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Reinforcing Effects of Psychostimulants in Humans Are Associated with Increases in Brain Dopamine and Occupancy of D_2 Receptors[1]

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ABSTRACT

Increases in dopamine concentration in limbic brain regions have been postulated to underlie the reinforcing effects of psychostimulant drugs in laboratory animals. However, neither the qualitative nor the quantitative relationship between drug-induced increases in brain dopamine and the reinforcing effects of psychostimulant drugs have been investigated in humans. Positron emission tomograph and [^{11}C]raclopride, a dopamine D_2 receptor radioligand that competes with endogenous dopamine for occupancy of the D_2 receptors, were used to measure changes in brain dopamine after different doses of i.v. methylphenidate in 14 healthy controls. In parallel, measures for self-reports of drug effects were obtained to assess their relationship to methylphenidate-induced changes in brain dopamine. The intensity of the "high" induced by methylphenidate was significantly correlated with the levels of released dopamine ($r = 0.78$, $p < .001$); subjects having the greatest increases were those who perceived the most intense high. This relationship remained significant after partialing out for dose and concentration of methylphenidate in plasma. Furthermore, subjects for whom methylphenidate did not increase dopamine did not perceive a high. These results represent the first clear demonstration that stimulant-induced high, a mood descriptor that reflects reinforcing effects of drugs in humans, is associated with increases in brain dopamine, and also that there is a quantitative relationship between levels of D_2 receptor occupancy by dopamine and the intensity of the high.

The concept that dopamine (DA) increases in the nucleus accumbens underlie the reinforcing effects of psychostimulant drugs has become central in drug abuse research (Koob and Bloom, 1988; Di Chiara and Imperato, 1988). Cocaine and "cocaine-like psychostimulants" such as methylphenidate (MP) increase extracellular DA by blocking the dopamine transporters (DAT) (Giros et al., 1996), and there is a strong correlation between their affinities for the DAT and their reinforcing effects (Ritz et al., 1987; Madras et al., 1989). However, the recent documentation that, in mice that lack DAT (DAT knockout), cocaine and MP are reinforcing (Sora et al., 1998; Rocha et al., 1998a), has led to a questioning of the role of DA on the reinforcing effects of psychostimulants (Caine, 1998). Note that the interpretation of the results from DAT knockout mice is confounded by the fact that they have marked compensatory changes in pre- and postsynaptic molecules involved in DA neurotransmission (Jones et al., 1998). Furthermore, although DAT blockade is the initial pharmacological effect of cocaine or MP, it is the increase in DA and the activation of DA receptors that are responsible for their behavioral effects (Egilmez et al., 1995). Although there are multiple studies documenting the importance of DA receptor activation by DA in the reinforcing effects of psychostimulants in laboratory animals (De Wit and Wise, 1977; Richardson et al., 1994; Self et al., 1996), its relevance in humans subjects, for whom its rewarding effects are associated with the subjective perception of pleasure or "high" (Fischman and Foltin, 1991), has not been investigated. It is also of importance to assess the role of DA in the reinforcing effects of psychostimulants in humans because the main strategies on drug development for cocaine addiction are those of drugs that target the DA system (Kleber, 1994; O'Brien, 1997; Kreek, 1997).

The purpose of this study was to investigate the relationship between DA increases as assessed by the levels of DA D_2 receptor occupancy and the intensity of the high induced by the i.v. administration of MP, which cocaine abusers report to

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ABBREVIATIONS: DA, dopamine; DAT, dopamine transporters; PET, positron emission tomograph; MP, methylphenidate; ST, striatum; CB, cerebellum; DV, distribution volumes.

be similar to that of cocaine (Wang et al., 1997). Increases in DA were measured with positron emission tomography (PET) and [^{11}C]raclopride, a radioligand that competes with DA for binding to DA D_2 receptors (Seeman et al., 1989; Gifford et al., 1996). Because [^{11}C]raclopride binding in the human brain is highly reproducible (Volkow et al., 1993), differences in binding between placebo and MP predominantly reflect MP-induced changes in synaptic DA, which occupies DA D_2 receptors (Volkow et al., 1994; Breier et al., 1997). Drug-induced changes in synaptic DA as assessed with PET and [^{11}C]raclopride have been shown to be reproducible when subjects are tested on separate occasions (Wang et al., 1999). The reinforcing effects of MP were assessed by periodically asking participants to rate the intensity of the high and of the "rush" (Volkow et al., 1996). These quantitative self-reports of drug effects have been shown to be reliable and consistent across studies and to predict administration of drugs in human subjects (Fischman and Foltin, 1991).

