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Dopamine D_2 Receptor Availability in Opiate-Dependent Subjects before and after Naloxone-Precipitated Withdrawal

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Dopamine may play a role in opiate withdrawal and dependence. We measured dopamine D_2 receptor availability in 11 opiate-dependent subjects using PET and [^{11}C]raclopride at baseline and during naloxone-precipitated withdrawal. Because [^{11}C]raclopride is sensitive to endogenous dopamine, this strategy enabled us to test whether we could document in humans the DA reductions reported in animal models of opiate withdrawal. Results were compared with values from 11 controls, two of which also received naloxone. The ratio of the distribution volume in striatum to that in cerebellum (B_{max}/K_d + 1) was used as model parameter for D_2 receptor availability. Baseline measures for B_{max}/K_d were lower in opiate-dependent subjects (2.44 ± 0.4) than in controls (2.97 ± 0.45, $p \leq .009$). Naloxone precipitated an intense withdrawal in the abusers but did not change the B_{max}/K_d ratio. This study documents decreases in D_2 receptors in opiate-dependent subjects but does not document significant changes in striatal DA concentration during acute withdrawal.

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KEY WORDS: *Naloxone; Opiate abuse; PET, Withdrawal*

As for the most addictive drugs, opiates appear to exert their reinforcing properties in part through their ability to increase dopamine (DA) concentration in the nucleus accumbens (Koob and Bloom 1988). The DA system has also been implicated in opiate withdrawal, and most of the recent studies suggest that withdrawal is associated with reduced DA activity (Harris and Aston-Jones 1994). For example, naloxone-precipitated withdrawal is accompanied by reductions in extracellular DA in the ventral tegmental area and in the nucleus accumbens (Pothos et al. 1991; Rossetti et al. 1992). Furthermore it has been suggested that the aversive symptomatology during opiate withdrawal may be in part due to the suppression of DA activity (Rossetti et al. 1990; Acquas et al. 1991). However, the results from pharmacological studies give evidence compatible with both decreases as well as increases in DA activity during withdrawal indicative of a more complex role of DA in opiate withdrawal. For example, some studies have shown that DA antagonists improve (Lal et al. 1971; Lal and Numan 1976; Levinson et al. 1995) and others that it worsens (Harris and Aston-Jones 1994) opiate withdrawal. Similarly, some studies have shown that DA-enhancing drugs exacerbate (Gunne 1965; Gomaa et al. 1989) and others that it ameliorates (Harris and Aston-Jones 1994) symptoms of opiate withdrawal. Other studies have even shown that DA agonists increase the intensity of some of the withdrawal symptoms and decrease that of others in the same animal (Ferrari and Baggio 1982; Ary

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Table 1. Demographic Data of Opiate-Dependent Subjects

Subject	Age (yrs)	Drug Use	Daily Dose	Years of Use
1	36	Heroin/methadone	1.5–4g/80 mg	16/4.5
2	44	Heroin	2-2.5 g	30
3	42	Heroin/methadone	0.5g/60 mg	20/20
4	45	Heroin/methadone	1g/60mg	24/0.5
5	46	Heroin/methadone	0.25g/40mg	15/2
6	35	Heroin/methadone	0.25g/100mg	3/18
7	43	Heroin	0.25g	2
8	40	Heroin/methadone	1.5g/70mg	12/0.75
9	43	Heroin/methadone	2g/80mg	16/0.75
10	38	Heroin/methadone	5g/80mg	21/2.5
11	36	Heroin/methadone	1.5g/60mg	15/2

et al. 1977). Thus, it has been suggested that some effects of opiate withdrawal may be due to increased DA activity and others to decreased activity (Ary et al. 1977).

Positron Emission Tomography (PET) in conjunction with [^{11}C]raclopride can be used to measure DA D_2 receptor availability noninvasively in human subjects (Farde et al. 1985). Because [^{11}C]raclopride is sensitive to endogenous DA concentration (Seeman et al. 1989), it can also be used to measure relative changes in DA concentration secondary to pharmacological interventions (Volkow et al. 1994). Interventions that increase DA concentration reduce D_2 receptor availability and vice versa (Dewey et al. 1993). In this study, we evaluated DA D_2 receptor availability with PET and [^{11}C]raclopride in opiate-dependent subjects who were abusing heroine either alone or in combination with methadone. We also assessed the effects of naloxone-precipitated withdrawal on D_2 availability to assess possible changes in striatal DA concentration during withdrawal. Values were compared with those obtained in age-matched controls.

