

# Brain DA D2 Receptors Predict Reinforcing Effects of Stimulants in Humans: Replication Study

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**ABSTRACT** We had shown that striatal DA D2 receptors levels predicted the reinforcing responses to the psychostimulant drug methylphenidate in nondrug-abusing subjects. Here, we assessed the replicability of this finding. We measured D2 receptors with PET and [<sup>11</sup>C]raclopride (twice to determine stability) in seven nondrug-abusing subjects to assess if they predicted the self-reports of “drug-liking” to intravenous methylphenidate (0.5 mg/kg). DA D2 measures were significantly correlated with “drug-liking” in both evaluations ( $r = 0.82$  and  $r = 0.78$ ); subjects with the lowest levels reported the higher ratings of “drug-liking” and vice versa. These results replicate our previous findings and provide further evidence that striatal DA D2 receptors modulate reinforcing responses to stimulants in humans and may underlie predisposition for drug self-administration. **Synapse 46:79–82, 2002.** © 2002 Wiley-Liss, Inc.

## INTRODUCTION

One of the most challenging problems in the neurobiology of drug addiction is to understand why some individuals abuse drugs while others do not. Studies in laboratory animals have provided evidence that dopamine (DA), a neurotransmitter involved with movement, cognition, and reward, modulates predisposition to drug abuse (Piazza et al., 1991). For example, in laboratory animals high DA activity in the striatum has been associated with decreased rates of cocaine self-administration (Glick et al., 1994). In humans, it has been hypothesized that low levels of D2 receptors lead to a “reward deficiency syndrome” that predisposes subjects to use drugs as a means to compensate for the decrease in activation of reward circuits by physiological reinforcers (Noble et al., 1991). However, the potential role that DA D2 receptors have in the predisposition to drug addiction is still controversial (Goldman et al., 1998). We recently showed that in nondrug-abusing human subjects the levels of DA D2 receptors in striatum predicted the reinforcing responses to the psychostimulant drug methylphenidate; subjects with low levels reported MP as pleasant, whereas those with high levels reported it as unpleasant (Volkow et al., 1999). In that study we postulated that high DA D2 receptor levels may protect against

drug self-administration. Here we assessed the replicability of our previous finding of a relationship between striatal DA D2 receptors and self-reports of “drug-liking.”

We used [<sup>11</sup>C]raclopride, a DA D2 receptor radioligand, and positron emission tomography (PET) to determine if there was a relationship between the DA D2 receptor levels in striatum (brain region where the nucleus accumbens, which is the structure associated with drug reinforcement, is located) and the reinforcing responses to methylphenidate (MP) (psychostimulant drug that like cocaine increases DA by blocking the DA transporters; Ritz et al., 1987). Since the measures of DA D2 receptors as assessed with [<sup>11</sup>C]raclopride have been shown to be sensitive to changes in extracellular

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DA (Volkow et al., 1994), which could fluctuate between experiments, we measured the correlation with drug-liking for two D2 receptor measures performed on separate days.

## MATERIALS AND METHODS

Subjects were seven healthy controls (two female and five male, mean  $31 \pm 8$  years of age, age range 24–42 years) were studied. Exclusion criteria were current or past psychiatric, neurological, or medical disease, dependence on any substance other than nicotine or caffeine. None of the subjects was taking medications at the time of the study. Toxicological drug screens were performed prior to the PET scan. Informed consent was obtained for all subjects. The study was approved by the Institutional Review Board of Brookhaven National Laboratory.

Subjects were scanned twice using a CTI 931 tomograph ( $6 \times 6 \times 6.5$  mm full width half maximum) after iv injection of 4–10 mCi of [ $^{11}\text{C}$ ]raclopride (specific activity 0.5–1.5 Ci/ $\mu\text{M}$  at EOB) using procedures previously described (Wang et al., 1993) and were tested on two different days at least 1 week apart. After the PET measures, subjects were given either an iv placebo (3 cc saline) or an iv dose of MP (0.5 mg/kg) after they were told that they would receive either placebo or MP. Sixty minutes after placebo or MP administration subjects were asked to rate their liking of the drug from 0 (not like at all) to 10 (maximal liking).

