .15$; putamen: $p > .65$). Change in BP did not correlate significantly with any other self-report variable.

Age ($r^2 = -0.46$, $p = .06$) and plasma concentrations of d-amphetamine ($r^2 = 0.47$, $p = .09$, $n = 7$) both tended to correlate with increases in extracellular DA in the ventral striatum, though not in other regions ($p > .20$).

DISCUSSION

The present study suggests that: (1) a moderately low oral dose of d-amphetamine (0.3 mg/kg) significantly increases extracellular DA in human striatum; (2) this

Figure 2. Statistically generated t-map of d-amphetamine-induced changes in [^{11}C]raclopride binding potential superimposed on average MRI. Right side on right.

effect occurs only in the ventral striatum; and (3) d-amphetamine-induced increases in extracellular DA may be more closely related to drug-induced drug wanting than mood-elevation; and (4) a relatively high score on the personality trait of Novelty Seeking predicts greater amphetamine-induced DA release and amphetamine-induced drug wanting. A non-significant trend ($p = .06$) suggested that the ability of d-amphetamine to induce DA release in the ventral striatum might decrease from age 20 to age 30.

The effect of d-amphetamine 0.3 mg/kg, given p.o., on [^{11}C]raclopride BP was smaller and more circumscribed than that reported to occur when the same dose is given intravenously. d-Amphetamine, 0.3 mg/kg, p.o. decreased [^{11}C]raclopride BP in the ventral striatum by an average of 10%; significant changes were not seen in caudate or dorsal putamen. In comparison, the same dose of d-amphetamine given i.v. decreases [^{11}C]raclopride BP by 10–20% in striatum as a whole (Breier et al. 1997; Drevets et al. 2001). A recent report suggests that

0.3 mg/kg d-amphetamine given i.v. also has larger effects on [^{11}C]raclopride BP in the ventral striatum than other subcompartments (anteroventral striatum, $-15.4 \pm 10.6\%$; dorsal putamen, $-10.2 \pm 10.6\%$; dorsal caudate, $-4.5 \pm 8.2\%$) (Drevets et al. 2001). The present study with a low oral dose more clearly identifies preferential effects in ventral striatum, and this regional specificity is supported by both manually drawn ROI and statistically generated clusters.

Individual variability in the ability of d-amphetamine to decrease [^{11}C]raclopride BP in the ventral striatum was correlated with self-reported drug-induced 'Want Drug.' To our knowledge, an association between DA release and drug wanting has not been assessed in previous neuroimaging studies. In comparison, PET and functional MRI studies suggest that both cue- and drug-induced activation of the ventral striatum and interconnected limbic regions correlates with drug craving in cocaine dependent subjects (Grant et al. 1996; Breier et al. 1997; Childress et al. 1999; Wang et al. 1999; Kilts et al. 2001). Moreover, accumulating findings in the animal literature also suggest a close association between mesolimbic DA transmission and interest in addictive drugs. Midbrain DA cell firing rates (Schultz 1998) and extracellular DA levels in nucleus accumbens (Gratton 1996) increase as animals approach rewards. Low to moderate doses of DA agonists increase drug seeking behavior (Stewart et al. 1984; Robinson and Berridge 1993). A larger DA response to acute stimulant drug administration predicts more rapid acquisition of drug self-administration (Zocchi et al. 1998).

The magnitude of amphetamine-induced increases in extracellular DA in the ventral striatum also correlated with the personality trait of Novelty Seeking. A positive association between TPQ Novelty Seeking and

Table 4. Pearson correlations with change in [^{11}C]raclopride binding potential.