Materials and Methods

Subjects. The participants were 14 right-handed healthy subjects [8 males, 6 females, age 33 ± 6 (S.D.) years] who did not have a present or past history of drug or alcohol abuse or dependence, as per the Diagnostic and Statistics Manual IV (DSM IV; American Psychiatric Association) (excluding nicotine/caffeine). Subjects were excluded if they had a current or past psychiatric, neurological, cardiovascular, or endocrinological disease. None of the subjects was taking medications at the time of the study. Toxicological drug screens were performed before each PET scan. Studies were approved by the Institutional Review Board at Brookhaven National Laboratory and informed consent was obtained from all subjects after procedures were explained.

Scans. All subjects were initially recruited to undergo a total of four scans with [^{11}C]raclopride (two scans/day over a 2-day period). However, because of scheduling problems or a subject's unwillingness to return, we completed the four scans on only nine of the subjects; on the other five we completed only two scans. The first scan on a given day was done after a placebo and the second scan was done 127 min later, after one of the following i.v. doses of MP (0.025, 0.1, 0.25, or 0.5 mg/kg). Subjects were randomly assigned to the dose received. Table 1 gives the numbers of subjects tested on each dose. Subjects were blind as to whether a placebo or MP was administered, which was injected 7 min before [^{11}C]raclopride. Scans were done on a CTI-931 PET tomograph (6 × 6 × 6.5 mm full width half maximum) and were started immediately after injection of 3.8 to 10 mCi of [^{11}C]raclopride (specific activity 0.5–1.5 Ci/μM at end of bombardment; 2–24 μg injected dose) for a series of 20 emission scans obtained through 60 min as described previously (Volkow et al., 1993). Details on synthesis of [^{11}C]raclopride, subject positioning, transmission and emission scans, arterial blood sampling for radiotracer quantification, and metabolite analyzes have been published previously (Volkow et al., 1993). Venous blood was drawn for quantification of plasma concentration of MP before and at 27 and 47 min after MP using capillary gas chromatography/mass spectrometry (Srinivas et al., 1991).

TABLE 1

Plasma concentration of methylphenidate (nanograms per milliliter) at different times after its administration for the various MP doses and number of subjects tested with each dose

Data points correspond to means and S.D.

MP Dose	Subjects Tested	MP in Plasma	
		27 min	47 min
mg/kg			
0.025	5	7 ± 2	3 ± 1
0.1	3	26 ± 5	13 ± 3
0.25	8	63 ± 14	38 ± 9
0.5	7	116 ± 20	72 ± 18

Drug Effect Ratings. Behavioral effects were evaluated using analog scales that assessed self-reports of high, rush, alertness, anxiety, and restlessness from 0 (felt nothing) to 10 (felt intensely) (Wang et al., 1997), recorded 5 min before placebo or MP and then every minute for the first 20 min and then again at 25, 30, 45, and 67 min. Recordings for heart rate and blood pressure were obtained continuously throughout the placebo and MP scans.

Image Analysis and Modeling. Regions of interest were outlined for striatum (ST) and cerebellum (CB) as described previously (Volkow et al., 1993). Briefly, regions of interest were initially outlined on the individual's summed baseline [^{11}C]raclopride image (images obtained between 15 to 54 min), and were then projected into the dynamic [^{11}C]raclopride images for the baseline and MP studies to generate time activity curves for ST and CB. These time-activity curves for tissue concentration, along with those for unchanged tracer in plasma, were used to calculate [^{11}C]raclopride's transfer constant from plasma to brain (K_1) and the distribution volumes (DV), which correspond to the equilibrium measurement of the ratio of tissue concentration to plasma concentration, in ST and CB using a graphical analysis technique for reversible systems (Logan et al., 1990). The ratio of DV in ST to that of DV in CB corresponds to (B_{max}/K_d) + 1 and is insensitive to changes in cerebral blood flow (Logan et al., 1994).