MATERIALS AND METHODS

Subjects

The patient group consisted of 11 male opiate-dependent subjects (mean age 40.7 ± 4.1 years old) who met DSM-IV diagnostic criteria for opiate dependence and had at least a 12-month history of continuous use of opiates (heroin and/or methadone; Table 1). Subjects with a history of cardiovascular, psychiatric, neurological, metabolic, or endocrinological disease, and/or history of drug dependence other than opiates, nicotine, or caffeine were excluded. The control subjects consisted of 11 healthy male volunteers (mean age 39.6 ± 4.4 years old). Exclusion criteria were the same as for opiate-dependent subjects, except for opiate use. As part of the evaluation, all subjects received a complete medical, neurological, and psychiatric evaluation. Urine toxicological studies were performed in all the subjects prior to the study to ensure the absence of drug use. The consent forms and protocol were approved by the Human Subjects Research Committee of Brookhaven National Laboratory.

PET Scanning

Scans were obtained using a CTI-931 PET camera (15 slices, 6.5×6.0×6.0 mm Full Width Half Maximum). Positioning, preparation for the study, and transmission and emission scans were carried out as previously described (Volkow et al. 1993b). Briefly, emission scans were started immediately after intravenous injection of 7 to 8 mCi of [^{11}C]raclopride, and sequential dynamic scans were obtained for a total of 60 minutes. Preparation of [^{11}C]raclopride (specific activity 0.5–1.5 Ci/μmol at the end of bombardment) and measurement of arterial input function were performed as described (Volkow et al. 1993b).

All subjects were scanned with [^{11}C]raclopride under baseline conditions. In addition, nine of the opiate-dependent subjects and two of the controls had a second scan

Table 2. Averaged Distribution Volume of Basal Ganglia and Cerebellum as well as B_{max}/K_d Estimates of Opiate-Dependent and Normal Subjects

	Opiate-Dependent Subjects		Normal Subjects	
	Distribution Volume	B_{max}/K_d	Distribution Volume	B_{max}/K_d
Caudate	1.52 ± 0.16	1.94 ± 0.30	1.52 ± 0.32	2.24 ± 0.24*
Putamen	1.78 ± 0.24	2.44 ± 0.40	1.86 ± 0.42	2.97 ± 0.45†
Cerebellum	0.52 ± 0.05	—	0.47 ± 0.07	—

Unpaired t-test: *$p \leq .02$, †$p \leq 0.009$.

with [^{11}C]raclopride done after admission of naloxone. Baseline scans were done 5 to 7 minutes after administration of placebo (3 ml saline IV). In the controls, a single dose of naloxone (0.15 mg/kg) was administered 5 to 7 minutes prior to [^{11}C]raclopride; for the opiate-dependent subjects, naloxone (0.01 mg/kg IV) was given every 4 minutes until signs of withdrawal (yawning, abdominal cramps, rhinorrhea, tearing) appeared. The average doses of naloxone given to the opiate abusers were 0.02 to 0.025 mg/kg. Subjects were blind to the drug received.

Behavioral and Cardiovascular Assessment

The mental state of the subjects before and after placebo or naloxone was evaluated using analog scales (activeness, alertness, annoyances, anxiety, concentration, loss of control, depression, distrustful thought, desire to use opiates, happiness, indifference, irritability, mood, optimism, pain, restlessness) rated from 0 (nothing) to 10 (maximum). The subjective perception of "withdrawal" after placebo or naloxone was evaluated using analog scales (yawning, running nose, lacrimation, profuse sweating, shivering, abdominal cramps, piloerection, hand tremors, muscle twitches, and vomiting) rated from 0 (felt nothing) to 3 (felt extremely). These scales were recorded 5 minutes before and 10, 30, and 60 minutes after injection of saline or naloxone. In addition, the subjective experience of drug effects was questioned every minute using analog scales rated from 0 (felt nothing) to 10 (felt extremely) for 20 minutes after naloxone or placebo administration.

Electrocardiographic recordings, blood pressure, and pulse rate were obtained every 15 minutes for 30 minutes prior to injection of saline or naloxone and then every minute for 20 minutes and then at 25, 30, 45, and 60 minutes after their administration.

Analysis

Regions of interest (ROI) in the striatum and the cerebellum were obtained directly from an averaged emission scan and were then projected to the dynamic scans as described previously (Volkow et al. 1993b). Images were not coregistered with magnetic resonance (MR) images, as we previously showed that coregistration does not improve quantitation for ligands such as [^{11}C]raclopride, which have selective and high accumulation in well-defined structures (Wang et al. 1996). The ROI were obtained bilaterally in the caudate (CA) and putamen (PU) at the planes where they were best identified (CA: 3 slices, PU: 2 slices; Figure 1). Right and left

