Neurochemical Mechanisms Underlying Responses to Psychostimulants

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STATEMENT OF THE PROBLEM

It is proposed to undertake a study to determine if differences in dopa-minergic reactivity among individuals could explain the variability in response to psychostimulants and to assess the relation of this reactivity to mental state and personality characteristics. Investigation of these relations may provide clues to the association between brain biochemistry and predisposition for drug abuse.

The underlying hypotheses are:

1. Behavioral response to a drug is not only a function of the chemical composition of the drug but also of the unique biochemical characteristics of an individual (Skrinskaya et al. 1992).

2. Personality and mental state of an individual reflect in part his/her unique metabolic and biochemical brain composition (Cloninger 1986).

3. Increased dopaminergic reactivity is associated with increased vulnerability for drug addiction (Deminiere et al. 1989).

Positron emission tomography (PET) (Fowler et al. 1990) in conjunction with 11C-raclopride (Farde et al. 1985), a dopamine (DA) type 2 (D2) receptor ligand that is sensitive to endogenous DA (Inoue et al. 1989; Seeman et al. 1989; Young et al. 1991), will be used to measure DA reactivity. Responsivity of the DA system will be assessed by monitoring changes in 11C-raclopride binding induced by methylphenidate (MP) (Scheel-Kruger 1971). MP increases synaptic DA concentration by inhibiting the DA transporter (Schweri et al. 1985). Changes in DA concentration induced by MP or other drugs that increase synaptic DA concentration interfere with 11C-raclopride binding, and the degree of its inhibition is a measure of

relative changes in DA concentration. This method has been successfully used to measure drug-induced changes in DA concentration in response to pharmacological challenge in the baboon (Dewey et al. 1992, 1993) and in the human brain (Volkow et al. 1994).

BACKGROUND AND SIGNIFICANCE

Cocaine is recognized as one of the more reinforcing and addictive drugs of abuse (Koob and Bloom 1988). The ability of cocaine to enhance dopaminergic activity appears to be critical in its reinforcing properties and is probably also involved in its addictive properties (DeWit and Wise 1977; DiChiara and Imperato 1988; Galloway 1988; Ritz et al. 1987; Roberts et al. 1977; Woolverton and Johnson 1992). It has been postulated that addiction is due to DA depletion resulting from chronic cocaine adminis-tration (Dackis and Gold 1985). However, the mechanisms underlying cocaine addiction are probably more complex, since there are inconsis-tencies in DA brain activity in studies of chronic cocaine use (Post et al. 1987), as well as in effectiveness of DA agonists in long-term treatment of the cocaine addict (Gawin and Ellinwood 1988; Kleber and Gawin 1984). Involvement of the DA system in cocaine addiction is also probably mediated via its regulation of brain regions that subserve addictive behaviors as opposed to these behaviors being encoded in the DA system itself (Le Moal and Simon 1991). Thus, the effects of chronic cocaine on brain DA could lead to addiction through its effects on these regulated brain regions. Alternatively, abnormalities in these brain regions prior to drug exposure could be associated with a higher vulnerability for drug addiction; activity of other neurotransmitters that regulate these regions may facilitate or interfere with addiction.

Cocaine Reinforcement and Addiction: The Role of Dopamine

Research has implicated the mesolimbic DA system as being critical in mediating the reinforcing properties of cocaine and participating in its addiction liability (Goeders and Kuhar 1987; Wise and Bozarth 1984). Furthermore, because most of the drugs abused by humans lead to increased DA concentration in nucleus accumbens (NACC), this has been suggested as being a common mechanism for reinforcement (Koob and Bloom 1988; Wise and Bozarth 1984). Although many investigators have attributed the reinforcing properties to the DA system itself, others have postulated that its role is that of a modulator of regions where the reinforcing and addicting

processes are encoded (Le Moal and Simon 1991). In the latter model, the importance of other neurotransmitters is emphasized since these brain regions are regulated not only by DA but also by other neurotransmitters such as serotonin, opiate peptides, and gamma aminobutyric acid (GABA), among others.