B_{max}/K_d can be related to the DV as follows:

$$DV = (K_1/k_2)(1 + NS + (B_{max} - RL)/K_d)$$

K_1 and k_2 are plasma-to-tissue and tissue-to-plasma transport constants, respectively. B_{max} is the total D_2 receptor concentration and RL is concentration of receptors occupied with endogenous DA. NS is the ratio of binding constants for nonspecific binding, which is considered to be essentially instantaneous (compared with receptor binding) and therefore in an equilibrium state. In a nonreceptor region, the DV is given by

$$DV = K_1/k_2(1 + NS)$$

Assuming that the ratio K_1/k_2 is the same for receptor and nonreceptor regions, the ratio of DV for ST to CB is

$$DV(ST)/DV(CB) = (B_{max} - RL)/(K_d(1 + NS)) + 1$$

Although the DV is an equilibrium quantity, it can be easily determined from nonequilibrium data using a graphical type analysis. The free receptor concentration (B_{max} − RL) is therefore a linear function of the DV ratio. We have designated B_{max}/K_d as the quantity (B_{max} − RL)/K_d, where we have replaced $K_d(1 + NS)$ with K_d, which is the K_d that comes out of PET measurements without having to separately measure the quantity NS.

The response to MP was quantified as the difference in B_{max}/K_d between placebo and MP and expressed as percentage of change from baseline $[(B_{max}/K_{d\ placebo} - B_{max}/K_{d\ MP})/B_{max}/K_{d\ placebo}] \times 100$.

Data Analysis. Differences in B_{max}/K_d and in the behavioral and cardiovascular measures after placebo and after the different doses of MP were tested with ANOVA. For the ratings of high and rush, we averaged the scores obtained from 7 to14 min after placebo or MP; for the ratings of restlessness, anxiety, and alertness, we averaged the scores from 5 to 30 min, and for the cardiovascular measures, we averaged the scores from 4 to 12 min, which were the time periods when peak effects for MP occurred. Post hoc *t* tests were then performed to determine for which doses the behavioral and cardiovascular effects were significant. Pearson product moment correlations analyses were calculated between the changes in B_{max}/K_d and the behavioral changes (MP versus placebo). On those correlations that were found to be significant we performed partial correlation anal-

ysis to determine whether the correlations remained significant after removing the contribution of dose and concentration of MP in plasma (Kirk, 1990). Also, because the 23 measures were not independent, because 9 subjects were tested twice (5 subjects only once), we tested separate correlations that included only the first data point for each subject (a total of 14 data points) and correlations that included the two data points per subject (a total of 23 data points). Values of $p < .01$ were considered significant and p values > 0.01 and < 0.05 are reported as trends.

Results

Plasma concentrations achieved with the different doses of MP are shown in Table 1. MP significantly reduced the binding of [^{11}C]raclopride in ST, but not in CB (Fig. 1). MP did not change K_1 values (transfer of [^{11}C]raclopride from plasma to tissue) in ST or in CB, nor did it change the DV in CB (DV_{CB}) (Table 2). However, MP decreased the DV in ST (DV_{ST}) (ANOVA $F = 5.7$, $p < .0005$; Table 2). Post hoc t tests showed that the decreases in DV_{ST} were significant for all the MP doses. MP decreased B_{max}/K_d, which is the measure of DA D_2 receptor availability (ANOVA, $F = 4.5$, $p < .002$). Post hoc t tests showed that the decreases in B_{max}/K_d were significant for the 0.25 and 0.5 mg/kg MP doses. Figure 2 shows the effects of the various MP doses on B_{max}/K_d expressed as percentage of change from baseline. MP-induced changes in B_{max}/K_d were correlated with the doses of MP given ($r = 0.55$, $p < .01$) and there was a trend for significance for the correlation with the concentration of MP in plasma ($r > 0.51$, $p < .05$; Fig. 2).