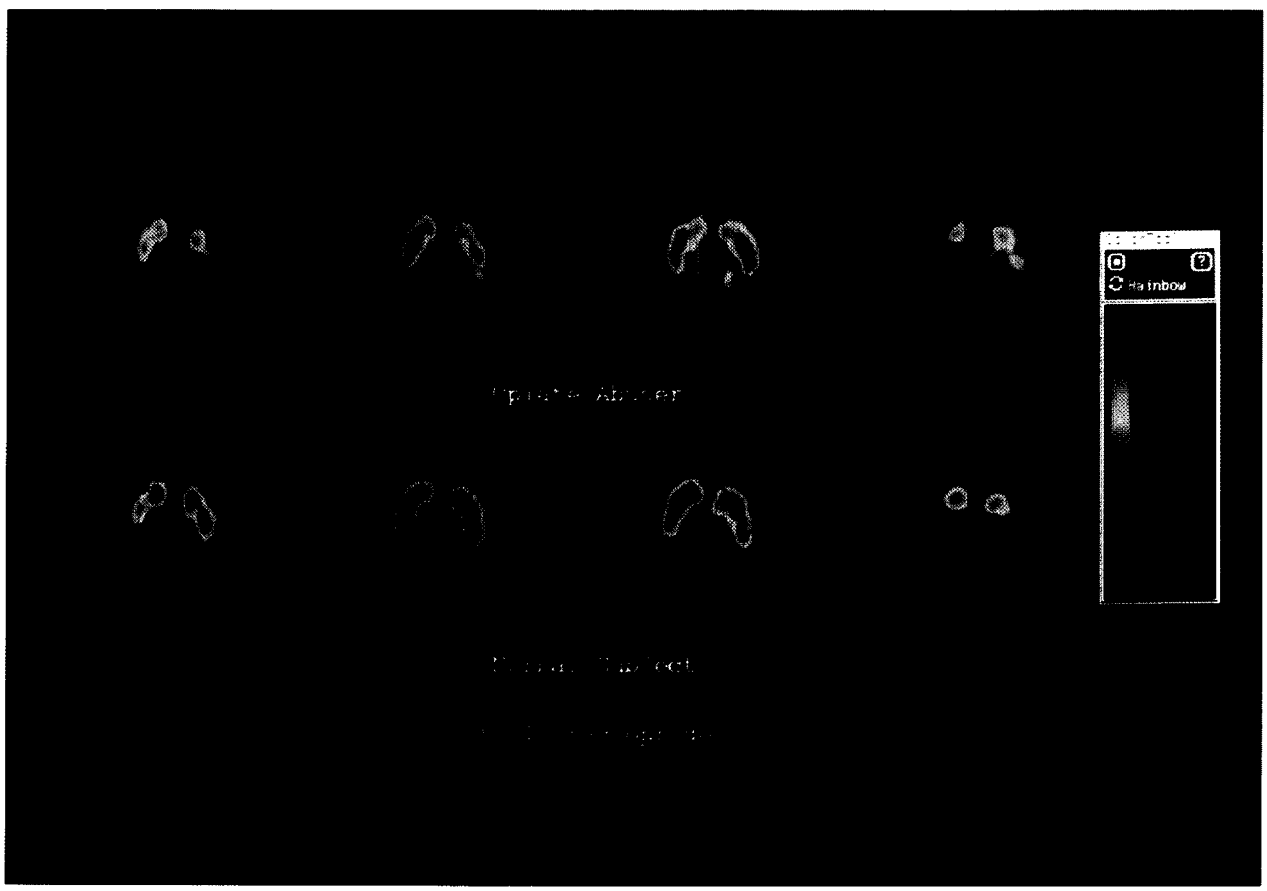

Figure 1. Images at the level of the basal ganglia obtained 30 to 60 minutes after injection of [^{11}C]raclopride for an opiate-dependent subject and a normal control. Images are normalized to dose injected.

cerebellar (CB: 2 slices) regions were obtained in two planes (1.0 and 1.7 cm above the CM lines). Values for the striatal and cerebellar regions were computed using the weighted average for the left and right regions from the different slices where the regions were obtained. The time activity curves in the striatum and cerebellum along with the concentration of the nonmetabolized tracer in plasma were used to obtain distribution volumes (DV) using a graphical analysis technique (Logan et al. 1990). The ratio of the DV in the striatum to that in the cerebellum, which corresponds to $(B_{max}'/K_d') + 1$ and is insensitive to changes in cerebral blood flow, was used as model parameter to quantify D_2 availability (Logan et al. 1990).

Comparisons of DA D_2 receptor availability at baseline between opiate-dependent subjects and normal subjects were tested with ANOVA. Differences between placebo and naloxone for the B_{max}/K_d estimates and for the behavioral and the cardiovascular measures were tested using repeated-measure analysis of variance (ANOVA). The magnitude of naloxone-induced changes in B_{max}/K_d also was compared against the test-retest changes in B_{max}/K_d obtained in a group of five controls tested twice with [^{11}C]raclopride (Volkow et al. 1993b). We set the level of significance to $p \leq .05$.