Regions of interest were outlined in striatum (STR) and cerebellum (CB) on the individual's summed [ $^{11}\text{C}$ ]raclopride image (images obtained between 15–54 min) and were then projected into the dynamic [ $^{11}\text{C}$ ]raclopride images to generate time–activity curves for STR and CB (Volkow et al., 1993b). These time–activity curves for tissue concentration along with the time–activity curves for unchanged tracer in plasma were used to obtain the distribution volumes (equilibrium measurement of the ratio of tissue concentration to plasma concentration) in STR and CB using a graphical analysis technique for reversible systems (Logan et al., 1990). The ratio of the distribution volumes in STR to that in CB corresponds to  $B_{\text{max}}/K_d + 1$  and was used as the measure of DA D2 receptor availability (Logan et al., 1994). Plasma MP concentration was measured using capillary GC/Mass spectrometry (Srinivas et al., 1991) for samples taken at 27 and 47 min after MP administration.

Paired Student's *t* Tests were done to compare the effects of placebo and MP on the self-reports of “drug liking.” Pearson product moment correlation analyses were done to assess the relationship between the levels of DA D2 receptors for the two separate measures and the self-reports for “drug-liking” after placebo and after MP.

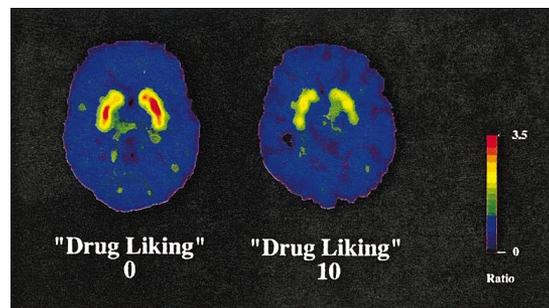


Fig. 1. Distribution volume ratio images for [ $^{11}\text{C}$ ]raclopride showing DA D2 receptor availability in a subject who scored the “drug-liking” effects of methylphenidate as “0” and one that scored it as “10.”

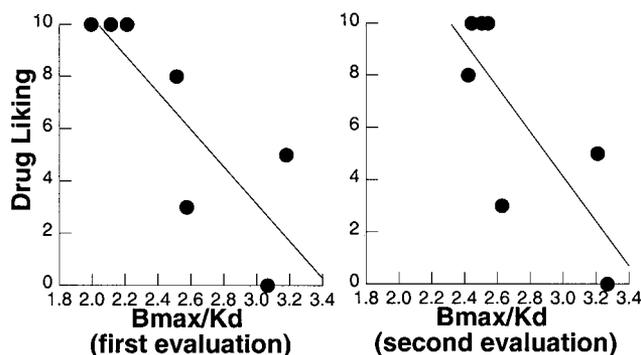


Fig. 2. Regression slopes between self-reports of “drug-liking” after methylphenidate and the DA D2 receptor measures ( $B_{\text{max}}/K_d$ ) in striatum obtained for the first and the second evaluations.

## RESULTS

Plasma MP concentrations corresponded to  $136 \pm 23$  ng/ml at 27 min and to  $80 \pm 19$  ng/ml at 47 min after MP administration. The self-report for “drug-liking” after iv MP ( $6.6 \pm 4$ ) and those after placebo ( $0.6 \pm 1$ ) differed significantly from each other ( $t = 4.3$ ,  $df$  6,  $P < 0.005$ ). The correlations between DA D2 receptor availability and the self-reports for “drug-liking” after MP were significant and corresponded for the first evaluation to  $r = 0.82$  ( $P = 0.02$ ) and for the second evaluation to  $r = 0.78$  ( $P = 0.04$ ) (Figs. 1, 2). Subjects with the lower DA D2 receptor availability were the ones that had the higher scores in “drug-liking” and those with the higher D2 receptor availability had the lower scores in “drug-liking.”

In contrast, the correlations between DA D2 receptor availability and the self-reports of “drug-liking” after placebo were not significant and corresponded for the first evaluation to  $r = 0.50$  ( $P = 0.25$ ) and for the second evaluation to  $r = 0.33$  ( $P = 0.47$ ). The correlations between plasma MP and the self-reports of “drug-liking” were also not significant (data not shown).