ROI	Want Drug	NS	NS-1	HA	RD	RD-2
T-Map	0.83**	0.43	0.79*	0.06	0.06	-0.01
Ventral Striatum	0.62†	0.75*	0.74*	0.16	-0.03	-0.28
Caudate	-0.14	-0.13	0.08	-0.25	-0.13	-0.24
Putamen	-0.19	-0.09	0.09	-0.34	-0.07	-0.14

† $p \leq .10$, * $p \leq .05$, ** $p \leq .01$. 'Want Drug': Self-reported drug wanting on the amphetamine administration test day. T-Map: statistically generated cluster of change; NS: Novelty Seeking; NS-1: Exploratory Excitability; HA: Harm Avoidance; RD: Reward Dependence; RD-2: Persistence

Figure 3. Correlations between d-amphetamine-induced increases in extracellular DA and Novelty Seeking and the Novelty Seeking subscale, Exploratory-Excitability. [^{11}C]Raclopride BP values were extracted from two regions, the manually drawn region of interest in ventral striatum and the statistically generated parametric t-map.

DA neurotransmission has been suggested previously, based on pharmaconeuroendocrine indices (Gerra et al. 2000). Novelty Seeking scores also predicted VAS 'Want Drug' on the amphetamine but not placebo test day. One possibility is that amphetamine elicits a DA-mediated appetitive state that increases drug wanting; this effect might be larger in high Novelty Seekers. Animal studies suggest that exploratory behavior in novel environments predicts the nucleus accumbens DA response to cocaine (Hooks et al. 1991) and propensity to self-administer amphetamine (Piazza et al. 1989) and cocaine (Marinelli and White 2000). These and other observations are consistent with the hypothesis that vulnerability to substance abuse in high novelty seekers (Howard et al. 1997; Gabel et al. 1999) could be related, in part, to an increased DA response to abused drugs. Repeated drug use might aggravate these pre-existing tendencies, altering cortico-striatal circuitry, potentiating reward seeking tendencies, and producing decision-making deficits that increase further the tendency to self-administer drugs (Robinson and Berridge 1993; Rogers et al. 1999; Rahman et al. 2001).

Amphetamine-induced DA release did not correlate with self-reported mood-elevation or overt stimulant effects of the drug. Some evidence suggests that psychostimulant and mood-elevating drug effects might be

more closely related to increases in norepinephrine (Rothman et al. 2001) and serotonin (Aronson et al. 1995) than DA transmission. Previously reported correlations between euphorogenic and DA releasing effects of intravenous amphetamine (Laruelle et al. 1995; Drevets et al. 2001) might be related to the ability of higher doses to release all three monoamines (Kuczenski and Segal 1989). The present results do not preclude a relation between DA and affect, though. Other evidence supports such an association (Murphy et al. 1971; Fibiger 1995; Willner 1995). One possibility is that DA influences mood via its regulation of motivational states. The present study suggests that mesolimbic DA transmission might be more closely related to the appetitive component of emotion than providing a sufficient substrate of euphoric mood, per se.

The neuroanatomical pathways innervating ventral versus dorsal striatum are well described (Alexander et al. 1986; Moore and Bloom 1978; Lynd-Balta and Haber 1994; Haber and McFarland 1999). In primates, the ventral striatum is interconnected with the limbic system and receives DA projections primarily from the dorsal tier of the midbrain tegmentum. Additional input to the ventral striatum comes primarily from limbic structures including amygdala, anterior cingulate and the medial and orbitofrontal cortex; these systems are thought to

Figure 4. Correlation between d-amphetamine-induced drug wanting and (left) d-amphetamine-induced DA release, and (right) TPQ Novelty Seeking-Exploratory Excitability scores.

play important roles in associating behavior with reward, attention to affectively relevant stimuli, and the initiation and inhibition of responses to rewards and punishments. In comparison, DA projections to the dorsal caudate-putamen originate primarily in the ventral tier of midbrain DA cell bodies. Cortical inputs to the caudate-putamen come from throughout the neocortex, particularly sensory-motor cortices and the dorsolateral prefrontal cortex.