RESULTS

The binding of [^{11}C]raclopride was lower in the striatum, but not in the cerebellum, of opiate-dependent subjects than controls (Figure 1). Measures of D_2 receptor availability were significantly lower in the opiate-dependent subjects than in controls (Table 1). B_{max}/K_d estimates were lower in the putamen of opiate-dependent subjects (2.44 ± 0.4) than of controls (2.97 ± 0.45, $p \leq .009$), and in the caudate of opiate-dependent subjects (1.94 ± 0.3) than of controls (2.24 ± 0.24, $p \leq .02$) and were not correlated with age of subject or with years of opiate use or doses abused. Figure 2 shows the individual B_{max}/K_d values in the putamen as a function of age.

Saline administration in the controls and in the opiate-dependent subjects and naloxone administration in the controls did not change any of the cardiovascular or the behavioral measures. In contrast, naloxone induced a robust withdrawal (subjectively rated 79% ± 17%) and significantly changed most of the behavioral and cardiovascular measures in the opiate-dependent subjects. Nine of the opiate-dependent subjects received a 0.2-mg/kg dose, and two requested not to be given any more doses after the first 0.1-mg/kg IV dose. The peak behavioral effect of naloxone occurred 6 to 12 minutes after its administration. Individual ratings were significant for lacrimation ($p \leq .01$), muscle twitches ($p \leq .01$), annoyance ($p \leq .005$), anxiety ($p \leq .0006$), restlessness ($p \leq .0005$), decreased happiness ($p \leq .001$), yawning ($p \leq .03$), shivering ($p \leq .03$), abdominal cramps ($p \leq .03$), vomiting ($p \leq .04$), and loss of control ($p \leq .02$; Figures 3 and 4). In the addicts, naloxone significantly increased pulse rate (paired t-test, $p \leq .006$), systolic ($p \leq .0001$) and diastolic pressure ($p \leq .003$; Figure 5). Maximal cardiovascular responses occurred within 4 to 20 (12 ± 5) minutes of injection. Naloxone-induced peak increases from baseline for pulse rate corresponded to 50.9% ± 43% (range 10% to 123%) for systolic pressure to 38.3% ± 15.9% (17% to 67%), and for diastolic pressure to 36.6% ± 20.3% (10% to 80%). The naloxone-precipitated withdrawal was of short duration: at 30 minutes none of the withdrawal symptoms were significant, and by 60 minutes subjects had returned to baseline.

Naloxone administration did not change significantly the measures of DA D_2 receptor availability in opiate-dependent subjects or in controls, and the effects did not differ between the nine opiate-dependent subjects and the two controls ($F = 2.87$, df = 1, 9; $p = .12$; Figure 6). $B_{max}/$

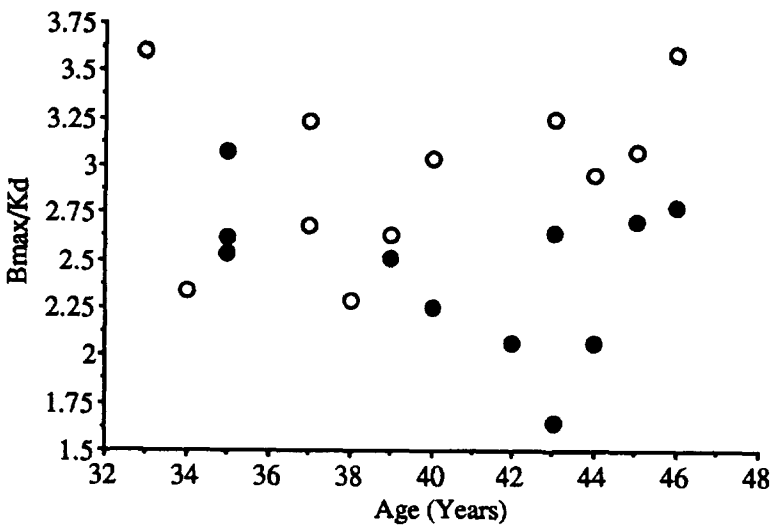

Figure 2. Estimates of B_{max}/K_d in opiate-dependent subjects (*solid circles*) and in normal subjects (*open circles*) as a function of age.

K_d) measures for subjects (opiate-dependent subjects and controls) who underwent both scans were for the putamen 2.53 ± 0.33 (saline), 2.29 ± 0.40 (naloxone), and for the caudate 1.99 ± 0.31 (saline), 1.81 ± 0.35 (naloxone).

