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Decreasing Striatal 6-FDOPA Uptake with Increasing Duration of Cocaine Withdrawal

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It has been hypothesized that a decrease in dopaminergic presynaptic activity during abstinence or withdrawal is related to relapse in cocaine-dependent subjects (Dackis and Gold 1985; Markou and Koob 1991). This study measured striatal 6-fluorodopa (6-FDOPA) uptake, an index of dopaminergic presynaptic activity, using positron emission tomography (PET) in 11 drug-free cocaine addicts compared to eight normal subjects. Middle abstinence cocaine addicts (n = 5, off cocaine 11–30 days) had significantly lower striatal 6-FDOPA uptake compared to normal controls or early abstinence cocaine addicts (n = 6, off cocaine 1–10 days). The cocaine-dependent subjects (n = 11) showed a significant negative correlation between days off cocaine and striatal 6-FDOPA uptake. The results suggest that during abstinence from cocaine there is a delayed decrease in dopamine terminal activity in the striatum.

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KEY WORDS: *Cocaine; Stimulants; Emission computed tomography; Brain radionuclide imaging; Dopamine metabolism; Dopa analogs and derivatives*

Cocaine is one of the most potent and reinforcing central nervous system stimulants (Withers et al. 1995). Cocaine's pharmacological effects are due to its binding of the dopamine transporter molecule, thereby increasing intrasynaptic dopamine concentration (Giros et al. 1996). Seventy-five percent of patients who withdraw from cocaine abuse relapse within a year (Paredes et al. 1991; Carroll et al. 1994).

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Gawin and Kleber (1986), Martin et al. (1989a), and Satel et al. (1991) found that there was a delayed cocaine craving with approximately 10 days of abstinence from cocaine. Gawin and Kleber (1986) have described a triphasic course during abstinence from cocaine for outpatients. The first phase is described as a crash phase with extreme dysphoria and hypersomnolence lasting 1 to 40 h. The second phase is described as the withdrawal period lasting up to 10 weeks. This phase is subdivided into two subphases. The early subphase is characterized initially by little cocaine craving, near-normal affective functioning, and normal sleep/wake cycles, and it lasts several days. The middle and late subphase is characterized by high cocaine craving, dysphoria, anhedonia, and anxiety and sensitivity to conditioned cues. Martin et al. (1989a) found that there was distinct increase in cocaine craving between 1 and 2 weeks after last cocaine use in six patients who were evaluated over a 21-day period during an inpatient recovery. Satel et al. (1991) found that there was an initial decrease in Beck Depression score between days 1–9

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compared to baseline in 22 inpatients observed over a 3-week period. Satel et al. (1991) then found that there was an increase in the Beck Depression score starting at days 10–12. Dysphoria during abstinence has been hypothesized to be associated with increased reuse of cocaine (Markou and Koob 1991). Similar patterns of delayed behavioral anxiety-like or depression-like behavior after cessation of long-term cocaine use in animal studies have also been reported (Fung and Richard 1994; Sarnyai et al. 1995).

Dackis and Gold (1985) and Markou and Koob (1991) have suggested that after cocaine withdrawal, vulnerability to cocaine craving and reuse might be due to a drop in dopamine synthesis. 6-FDOPA PET scans provide the capability to assess presynaptic dopaminergic activity in vivo in the neostriatal terminal projections in humans (Garnett et al. 1983; Calne et al. 1985)

METHODS

Subjects

Eleven cocaine-dependent subjects in withdrawal (<30 days since last use) were studied using 6-FDOPA uptake. Inclusion criteria were: (1) DSM-III-R diagnostic criteria for active cocaine dependency, (2) continuous use of cocaine for at least the prior 6 months with claimed cocaine use of at least 2 g/week (estimated cost of $200/week), (3) expressed willingness to participate in the research study, (4) right-handedness. All subjects were male. All cocaine-dependent subjects received a comprehensive psychiatric evaluation and physical examination. All subjects were admitted to an inpatient psychiatric ward where frequent random urine drug screens were performed, and abstinence from cocaine was documented. All consecutively admitted patients who were eligible for the study and who signed an informed consent were recruited for the study.