The conclusions suggested by the present study should be interpreted in light of the following considerations. The sample size is modest ($n = 8$) though within the norms for assessing effects of pharmacological challenges within subjects. The identified correlations would not have withstood Bonferroni corrections, but they were replicated in ventral striatum as identified by two methods, parametric mapping and manually drawn ROI. Second, administering drugs p.o. is associated with lower and more variable bioavailability than the i.v. route (Angrist et al. 1987; Ylitalo 1991). However, plasma d-amphetamine levels could be measured, and there was some evidence of an association between plasma concentrations and change in both extracellular DA and subjective state. Third, as typically seen, only half of the subjects indicated that they wanted more of the drug (Uhlenhuth et al. 1981). However, it was this individual variability that correlated with change in $[^{11}\text{C}]\text{raclopride}$ BP. Fourth, recent studies have questioned the mechanisms by which DA agonists decrease labeled D2 ligand BP. The original model had proposed competition between the labeled ligand and endogenous DA for occupancy of DA D2 receptors (Seeman et al. 1989). More recent work raises the possibility that increased synaptic DA levels might induce receptor internalization (Laruelle 2000). Benzamide ligands, though, seem not to cross the cell membrane, thereby restricting their access to cell surface receptor sites (Laruelle 2000; Seeman and Kapur 2000). Moreover, combination PET-microdialysis studies conducted in the same animal indicate that decreases in benzamide ligand BP have a strong linear association with increases in dialysate DA

concentrations (Laruelle et al. 1997; Endres et al. 1997). These observations suggest that decreases in $[^{11}\text{C}]\text{raclopride}$ BP in the same individual can be considered to reflect increases in extracellular DA.

In conclusion, the small sample size emphasizes the need for caution, but the present results suggest that DA transmission in subcompartments of human striatum is differentially affected by amphetamine and has different behavioral significance. First, a low oral dose of d-amphetamine increased extracellular DA with significant effects seen in ventral striatum only. Second, there was a close association between three variables: (1) amphetamine-induced DA release; (2) amphetamine-induced drug wanting; and (3) the personality trait of novelty seeking. All three variables might be related to susceptibility to drug seeking behavior and collectively be predictive of vulnerability to substance abuse.

ACKNOWLEDGMENTS

A preliminary report based on this study was presented at the 23rd Annual Meeting of the Canadian College of Neuropsychopharmacology (2000).

This work was supported by two operating grants from the Canadian Institutes of Health Research, MOP-36429 to M.L., C.B. and A.D., and MOP-49480 to A.D. M.L. and C.B. are recipients of salary awards from Fonds de la Recherche en Santé du Québec (FRSQ). We thank Rick Fukusawa, Gary Sauchuk, Dean Jolly, Shadreck Mzengeza, and Mirjana Kovacevic for excellent technical assistance, Dr. Robert Lisbona, Chief of Nuclear Medicine at the MNI, for valuable help during the PET scans, and Dr. Gabriel Léger, Dr. Roger Gunn, and Dr. John Aston for assistance in analyzing the PET data.

REFERENCES

- Alexander GE, DeLong MR, Strick PL (1986): Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9:357–381
- Angrist B, Corwin J, Bartlik B, Cooper T (1987): Early phar-