The results of the ANOVA comparing the responses to naloxone between the opiate-dependent subjects who received the larger dose (0.02 mg/kg, $n = 7$) and those who received the lower dose (0.01 mg/kg, $n = 2$) showed a significant drug effect ($F = 11.4$, df = 1, 7, $p \leq .01$) and a significant drug-by-group interaction effect ($F = 19.5$, df = 1, 7, $p \leq .003$). The opiate-dependent subjects that received the higher naloxone dose showed a significant decrease in B_{max}/K_d during withdrawal ($F = 8.5$, df = 6, $p \leq .03$). Because this effect was small and very close to the test-retest variability for B_{max}/K_d measures with [^{11}C]raclopride, we compared it with the B_{max}/K_d values we had previously obtained in five controls subjects tested twice after placebo. The percent changes in B_{max}/K_d in the opiate-dependent subjects who received the 0.02-mg/kg dose was significantly different from the test-retest measures ($F = 5.4$, df = 11, $p \leq .04$; Figure 6).

DISCUSSION

This study shows significant decreases in DA D_2 receptor availability in the striatum of opiate-dependent subjects compared with controls. Decrements in DA D_2 receptors also were documented in cocaine abusers (Volkow et al. 1990, 1993a) and in alcoholics (Hietala et al. 1994; Volkow et al. 1996), indicating that they are not specific for any one particular drug addiction. Because increases in DA concentration during acute administration have been reported to occur with most of the abused drugs (Hurd and Ungerstedt 1989; Brodie and Dunwiddie 1990; Pothos et al. 1991; Yoshimoto et al. 1992), one could predict that their chronic administration could lead to changes in DA function. In fact, decreases in DA function have been documented after withdrawal from chronic exposure to alcohol, morphine, or cocaine (Rossetti et al. 1992). Thus, one could postulate that the decrements in D_2 receptors present a downregulation to compensate for DA increases during drug intoxication. However, this is unlikely as, at least for cocaine abusers, these reductions persist even after protracted withdrawal (Volkow et al. 1993a). An alternative explanation is that the individuals had low D_2 receptor measures even prior to starting abusing drugs and that this reduction may have made them more vulnerable to drug self-administration. Though a direct link between D_2 receptors and drug abuse has not been demonstrated, there are data indicating that certain markers of D_2 receptors genes may be associated with a higher frequency and severity for drug abuse (Review Uhl et al. 1995; Blum et

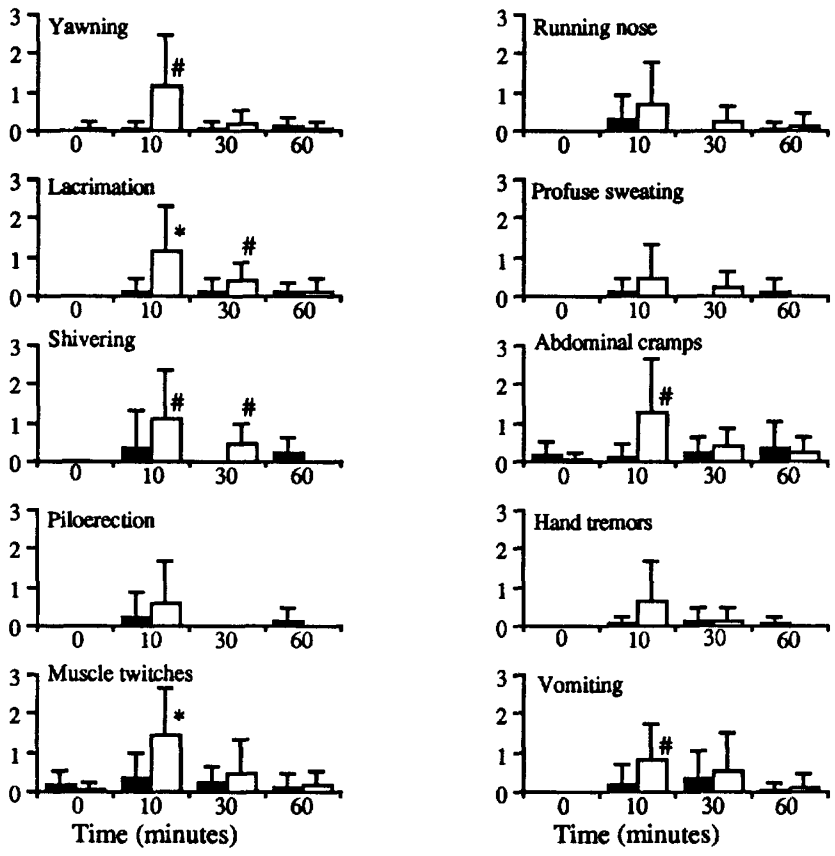

Figure 3. Opiate withdrawal symptoms (rated 0–3) prior to (0), 10, 30, and 60 minutes after injection of placebo (*solid squares*) or naloxone (*open squares*). (*$p \leq .01$, #$p \leq .05$).

al. 1996). The measures of DA D_2 receptor availability were not correlated with the age of the opiate abuse or with the age in the controls or in the opiate-addicted subjects. Failure to document an age-related decline in DA D_2 receptors in this group of subjects is probably due to the small sample size and the restricted age range.