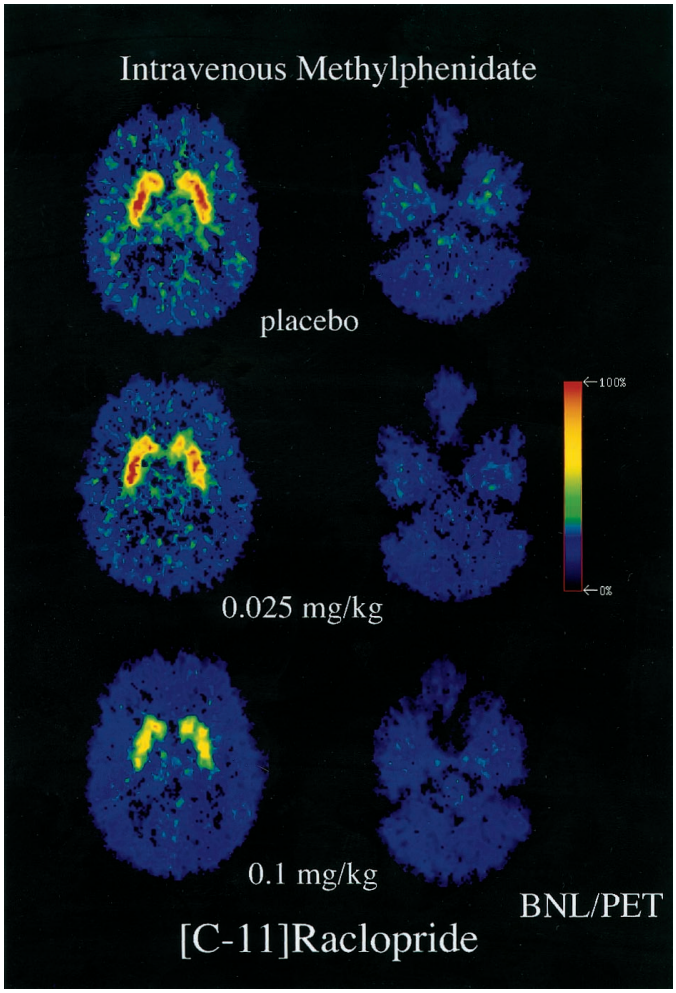

Fig. 1. DV images of [^{11}C]raclopride at the level of the ST and at the level of the CB for one of the subjects at baseline and after administration of 0.1 and 0.025 mg/kg i.v. of MP. MP reduced binding of [^{11}C]raclopride in the ST where it competes with DA for binding to DA D_2 receptors, but not in CB, where binding is predominantly nonspecific.

MP significantly increased ratings of high and rush ($F > 47$, $p < .0001$) and post hoc t tests showed these effects were significant for the 0.5 and 0.25 mg/kg doses (Fig. 3). MP increased restlessness ($F = 5$, $p < .05$) and the 0.5 MP dose induced a trend of an increase in anxiety and alertness that was not significant (data not shown). MP increased heart rate and systolic and diastolic blood pressure ($F > 33$, $p < .0001$) and these effects were significant for the 0.5, 0.25, and 0.1 mg/kg doses (data not shown). The 0.025 mg/kg i.v. dose had no measurable behavioral or cardiovascular effects.

MP-induced changes in D_2 receptor availability (B_{max}/K_d) were significantly correlated with MP-induced changes in self-reports of a high ($r = 0.78$, df, 22, $p < .0001$) and rush ($r = 0.75$, $p < .0001$), and these correlations remained significant ($p < .001$) after partialing out for the dose of MP and for the concentration of MP in plasma (Fig. 3). MP-induced changes in D_2 receptor availability were also correlated with changes in restlessness ($r = 0.52$, $p < .01$), but this correlation was lost after partialing out for dose and concentration of MP in plasma. The results were the same when the correlations were done using only one data point per subject; this corresponded for the high to $r = 0.78$, (df_{13}, $p < .001$, for the rush to $r = 0.74$ (df_{13}, $p < .003$), and for restlessness to ($r = 0.54$, df_{13}, $p < .05$).