- macokinetics and clinical effects of oral d-amphetamine in normal subjects. *Biol Psychiatry* 22:1357–1368
- Aronson SC, Black JE, McDougale CJ, Scanley BE, Jatlow P, Kosten TR, Heninger GR, Price LH (1995): Serotonergic mechanisms of cocaine effects in humans. *Psychopharmacology (Berl)* 119:179–185
- Aston JA, Gunn RN, Worsley KJ, Ma Y, Evans AC, Dagher A (2000): A statistical method for the analysis of positron emission tomography neuroreceptor ligand data. *Neuroimage* 12:245–256
- Bond A, Lader M (1974): The use of analog scales in rating subjective feelings. *Br J Med Psychol* 47:211–218
- Brauer LH, De Wit H (1997): High dose pimozone does not block amphetamine-induced euphoria in normal volunteers. *Pharmacol Biochem Behav* 56:265–272
- Breier A, Su T-P, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D (1997): Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: Evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA* 94:2569–2574
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997): Acute effects of cocaine on human brain activity and emotion. *Neuron* 19:591–611
- Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999): Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 156:11–18
- Cloninger CR (1987): A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry* 44:573–588
- Cloninger CR, Przybeck TR, Svrakic DM (1991): The Tridimensional Personality Questionnaire: U.S. normative data. *Psych Rep* 69:1047–1057
- Collins DL, Neelin P, Peter TM, Evans AC (1994): Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr* 18:192–205
- Cousins MS, Stamat HM, de Wit H (2001): Acute doses of d-amphetamine and bupropion increase cigarette smoking. *Psychopharmacology (Berl)* 157:243–253
- Di Chiara G, Imperato A (1988): Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 85:5274–5278
- Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA (2001): Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry* 49:81–96
- Endres CJ, Kolachana BS, Saunders RC, Su T, Weinberger RC, Breier A, Eckelman WC, Carson RE (1997): Kinetic modeling of [¹¹C]raclopride: combined PET-microdialysis studies. *J Cereb Blood Flow Metab* 17:932–942
- Evans AC, Marrett S, Neelin P, Collins L, Worsley K, Dai W, Milot S, Meyer E, Bub D (1992): Anatomical mapping of functional activation in stereotactic coordinate space. *Neuroimage* 1:43–53
- Fibiger HC (1995): Neurobiology of depression: focus on dopamine. In Fratta W, Pani L, Serra G (eds), *Depression and Mania: From Neurobiology to Treatment*. New York, Raven Press, pp 1–17
- First MB, Spitzer RI, Gibbon M (1995): *Axis I Disorders*. New York, New York State Psychiatric Institute
- Gabel S, Stallings MC, Schmitz S, Young SE, Fulker DW (1999): Personality dimensions and substance misuse: relationship in adolescents, mothers and fathers. *Am J Addict* 8:101–113
- Gerra G, Zaimovic A, Timpano M, Zambelli U, Delsignore R, Brambilla F (2000): Neuroendocrine correlates of temperamental traits in humans. *Psychoneuroendocrinology* 25:479–496
- Grant S, London ED, Newlin DB, Villemange VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A (1996): Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA* 93:12040–12045
- Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997): Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* 6:279–287
- Haber SN, McFarland NR (1999): The concept of the ventral striatum in nonhuman primates. *Ann NY Acad Sci* 877:33–48
- Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994): Distribution of D₁- and D₂-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology* 11:245–256
- Hill HE, Haertzen CA, Wolbach AB Jr, Miner EJ (1963): The addiction research center inventory: Appendix I. Items comprising empirical scales for seven drugs. II. Items which do not discriminate placebo from any drug condition. *Psychopharmacologia* 4:184–205
- Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB Jr (1991): Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. *Synapse* 9:121–128
- Howard MO, Kivlahan D, Walker RD (1997): Cloninger's tridimensional theory of personality and psychopathology: applications to substance use disorders. *J Stud Alcohol* 58:48–66
- Jaffe JH, Cascella NG, Kumor KM, Sherer MA (1989): Cocaine-induced cocaine craving. *Psychopharmacology (Berl)* 97:59–64
- Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KPG (2001): Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry* 58:334–341
- Kuczenski R, Segal D (1989): Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. *J Neurosci* 9:2051–2065
- Laruelle M (2000): Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. *J Cereb Blood Flow Metab* 20:423–451
- Laruelle M, Abi-Dargham A, van Dyck CH, Rosenblatt W, Zea-Ponce Y, Zoghbi SS, Baldwin RM, Charney DS, Hoffer PB, Kung HF, Innis RB (1995): SPECT imaging of striatal dopamine release after amphetamine challenge. *J Nucl Med* 36:1182–1190