The cocaine-dependent subjects had a mean age of 39.1 ± 6.9 years. They had a mean of 12.2 ± 4.7 years of cocaine use with an average use of 1.3 ± 0.8 g of cocaine/day. The cocaine-dependent subjects were subdivided into early abstinence (EAC, <10 days) and middle abstinence (MAC, days 11–30) subgroups. There were six subjects in early abstinence (age = 39.3 ± 7.5 years,number of years of cocaine usage = 12.3 ± 5.4 years, g cocaine/day = 1.1 ± 0.85). There were five subjects in middle abstinence (age = 38.8 ± 7.0 years, number of years of cocaine usage = 12.0 ± 4.3 years, g cocaine/day = 1.7 ± 0.7). the early abstinent and middle abstinent subjects did not differ significantly in age, amount, or duration of cocaine use. The eight control subjects had a mean age of 30.1 ± 17.0 years. No significant difference in age was found between normal controls and cocaine-dependent subjects. All control subjects had a negative urine drug screen and had a negative history of personal psychiatric illness after being assessed by a Structured Clinical Interview for Diagnosis (SCID) screening.

PET Scan

Subjects were studied in an OrtecECAT scanner (full-width, half-maximum resolution was equal to 7.5 mm in plane and 10.9 mm axially). Each subject was positioned with the aid of a vertical laser line. During the scanning procedure, subjects were lying supine. A custom molded thermoplastic head holder was used to minimize head movements. The studies were performed by estimating the position (z-offset) of the striatum 40 mm above the canthomeatal (CM)-line. Subjects were administered 6-FDOPA intravenously (2–3.75 mCi) in a forearm vein. 6-FDOPA was made using a "no-carrier added" synthesis resulting in high specific activity 6-FDOPA (Najafi 1995). The left arm was used for injection and the right arm for sampling. Sixteen 2-ml venous blood samples (approximately 32 ml total) were taken to determine kinetics of metabolism and uptake of 6-FDOPA. (See Figure 1 for mean time-activity relationship between 6-FDOPA and its metabolite, 3-O-methyl-6-FDOPA (3-OMFD) for normal controls and early and middle abstinence cocaine subjects). Twelve 10-min sequential scans for 6-FDOPA uptake in dorsal striatum were obtained. Calculated attenuation correction was performed on each slice by fitting an ellipse around the whole brain slice. FDOPA uptake was evaluated by using a graphical analysis method (Patlak et al. 1983; Patlak and Blasberg 1985; Martin et al. 1989b).

Data Analyses and Statistics

Individual scan images were stretched to fit a normalizing brain perimeter (170 mm length, 130 mm wide) in a 256 × 256 pixel grid array. Each pixel corresponds to 1 mm^2. Normalized individual 6-FDOPA uptake images were averaged, pixel-by-pixel, to generate superimposable, two-dimensional, averaged 6-FDOPA rate uptake constant for the control and patient groups (Figure 2: top row, left: early abstinence cocaine subjects, middle: middle abstinence cocaine subjects; right: normal controls). Significant difference images (Figure 2, bottom row) were calculated for each comparison (t-test, $p < .05$, two-tailed).

Standard alpha corrections for multiple t-tests (e.g., Bonferroni) assume independence of the tests. The image average maps and image t-test maps do not meet this assumption, because there is a high correlation between adjacent pixels so that a standard correction would be overly conservative. The spatial distribution of the profile of 6-FDOPA uptake difference was assessed by using a resampling-based image cluster analysis. An estimate of the probability for a given profile of