Discussion

To the extent that increases in self-report measures of high and rush are predictive of reinforcing effects (Fischman and Foltin, 1991), our findings of a significant correlation between MP-induced changes in DA and changes in self-reports of high and rush document in humans a very clear association between increases in DA and MP's reinforcing effects. The fact that correlations remained significant after partialing out for dose effects and the concentration of MP in plasma suggests that this is not a spurious correlation reflecting an association between higher doses and more intense high. In cocaine-addicted subjects we have shown that MP-induced changes in DA, as well as the high, were lower than in nonabusing controls (Volkow et al., 1997a). In that study, we postulated that the reason we did not find a quantitative association between the high and the DA increases induced by MP was the fact that we measured the high 27 min after administration of MP when the peak effects had subsided. This is corroborated in the current study in which we found a significant association between DA increases and the high when we measured its peak effects.

Using single photon emission-computed tomography, Laruelle and colleagues (Laruelle et al., 1995) reported an association between decreases in the specific binding of the D_2 receptor radioligand [^{123}I]iodobenzamide, which also serves as a marker for changes in synaptic DA, and amphetamine-induced increases in a composite of behavioral scores referred to as "subjective activation", which included euphoria, alertness, and restlessness. Different from the current study, the association with amphetamine-induced DA increases was

TABLE 2

Plasma to brain transfer constant (K_1) and DV for [^{11}C]raclopride in ST and CB for the two baselines (placebo) and for the different doses of MP
Data points correspond to means and S.D.

	Placebo 1	Placebo 2	0.025 mg/kg	0.1 mg/kg	0.25 mg/kg	0.5 mg/kg	p
K_1 CB	.07 ± .01	.07 ± .01	.09 ± .03	.06 ± .01	.07 ± .01	.08 ± .01	N.S.
K_1 ST	0.10 ± .01	0.10 ± .01	0.10 ± .02	0.09 ± .01	0.10 ± .01	0.11 ± .01	N.S.
DV CB	0.44 ± .08	0.41 ± .04	0.35 ± .10	0.37 ± .04	0.38 ± .05	0.44 ± .08	N.S.
DV ST	1.73 ± .19	1.68 ± .22	1.42 ± .37*	1.40 ± .11*	1.35 ± .17*	1.35 ± .19*	.0005

* $p < .01$, post-hoc t test.

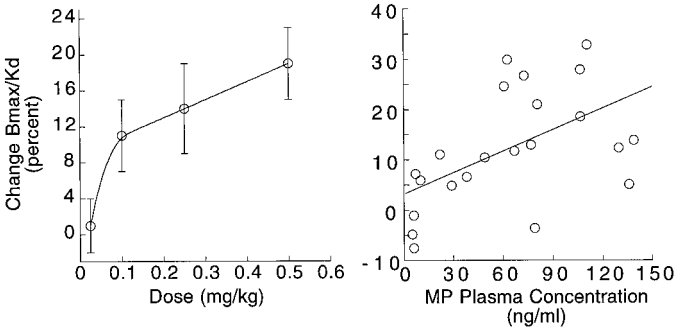

Fig. 2. Percentage of change in B_{max}/K_d as a function of dose of MP (data points correspond to means and S.E.), and the concentration of MP in plasma (27-min samples).