- Laruelle M, Iyer RN, al-Tikriti MS, Zea-Ponce Y, Malison R, Zoghbi SS, Baldwin RM, Kung HF, Charney DS, Hoffer PB, Innis RB, Bradberry CW (1997): Microdialysis and SPECT measurements of amphetamine-induced dopamine release in nonhuman primates. *Synapse* 25:1–14
- Logan J, Fowler JS, Dewey SL, Volkow ND, Gatley SJ (2001): A consideration of the dopamine D2 receptor monomer-dimer equilibrium and the anomalous binding properties of the dopamine D2 receptor ligand, N-methylspiperone. *J Neural Transm* 108:279–286
- Lynd-Balta E, Haber SN (1994): The organization of mid-brain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. *Neuroscience* 59:625–640
- Marinelli M, White FJ (2000): Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. *J Neurosci* 20:8876–8885
- Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang D-R, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001): Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D₂ receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* 21:1034–1057
- Moore RY, Bloom FE (1978): Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. *Annu Rev Neurosci* 1:129–169
- Murphy DL, Brodie HK, Goodwin FK, Bunney WE Jr (1971): Regular induction of hypomania by L-dopa in “bipolar” manic-depressive patients. *Nature* 229:135–136
- Nurnberger JI Jr, Gershon ES, Simmons S, Ebert M, Kessler LR, Dibble ED, Jimerson SS, Brown GM, Gold P, Jimerson DC, Guroff JJ, Storch FI (1982): Behavioral, biochemical and neuroendocrine responses to amphetamine in normal twins and ‘well-state’ bipolar patients. *Psychoneuroendocrinology* 7:163–176
- Paetsch PR, Baker GB, Caffaro LE, Greenshaw AJ, Rauw GA, Coutts RT (1992): Electron-capture gas chromatographic procedure for simultaneous determination of amphetamine and N-methylamphetamine. *J Chromatogr Biomed Appl* 573:313–317
- Piazza PV, Deminière JM, Le Moal M, Simon H (1989): Factors that predict individual vulnerability to amphetamine self-administration. *Science* 245:1511–1513
- Rahman S, Sahakian BJ, Cardinal RN, Rogers RD, Robbins TW (2001): Decision making and neuropsychiatry. *Trends Cog Sci* 5:271–277
- Robinson TE, Berridge KC (1993): The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 18:247–291
- Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NB, Hunter J, Carthy T, Booker E, London M, Deakin JFW, Sahakian BJ, Robbins TW (1999): Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology* 20:322–339
- Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS (2001): Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 39:32–41
- Sax KW, Strakowski SM (1998): Enhanced behavioral response to repeated d-amphetamine and personality traits in humans. *Biol Psychiatry* 44:1192–1195
- Schultz W (1998): Predictive reward signal of dopamine neurons. *J Neurophysiol* 80:1–27
- Seeman P, Guan HC, Niznik HB (1989): Endogenous dopamine lowers the dopamine D2 receptor density as measured by [³H]raclopride: implications for positron emission tomography of the human brain. *Synapse* 3:96–97
- Seeman P, Kapur S (2000): Schizophrenia: more dopamine, more D2 receptors. *Proc Natl Acad Sci USA* 97:7673–7675
- Sills TL, Crawley JN (1996): Individual differences in sugar consumption predict amphetamine-induced dopamine overflow in nucleus accumbens. *Eur J Pharmacol* 303:177–181
- Stewart J, de Wit H, Eikelboom R (1984): Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol Rev* 91:251–268
- Talairach J, Tournoux P (1988): *Co-planar Stereotactic Atlas of the Human Brain*. Stuttgart, Thieme
- Uhlenhuth EH, Johanson CE, Kilgore K, Kobasa SC (1981): Drug preference and mood in humans: preference for d-amphetamine and subject characteristics. *Psychopharmacology (Berl)* 74:191–194
- Wang G-J, Volkow ND, Fowler JS, Cervany P, Hitzeman RJ, Pappas NR, Wong CT, Felder CT (1999): Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life Sci* 64:775–784
- Willner P (1995): Dopaminergic mechanisms in depression and mania. In Bloom FE, Kupfer DJ (eds), *Psychopharmacology: The Fourth Generation of Progress*. New York, Raven Press, pp 921–931
- Wise RA (1982): Neuroleptics and operant behavior: the anhedonia hypothesis. *Behav Brain Sci* 5:39–87
- Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996): A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58–73
- Ylitalo P (1991): Effect of exercise on pharmacokinetics. *Ann Med* 23:289–294
- Zocchi A, Orsini C, Cabib S, Puglisi-Allegra S (1998): Parallel strain-dependent effect of amphetamine on locomotor activity and dopamine release in the nucleus accumbens: an in vivo study in mice. *Neuroscience* 82:521–528