Although the group measures for DA D_2 receptor availability were not significantly changed by naloxone, a separate analysis showed a significant decrease in the opiate abusers that received the larger naloxone dose (0.2 mg/kg IV). This was surprising as microdialysis studies have shown significant decreases in extracellular DA concentration during naloxone-precipitated withdrawal (Rossetti et al. 1990; Acquas et al. 1991). [^{11}C]Raclopride's relatively low affinity for the DA D_2 receptor makes it sensitive to changes in endogenous DA concentration. Hence one would have expected increases in [^{11}C]raclopride binding during withdrawal. If anything, the significant reductions induced by naloxone in B_{max}/K_d in the opiate abusers receiving the larger naloxone dose are compatible with an increase in striatal DA release. There are several possible explanations for the discrepancies with the microdialysis studies. One is that microdialysis studies have documented DA reductions in the nucleus accumbens and in the ventral tegmental area, which are brain regions too small to be measured

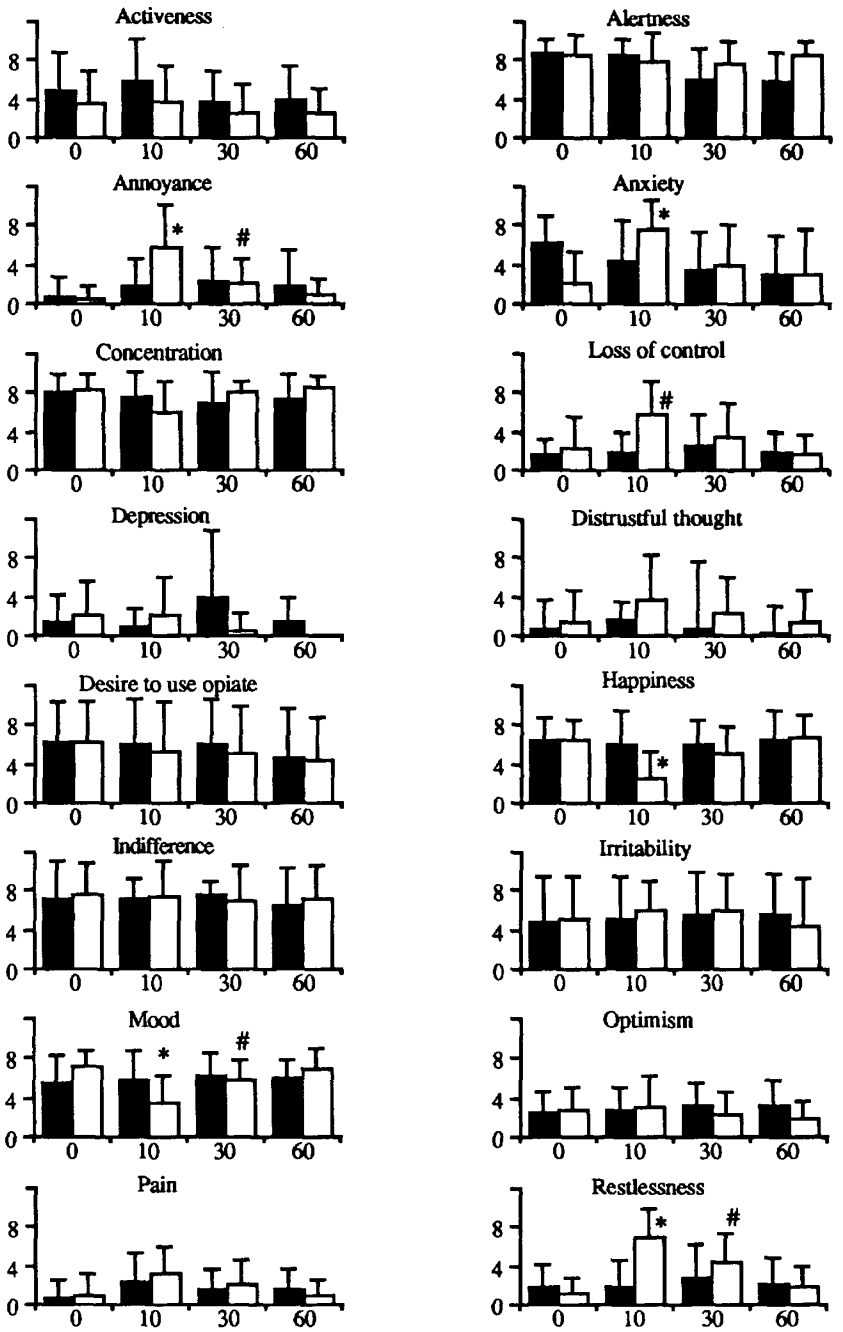

Figure 4. Behavioral scores (rated 0–10) prior to (0), 10, 30, and 60 minutes after injection of placebo (*solid squares*) or naloxone (*open squares*). (*$p \leq .01$, #$p \leq .05$).