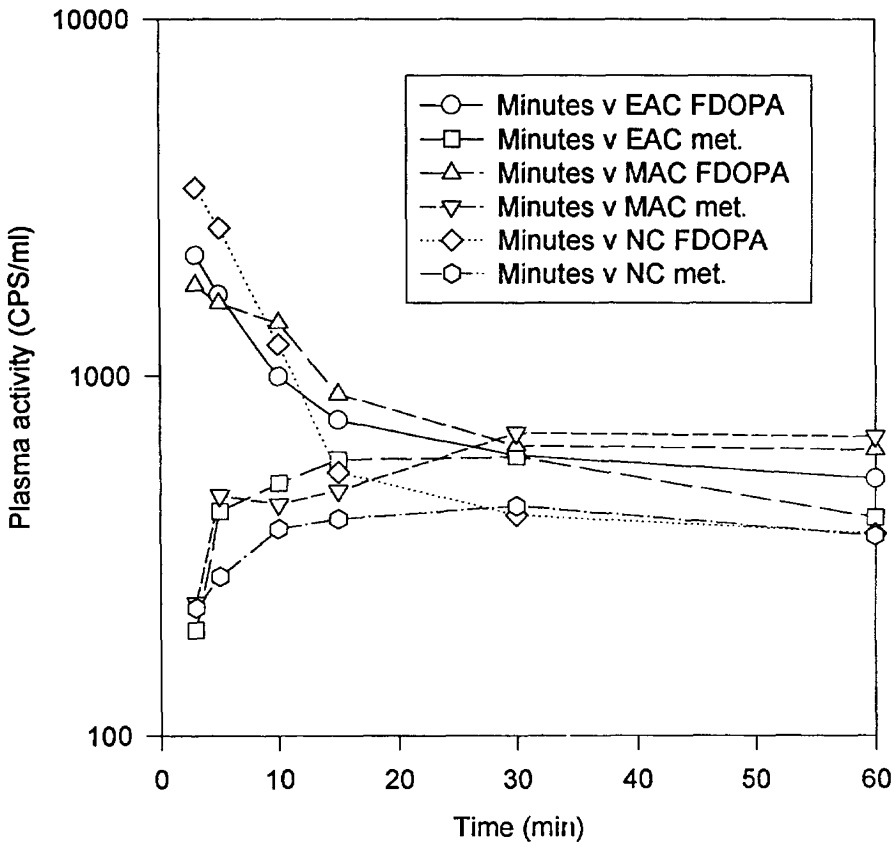

Figure 1. Figure 1 depicts mean time-activity relationship for 6-FDOPA and its metabolite, 3-O-methyl-6-FDOPA (3-OMFD), for early abstinence cocaine subjects (EAC), middle abstinence cocaine subjects (MAC), and normal controls (NC) in peripheral arteriolized venous plasma after administration of 6-FDOPA. 6-FDOPA and 3-OMFD activity were determined by high-performance liquid chromatography analysis.

suprathreshold contiguously connected clusters exceeding a defined probability threshold (e.g., $p < .05$) can be assessed if one knows the distribution of profiles of activation that are due to chance alone. The probability of a given size contiguous cluster were assessed using this distribution. Monte Carlo simulations using sample sizes corresponding to the n's in our comparison ($n = 6$ for early abstinence cocaine subjects, $n = 5$ for middle abstinence cocaine subjects, $n = 8$ for normal controls) were run using our normal control pool with 100 random drawings to determine empirically the distribution (Pollack et al. 1994; Sobol 1975; Widman 1988; Good 1994). A significance level for the p-value was chosen (<.05), and the p-maps were thresholded so that only pixels above the significance level were kept. These thresholded p-maps were then analyzed for cluster size and their frequency of occurrence. A probability distribution was then obtained for every p-map. These 100 probability distributions are then averaged into one probability distribution function and a corresponding cumulative distribution was calculated. Based on the simulated cumulative distribution, an estimate of the cluster size versus probability of random occurrence was obtained. The p-map calculated from the actual experiment was then analyzed with a second level threshold that corrected for randomly significant t-tests. First, it was thresholded to the chosen significance level. The remainder of the significant pixels were then analyzed and tabulated by cluster size. A significance level ($p < .05$) was then chosen from the cumulative distribution, and the threshold cluster size was then obtained. All the significant pixel clusters whose size was less than the threshold cluster size were then eliminated. This method to threshold continguous cluster was applied to between-group comparisons for normal controls versus early abstinence cocaine subjects versus middle abstinence cocaine subjects to test the three sets of hypotheses described in the introduction.