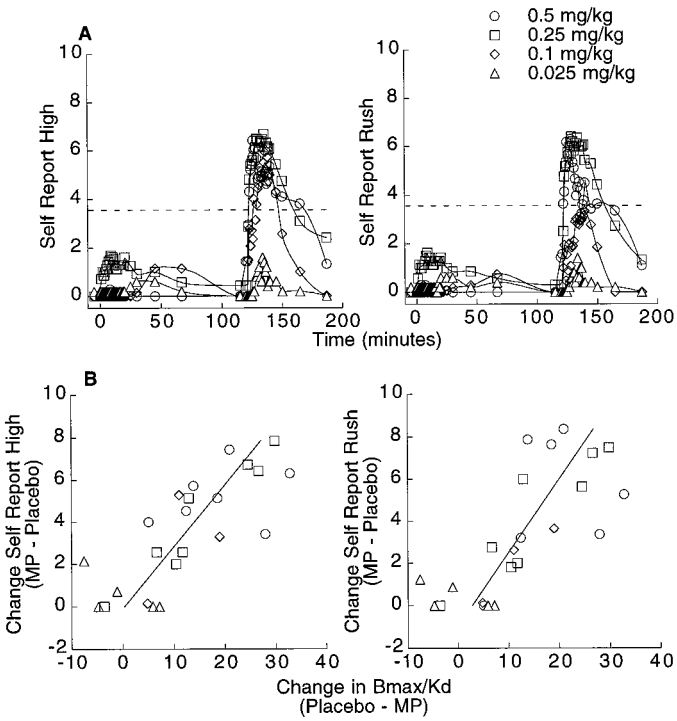

Fig. 3. Effects of MP on high and rush and relationship to its effects on brain DA. A, effects of the different doses of MP on the ratings of high and rush. The placebo was administered at time 0 and MP was administered at 120 min. MP significantly increased ratings of high and rush. Dotted line marks the level at which measures are significantly different from placebo ($p < .01$). B, regression lines for the correlation between MP-induced changes in DA D_2 receptor availability in ST and MP-induced changes in self-reports of high ($r = 0.78$, df_{22}, $p < .0001$) and rush ($r = 0.75$, $p < .0001$).

not specific to self-ratings of reinforcing effects (euphoria, high, or rush). These differences, among others, are likely to reflect differences between MP and amphetamine; namely, that amphetamine induces much larger DA increases than does MP, and that its effects are not dependent, like those of MP, on DA cell firing (Kuczenski and Segal, 1997).

Using PET, we had previously documented a relationship between the levels of DAT blockade and the intensity of the high induced by i.v. cocaine in active cocaine abusers (Volkow et al., 1997b), and by i.v. MP in nonabusing subjects (Volkow et al., 1999). However, there were subjects who had significant levels of DAT blockade (>60%) but who did not experience a high. Because DAT blockade by cocaine or MP is the triggering event that leads to increases in synaptic DA, we hypothesized that the lack of a high in those subjects reflected a failure to sufficiently raise synaptic DA (Volkow et al., 1999). The current results would corroborate this hypothesis, because the high was perceived by all the subjects in whom MP decreased D_2 receptor availability more than 15%, regardless of the dose given (Fig. 3). These results indicate that MP-induced increases in DA, as assessed by its occupation of DA D_2 receptors, is a much better predictor of the intensity of the high than the actual levels of DAT blockade. Also, different from the studies that measured DAT blockade by i.v. MP for which the correlation with the plasma MP concentration was very high, it accounted for 51% of the variance (Volkow et al., 1999); in the current study, the correlation between increase in DA and plasma MP accounted for only 26% of the variance. This suggests that part of the intersubject variability in response to similar concentrations of MP is caused by differences in the magnitude of the increases in DA, which are a function not only of the levels of DAT blockade, but also of the levels at which DA is being released. This could provide an explanation for the differences in the reinforcing effects of psychostimulants between subjects (Wang et al., 1997); one could postulate that for an equivalent level of DAT blockade, cocaine or MP would be more reinforcing in a subject whose baseline release of DA is high (high DA tone) than in a subject whose baseline release of DA is low (low DA tone) (Fig. 4).

These results are therapeutically relevant in that they support strategies that target the DA system in the treatment of cocaine addiction, such as the use of drugs to block psychostimulant-induced increases in DA (e.g., by γ-vinyl-γ-aminobutyric acid; Dewey et al., 1998), or drugs that would interfere with cocaine's binding to the DA transporters (e.g., [1-2(diphenylmethoxy)ethyl]-4-3(-phenylpropyl)piperazine dihydrochloride; Villemagne et al., 1999).