## DISCUSSION

The significant association between DA D2 receptor availability and the self-reports of “drug-liking” repli-

cates our previous findings showing that subjects who reported MP as pleasant had significantly lower levels of DA D2 receptors than those who reported it as unpleasant. In the previous study differences in DA D2 receptors were measured between subjects grouped on the basis of whether they reported the effects of MP as pleasant, unpleasant, or neutral. In the current study we assessed the relationship between DA D2 receptor availability and a continuous measure of "drug-liking" (subjects rated drug-liking from 0–10). The results are the same for both studies; that is, subjects with low D2 receptor availability tend to like the effects of MP more than subjects with high DA D2 receptor availability. This finding could be explained if there is an optimal range for DA D2 receptor stimulation by MP to be perceived as reinforcing; too little may not be sufficient but too much may be aversive. Thus, it is possible that in subjects with high DA D2 receptors a smaller dose of MP may have been perceived as pleasant. If DA D2 levels modulate sensitivity to physiological reinforcers, then one could postulate that low DA D2 receptors would predispose a subject to use drugs as a means to compensate for the decreased activation of reward circuits ("reward deficiency syndrome") (Blum et al., 1996). Alternatively, it is possible that low DA D2 receptors could predispose to psychostimulant abuse by favoring initial "pleasant" drug responses, which have been shown to predict future drug use (Davidson et al., 1993), and/or that high DA D2 receptors may protect against drug abuse by favoring "unpleasant" drug responses. Evidence that high levels of DA D2 receptors are causally associated with a reduction in drug intake and may therefore serve as a protective factor was recently demonstrated for alcohol self-administration (Thanos et al., 2001). The latter study used an adenoviral vector to deliver the DA D2 receptor gene into the nucleus accumbens of rats which had been previously trained to self-administer alcohol. This resulted in increases in DA D2 receptors that were within the physiological range ( $\pm 50\%$ ) and in marked reductions in alcohol intake, which recovered as the DA D2 receptors returned to baseline levels. These results could be taken as indirect evidence of a protective role of high DA D2 receptor levels against drug abuse. The expression of DA D2 receptors in the brain, which has been shown to be modulated by both genetic and environmental factors, such as social hierarchy (Morgan et al., 2002) and stress (Papp et al., 1994), provides a molecular mechanism that can account for the involvement of both genetic as well as environmental factors in the predisposition to drug abuse. It also opens up the possibility for developing strategies to increase the expression of DA D2 receptors as a means of decreasing drug abuse and help treat drug addiction.

The fact that the correlation between plasma MP concentration and "drug-liking" was not significant suggests that the variability in the responses to MP

was not due to differences in plasma MP concentration. We had previously shown that differences in striatal DA D2 receptor availability, but not plasma MP concentration, contributed to the large intersubject variability in the regional brain metabolic response to intravenous MP (Volkow et al., 1997). In that study MP increased metabolism in frontal and temporal cortices in subjects with high DA D2 receptor levels, whereas it decreased it in subject with low levels. This suggests that part of the variability in responses to MP is related to differences in D2 receptor availability between subjects.

We had previously shown lower levels of DA D2 receptors in the brains of drug abusers (cocaine, methamphetamine, heroin, alcohol) than in that of nonabusing controls (Volkow et al., 1993a, 1996, 2001; Wang et al., 1997). Thus, the results in the current report bring to light the possibility that the low DA D2 receptors in drug abusers may have antedated their drug use and may have increased their vulnerability to drug abuse. However, even if this possibility were to be corroborated, the fact that the subjects that liked MP had DA D2 receptor levels similar to those reported in drug-addicted subjects but were not drug abusers indicates that additional biological and/or environmental variables are involved in the vulnerability to drug abuse and addiction.

Limitations for this study include the limited spatial resolution of the PET scanner, as a result of which one cannot accurately measure DA D2 receptor levels in the nucleus accumbens, which is more directly related to drug abuse than the dorsal striatum. Although raclopride binds to both DA D2 and DA D3 receptors the concentration of DA D3 receptors in dorsal striatum is very low ( $\approx 1\%$  of D2 receptors) (Sokoloff and Schwartz, 1995) so that the PET measurements mainly reflect binding to DA D2 receptors. Since [ $^{11}\text{C}$ ]raclopride is sensitive to competition with endogenous DA (Volkow et al., 1994), one could question whether the association between "drug-liking" and low DA D2 receptor availability reflects increased competition with extracellular DA rather than low DA D2 receptor levels. However, the fact that the correlation with DA D2 receptor measures was present in two separate evaluations suggests that it is due to DA D2 receptor levels, which are stable measures (Volkow et al., 1993b), rather than differences in the concentration of extracellular DA.

This study replicates our previous findings showing an association between DA D2 receptors levels in brain and the reinforcing responses to psychostimulants. These results in conjunction with the preclinical studies provide evidence of the role of DA D2 receptors in modulating predisposition to drug abuse. They also corroborate the involvement of DA D2 receptors in the perception of the reinforcing effects of psychostimulants in human subjects.

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