Striatal 6-FDOPA uptake values were measured for each subject in each group. A two-way analysis of variance was done comparing striatal 6-FDOPA uptake values with a between-group measure (Table 1, groups: normal controls versus early abstinence cocaine subjects versus middle abstinence cocaine subjects) and a within-group measure (hemispheres: left, right). Correlations with 6-FDOPA uptake versus days off cocaine were plotted for cocaine subjects.

RESULTS

A significant group effect was found, indicating that middle abstinence cocaine subjects are significantly lower in striatal FDOPA uptake than normal controls or

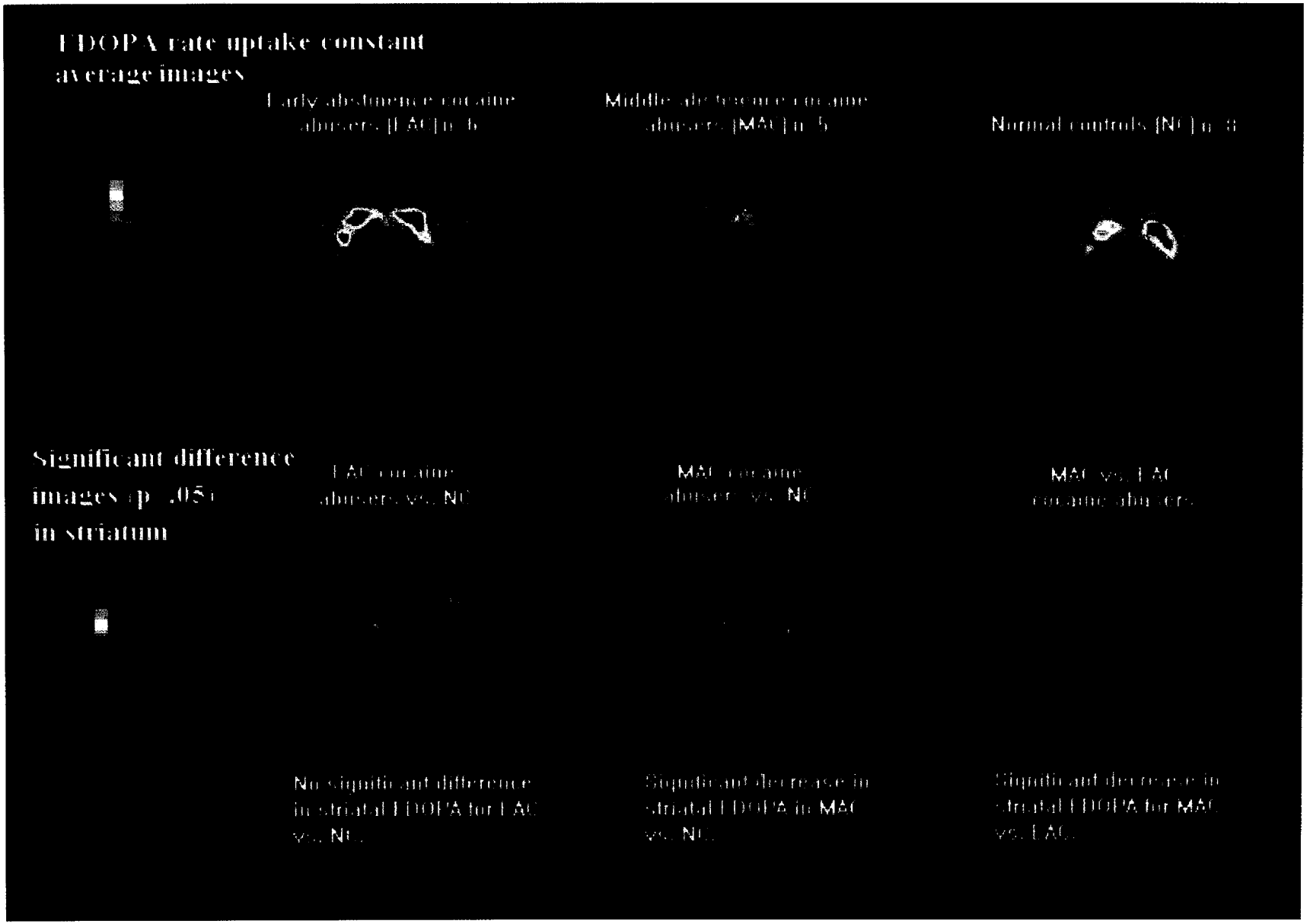

Figure 2. The thresholded ($p < .05$) *t*-test image in the bottom row, left position, shows that there are no significant differences between early abstinence cocaine subjects and normal controls. The middle abstinence cocaine subjects are significantly lower than normal controls (middle position). The middle abstinence cocaine subjects are significantly lower than the early abstinence cocaine subjects (right position).

Table 1. 6-FDOPA Rate Uptake Constant Average for Striatal Region (Significant ANOVA)

	EAC		MAC		NC	
Structure	Mean	SD	Mean	SD	Mean	SD
Striatum	0.60	0.07	0.28	0.10	0.53	0.22

Total striatal 6-FDOPA uptake mean and SD for the early abstinence cocaine (EAC) subjects, the middle abstinence cocaine (MAC) subjects, and the normal controls.