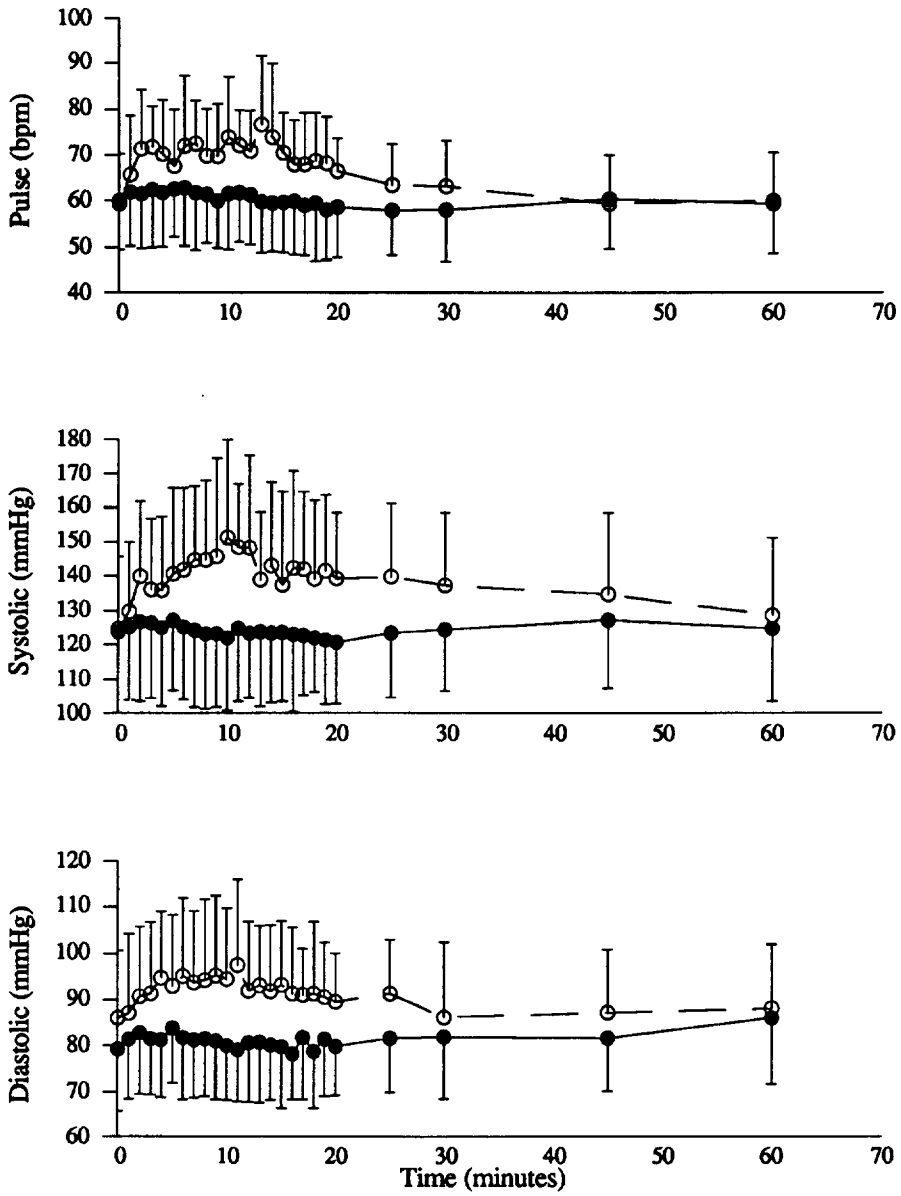

Figure 5. Effect of naloxone on pulse rate and blood pressure of opiate-dependent subjects (*solid circles*, placebo; *open circles*, naloxone).