Although the changes in DA induced by MP accounted for a significant proportion of the variance on the high (r^2 = 61%), they could not account for it completely. This could reflect not only the inherent limitations of the procedures, but also differences in DA receptor sensitivity between subjects and/or the importance of other neurotransmitters (e.g., excitatory amino acids, serotonin, or γ-aminobutyric acid) in drug reinforcement, as highlighted, for example, by studies

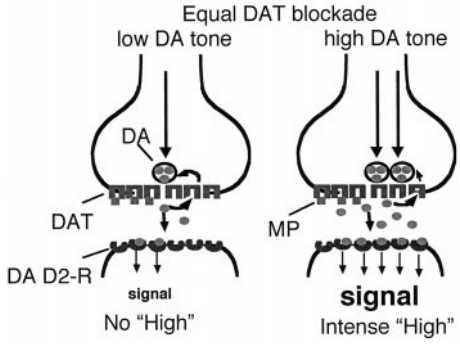

Fig. 4. Diagram illustrating the proposed mechanism for the intersubject variability in the reinforcing responses to MP. We postulate that, for equivalent levels of DAT blockade, the increases in DA induced by MP will be larger in subjects with a high DA tone than in those with a low DA tone; this will result in a larger DA occupancy of DA D_2 receptors (DA D_2-R) and a more intense high.

showing that mice lacking 5-hydroxytryptamine$_{1B}$ are more likely than normal mice to self-administer cocaine (Rocha et al., 1988b; Parsons et al., 1998).

These results are also highly suggestive of an involvement of DA D_2 receptors in the perception of the high, because the changes in DA are monitored directly by their competition for binding to DA D_2 receptors. These results are in agreement with studies in laboratory animals, which have shown that D_2 receptors are involved in drug reinforcement as evidenced by, among others, the decrease in the reinforcing effects of alcohol and morphine in D_2 receptor knockout mice (Maldonado et al., 1997; Crabbe and Phillips, 1998), and by the decrease in the reinforcing effects of cocaine with DA D_2 receptor blockers (De Wit and Wise, 1977; Woolverton, 1986). Although DA D_2 receptor blocker drugs in humans have not been shown to consistently block cocaine's reinforcing effects (Ohuoha et al., 1997), this could be caused by incomplete blockade by the doses given (Nyberg et al., 1996) and/or the fact that both D_2 and D_1 receptor blockade may be necessary to antagonize cocaine's reinforcing effects (Geter-Douglass and Riley, 1996). This study could not assess the relative contribution of the other DA receptors to the reinforcing effects of psychostimulant drugs.

It is intriguing that relatively low levels of D_2 receptor occupancies by DA were achieved after doses of MP that are known to induce almost complete DAT blockade. For example, DAT occupancies achieved by 0.5 mg/kg i.v. MP doses averaged 78% (Volkow et al., 1999) but changed D_2 receptor availability only 19%. Considering that, at baseline, imaging studies using single photon emission-computed tomography and [^{123}I][1-2(diphenylmethoxy)ethyl]-4-3(-phenylpropyl)piperazine dihydrochloride, have estimated occupancy levels of approximately 20 to 30% in the human brain (Laruelle et al., 1997a), these findings would indicate that, at the highest dose given (0.5 mg/kg), MP only doubled the numbers of DA D_2 receptors that are occupied by endogenous DA. Although this could be interpreted to indicate that relatively low levels of D_2 receptor occupancy by DA are required for drugs to be perceived as reinforcing, it could also reflect an underestimation of the actual percentage of D_2 receptors that are occupied by DA, because raclopride has a higher affinity for the D_2 receptor than DA (Seeman et al., 1989). It should also be kept in mind that because raclopride is an antagonist, it may favor a different conformation of the receptor than that of an agonist (Strange, 1997).