early abstinence cocaine subjects. Middle abstinence cocaine subjects are significantly lower than either early abstinence cocaine subjects or normal controls (EAC vs. MAC vs. NC: $F = 6.04$ $df = 2,16$ $p = .011$, NC = normal control, EAC = early abstinence cocaine subjects, MAC = middle abstinence cocaine subjects, see Table 1). Middle abstinence cocaine subjects are significantly lower in striatal FDOPA uptake than early abstinence cocaine subjects (EAC vs. MAC: $F = 37.97$ $df = 1,9$ $p = .0002$, see Table 1). Early abstinence cocaine subjects do not show a significant group effect when compared with normal controls. Middle abstinence cocaine subjects are significantly lower than normal controls (MAC vs. NC: $F = 5.67$ $df = 1,11$ $p = .0365$, see Table 1). There were no significant group-by-hemisphere interactions.

Figure 3 shows averaged striatal 6-FDOPA uptake decreases significantly with increasing duration of abstinence from cocaine using a dot plot.

DISCUSSION

Potential limitations in our study include the resolution of the images (FWHM = 7.5 mm) and that one horizontal slice view was obtained. Higher resolution with multiple slices will provide delineation of which part of the basal ganglia may be involved.

FDOPA is an analogue of l-dopa, which has been widely used to evaluate striatal presynaptic metabolism using positron emission tomography in living humans (Garnett et al. 1983; Calne et al. 1985). FDOPA is ac-