with PET. Our measurements mainly represent the dorsal striatum, and to our knowledge no microdialysis studies have been performed in a comparable anatomical region. Furthermore, because there is evidence that opiate withdrawal symptoms respond differently to DA drugs (Ary et al. 1977), it cannot be assumed that DA changes during opiate withdrawal are homogeneous throughout the various DA projecting regions. Also, although microdialysis studies have shown that there is a reduction in DA concentration in the nucleus accumbens, the temporal course of this reduction does not correspond with the temporal course of the abstinence symptoms (Pothos et al. 1991) indicating that other brain regions and/or neurotransmitters are likely to participate in withdrawal. There also is evidence that in opiate-dependent subjects DA antagonists ameliorate some of the abstinence symptoms, which would suggest that in these subjects symptomatology may also be associated with an increase in DA activity (Lal et al. 1971; Lal and Numan 1976; Levinson et al. 1995). Our results, with the larger naloxone dose (0.02 mg/kg IV), if anything, are consistent with an increase in DA release in the dorsal striatum during withdrawal. Another difference is that microdialysis studies were carried out with much larger naloxone doses (0.5 mg/kg to 20 mg/kg IP). (Harris and Aston-Jones 1994; Pothos et al. 1991) than the one we gave the subjects (0.01 and 0.02 mg/kg IV) and using different routes of administration. Although the doses used in this study were sufficient to elicit an intense withdrawal and are similar to those used by others to induce withdrawal (Kanof et al. 1992), larger doses may be required to observe a reduction in DA. The conditions of the experi-

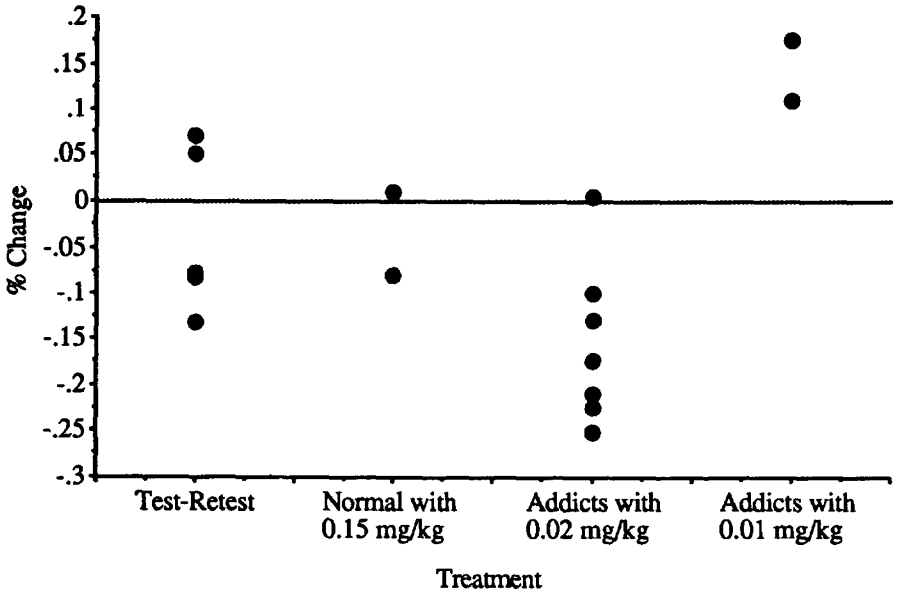

Figure 6. Percent changes in B_{max}/K_d (naloxone-placebo) in controls receiving the 0.15-mg/kg IV dose, opiate-dependent subjects receiving the 0.01 mg/kg IV dose, and those receiving the 0.02-mg/kg IV dose of naloxone. Percent changes in B_{max}/K_d for subjects tested twice after placebo are also shown as reference for test-retest variability.

ment also differed; microdialysis studies were done in freely moving animals, whereas in our experiments the subjects were in the scanner lying still and were specifically asked to refrain from moving. There may also be species differences in the response to opiates. For example, in anesthetized nondependent baboons, we have shown decrements in DA concentration (30–60 minutes after 1 mg/kg of naloxone IV) using [^{11}C]raclopride (Smith et al. 1993). The sensitivity to naloxone also is dependent on the individual's prior opiate history, and exposure in animal models (1–15 days) is not comparable to that in humans (2–24 years). Irrespective of these variables, these results do not document a reduction in striatal DA concentration during naloxone-precipitated acute opiate withdrawal in human subjects.

A limitation for this study was that MR images were not obtained, so we cannot exclude the possibility of morphological changes in the opiate-dependent subjects as a confounder in our measurements. Also, our measures are an index of DA D_2 receptor availability, not of receptor concentration itself as [^{11}C]raclopride is sensitive to endogenous DA concentration (Dewey et al. 1993). Hence our findings are confounded by possible changes in synaptic DA concentration between opiate-dependent subjects and controls. Future studies using PET scanners with higher resolution and sensitivity may enable us to determine whether there are subregions in the striatum during withdrawal where there are DA reductions (i.e., nucleus accumbens) and others where there are DA increases.

In summary, DA D_2 receptors in opiate-dependent subjects were decreased when compared to controls. Group measures for DA D_2 availability did not change during naloxone-precipitated withdrawal and failed to support a reduction in DA concentration in the dorsal striatum during acute opiate withdrawal.

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