The D_2 radioligand competition method offers a relative estimate of changes in DA concentration, which has been shown to be linearly related to measures of extracellular DA as assessed with microdialysis in nonhuman primate studies (Breier et al., 1997; Laruelle et al., 1997b). In fact, it has been estimated that a 1% decrease in [^{11}C]raclopride binding corresponds to at least an 8-fold increase in extracellular DA (Breier et al. 1997). However, the precise relationship between synaptic DA and availability of D_2 receptors to labeled antagonists is not yet known with certainty.

Although this study evaluated the effects of MP and not those of cocaine, it is likely that a similar relationship between DA and the high would occur for cocaine. In the human brain, cocaine and MP have a similar distribution, have equivalent levels of uptake (8–10% per injected dose), similar rates of uptake (peak concentrations in brain: 4–6 and 8–10 min, respectively; Volkow et al., 1995), and similar in vivo potencies in blocking the DAT (ED_{50}: 0.13 and 0.07 mg/kg i.v., respectively; Volkow et al., 1999). Moreover, when correcting for the differences in $ED_{50,}$ we have shown similar levels of [^{11}C]raclopride displacement by cocaine and MP in the baboon brain (Volkow et al., 1998). The doses selected in this study were chosen to achieve DAT levels of blockade equivalent to those achieved by reinforcing doses of i.v. cocaine, as well as doses without observable behavioral effects (Volkow et al., 1997a, 1999). However, there are differences between these two drugs; cocaine's half-life in the human brain is much shorter than that of MP (20 and 90 min, respectively; Volkow et al., 1995), cocaine but not MP inhibits the serotonin transporter, and MP's affinity for the norepinephrine transporter is higher than that of cocaine (Gatley et al., 1996).

In this study we did not see a significant increase with MP on ratings of anxiety and alertness. This could reflect the conditions of MP administration; subjects are lying on a PET scanner in a dimly lit room with minimal noise and are asked to refrain from moving or speaking, except to respond to the periodic questioning about drug effects. It is possible that if we had given MP in an environment with active stimulation and/or where subjects were required to perform a task, it would have induced higher levels of anxiety and/or alertness. It is also possible that if MP had been given to subjects whose levels of alertness at baseline were low (not the case for this study), we may have been able to detect an effect of MP on alertness. Also, the sample sizes used to test a given dose were small and limited the power of observing a significant effect.

A technical aspect in the results that merits discussion is the discrepancies between some of the results obtained for the effects of MP when using the DV and those when using the B_{max}/K_d. Specifically, MP showed a dose effect for the B_{max}/K_d measures, but not for the DV; and MP significantly decreased the DV for all of the doses tested, whereas its effects on B_{max}/K_d reached significance only for the 0.25 and 0.5 mg/kg MP dose. The discrepancies obtained between the DV and the B_{max}/K_d measures most likely reflect the fact that these two measures are not identical; the B_{max}/K_d includes a normalization for nonspecific binding in brain, whereas the DV does not. As a result, the DV measure is a less reliable

estimate of DA receptor availability than is the B_{max}/K_d measure (Logan et al., 1994).

Limitations for this study are that because of the limited spatial resolution of the PET scanner, measurements were made in the dorsal ST and not in the nucleus accumbens, the brain region in ST associated with drug reinforcement (Koob and Bloom, 1988; Di Chiara and Imperato, 1988), and that the PET [^{11}C]raclopride studies predominantly reflect tracer binding over a 15- to 30-min period, and thus are likely to underestimate the peak effect of MP on synaptic DA. Also, this study documents an association between the high and MP-induced changes in synaptic DA in control subjects; but additional studies are required to evaluate whether a similar association occurs in cocaine abusers.

In summary, this study provides the first documentation of a significant relationship between increases in brain DA in response to a psychostimulant drug and the ratings of high and rush in humans. These results confirm the important role that DA and DA D_2 receptors play in the reinforcing responses to psychostimulants in humans. They also suggest that differences between subjects in the rate of DA release contributes to the intersubject variability in response to psychostimulant drugs in humans and may participate in the predisposition to drug abuse. These results also support the development of drugs that directly or indirectly interfere with drug-induced increases in DA as potential treatments for addiction.

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