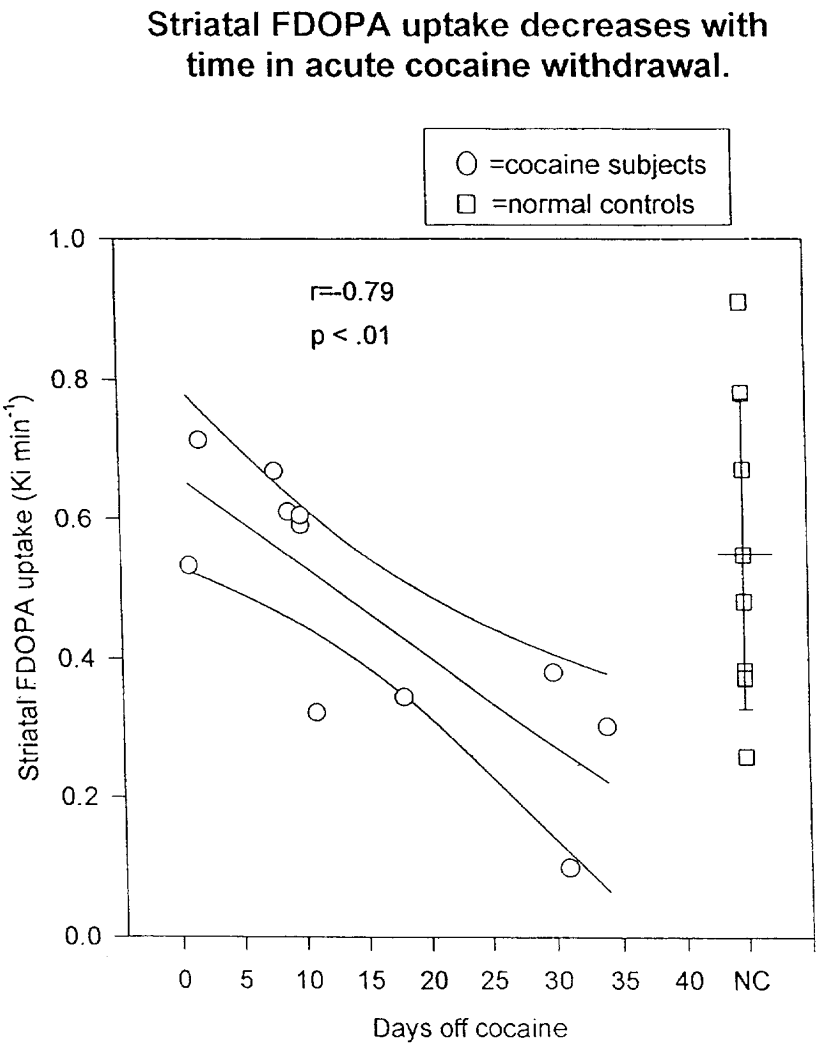

Figure 3. Dot plot of each cocaine subject's striatal 6-FDOPA uptake value versus days off cocaine. A regression was run and is plotted. There is a significant negative correlation between striatal 6-FDOPA uptake values and days off cocaine. Curved lines represent 95% confidence intervals.

tively transported across the blood-brain barrier and then perfuses the brain. FDOPA is synthesized into fluorodopamine (FDA) in the nigrostriatal nerve endings, where it becomes trapped irreversibly in a specific striatal compartment (Patlak et al. 1983; Patlak and Blasberg 1985; Martin et al. 1989b). Thus, 6-FDOPA uptake has been used to provide a useful index of overall presynaptic dopaminergic activity.

Although tyrosine hydroxylase is generally regarded as the rate-limiting step for the synthesis of catecholamines (Nagatsu et al. 1964), there is evidence that aromatic amino acid decarboxylase (AADC, also known as dopa decarboxylase or DDC) may be the rate-limiting enzyme for dopamine formation in the striatum for l-dopa (Neff and Hadjiconstantinou 1995). 6-FDOPA uptake is dependent on AADC activity and subsequent vesicular storage of the product (Kish et al. 1995). This enzyme is regulated by the level of dopaminergic transmission (Zhu et al. 1994) with long-term change dependent upon regulation of protein synthesis (Li et al. 1994). Reserpine depletion has been found to inhibit AADC activity as has subchronic treatment with haloperidol, sulpiride, or SCH-23390 (Hadjiconstantinou et al. 1993), whereas subchronic administration of l-dopa or D1 or D2 agonists have been found to lower striatal AADC. Our finding of decreased FDOPA uptake is compatible with these reports that subchronic administration of dopaminergic agonists results in decreased AADC activity.

The finding of decreasing 6-FDOPA uptake with increasing duration during early and middle abstinence is compatible with predictions generated by animal models of decreasing dopamine synthesis and decreased dopamine concentration during abstinence of cocaine following chronic administration after an initial period of no change (Parsons et al. 1991; Robertson et al. 1991; Ackerman and White 1992; Rossetti et al. 1992; Weiss et al. 1992). A time-dependent decrease in dopamine synthesis and levels has potential clinical implications. Our finding is compatible with the hypothesis that a profound and lasting compensatory downregulation of the presynaptic dopamine system becomes progressively unmasked by cocaine withdrawal (Rossetti et al. 1992). Chronic cocaine usage may lead to excessive duration of intrasynaptic dopamine, which is hypothesized to activate negative feedback components of the presynaptic dopamine system which persists during withdrawal (Volkow et al. 1993; Grace 1995; Giros et al. 1996).

There have been a number of brain imaging studies on the interactions of cocaine with brain function. London et al. (1990) found that acute cocaine administration and euphoria were associated with significant reduction in FDG uptake in neocortex, basal ganglia, hippocampus, thalamus, and midbrain but not in cerebellum for eight polydrug abusers in a double-blind, crossover study. Cue-induced cocaine craving was found to increase FDG uptake in prefrontal lobe, limbic system, middle temporal gyrus, and occipital cortex (Grant et al. 1995). Volkow et al. (1988, 1991, 1992b) have done several brain imaging studies of cocaine dependent subjects, which documented persistent functional abnormalities such as decreased blood flow in prefrontal cerebral blood flow (CBF) during withdrawal, higher orbitofrontal and basal ganglia metabolism during withdrawal, and significant decrease in dorsomedial and dorsolateral frontal cortex metabolism during abstinence. These studies indicate that functional alterations associated with chronic cocaine use continue through withdrawal, which would be compatible with our findings of persistent abnormalities in dopamine system function during withdrawal.

Volkow et al. (1993) also found that decreased dopamine receptor availability in cocaine-dependent subjects is correlated with decreased metabolic activity in frontal and limbic areas. Decreased dopamine receptor availability could be due to postsynaptic downregulation induced by excessive dopaminergic activity. In addition to the cerebral metabolic studies, Volkow et al. (1992a) reported that [^{11}C]cocaine was decreased in the basal ganglia of cocaine abusers compared to normal controls. This finding was interpreted as a possible downregulation of the dopamine transporter or degeneration of the presynaptic dopamine terminal. Our study is unique in utilizing FDOPA uptake to assess presynaptic dopamine activity to find additional evidence for a downregulatory compensatory response that appears to involve several different mechanisms (as reviewed above) to counteract the high episodic, intrasynaptic dopamine levels produced by cocaine addition.

One important issue to consider is whether cocaine addicts undergoing withdrawal are inpatients or outpatients. Most studies have documented severe withdrawal symptoms in outpatients (Gawin and Kleber 1986), but not as prominently as in inpatients. Inpatients who are not exposed to cocaine-related cues have not been reported to have worse cocaine craving or anhedonia (Weddington et al. 1990; Satel et al. 1991). Self-reports of cocaine craving within an inpatient hospital setting are done outside of the natural milieu of the cocaine-dependent subjects, where subjects are protected from stress-induced anhedonia or cue-induced cocaine craving. Cue-induced cocaine craving has been utilized to study subjective change in response to environmental cues. Significant craving with associated physiological changes (e.g., decreased skin temperature, increased skin conductance level) have been found with video presentation of cocaine-related paraphernalia and behavior (Childress et al. 1988a,b; Robbins, et al. 1992). Based on our findings, we hypothesize that the decreased FDOPA uptake during "middle abstinence" would be associated with greater cue-induced cocaine craving with inpatients who may not otherwise be

manifesting withdrawal symptoms due to the hospital environment that shields them from environmental cues. Testing such a relationship between decreased FDOPA uptake and relapse vulnerability may allow us to identify and treat patients at risk for relapse.

Longitudinal studies where the same subjects are tested during the "early," "middle," and "late" phases would be methodologically superior to doing a cross-sectional study and thus would be important for future studies.

We have presented biochemical brain imaging data that document that a significant decrease in dopamine presynaptic uptake occurs during abstinence in cocaine-dependent subjects between days 11–30 compared to days 1–10. We are now in a position for future studies to evaluate systematically the relationship between the timing of our reported finding of decreased dopamine activity during days 11–30 and the clinical impression that there is increased relapse and vulnerability to reuse of cocaine during this time period. Such a relationship between decreased FDOPA uptake and relapse vulnerability may allow us to identify and treat patients at risk for relapse.

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