Animal studies investigating dopaminergic changes underlying drug addiction have implicated multiple mechanisms such as changes in DA concentration, dopamine type 1(D1) and D2 receptors, cyclic amethyl-phenidate, and tyrosine hydroxylase (Beitner-Johnson et al. 1992). However, reports on the nature of the changes occurring during chronic cocaine administration are marked by inconsistencies (for review see Post et al. 1987; Woolverton and Johnson 1992). For example, while some studies report decreases in receptor numbers, DA concentration, and DA release in chronically treated animals, others have failed to document such changes. The reasons for these discrepancies are probably multiple and may relate to the dynamic nature of the changes, the interaction of DA with other neurotransmitters also affected by cocaine, and biological variability, among others.

Studies of the DA System in Cocaine Abusers

Various strategies have been used to evaluate the DA system in cocaine abusers. One has been to measure endocrinological parameters that reflect the function of the tuberoinfundibular DA system. Thus, peripheral measurements of prolactin and growth hormone have been used as indirect indices of central nervous system (CNS) DA activity. Although several investigators have reported increased prolactin levels in cocaine abusers (Cocares et al. 1986; Dackis and Gold 1985; Kranzler and Wallington 1989; Mendelson et al. 1988a, 1988b), others have failed to find increased levels (Swartz et al. 1990). Studies measuring plasma growth hormone in cocaine abusers have also yielded similar inconsis-tencies among investigators (Satel et al. 1991). Another strategy has been to evaluate plasma concentration of the DA metabolite homovanillic acid (HVA) in cocaine abusers. Such studies have also been unsuccessful in delineating a consistent pattern of abnormalities (Extein et al. 1989; Martin et al. 1989; Satel et al. 1991).

Postmortem studies have been performed on the brains of known cocaine abusers. Investigators have found decreased brain DA concentration (Wilson et al. 1990; Wyatt et al. 1988), decreases (Staley et al. 1992) and increases (Little 1992) in the number of DA

transporter sites, decreases in messenger ribonucleic acid (mRNA) for D2 receptors (Meador-Woodruff 1992), and decreases in D1 receptors (Toiba et. al. 1992). Pharmaco-logical studies have reported findings suggestive of decreased and/or abnormal function of DA receptors in cocaine abusers, including blunted response to DA agonists (Hitzemann et al., in press; Hollander et al. 1990) and increased sensitivity to DA antagonists (Choy-Kwang and Lipton 1989; Hegarty et al. 1990; Kumor et al. 1987).

Imaging studies evaluating the DA system in chronic cocaine abusers have reported findings that are consistent with decreased activity of the DA system. For example, cocaine abusers have decreases in DA receptor availability (Volkow et al. 1990, 1993a), decreased DA metabolism (Baxter et al. 1988), and decreased metabolism in projection areas of the mesocortical DA system (Volkow et al. 1992). However, because these studies evaluated individuals only after they have become addicted, it could not be determined if these abnormalities were present prior to drug use. It is possible that the abnormalities in DA function preceded drug use and may have contributed to a higher vulnerability for drug addiction. Because prospective studies to evaluate DA function prior to drug abuse would be extremely costly, it is proposed that the association between DA function and response to psychostimulants in normal nonaddicted individuals be investigated.

Genetics and Predisposition to Psychostimulant Abuse

There is increasing evidence that genetic factors contribute to the predisposition to drug abuse (Deminiere et al. 1989). The investigation of the genetic differences in the function of various neurotransmitters and their relationship to drug abuse has found the strongest link to be with the DA system. In animals, heightened responsivity to novel stimuli or to psychostimulants predicts their vulnerability to drug self-administration (Deminiere et al. 1989), and this behavior, in turn, has been associated with dopaminergic activity (Rouge-Pont et al. 1993). Thus, studies on the relation between DA reactivity and behavioral characteristics may be useful in understanding not only the neurochemical correlates of human behavior but also the neurochemical mechanisms underlying vulnerability for drug abuse.

Measuring the Responsivity of the DA System with PET

PET, an imaging technique for mapping neurochemical processes (Fowler et al. 1990), has been used with 11C-raclopride, a D2 PET ligand (Farde et al. 1985) to measure the response of the DA system to pharmacological challenge. 11C-Raclopride has a relatively low affinity for the D2 receptor (Kd = 1.9 nanomolars (nM)), which makes it sensitive to synaptic DA concentration. PET brain imaging studies demonstrating the sensitivity of 11C-raclopride to drug-induced changes in synaptic DA were first done in baboons (Dewey et al. 1992, 1993). Human studies with PET monitoring the response of the DA system to challenge (Volkow et al. 1994) used MP, a psychostimulant drug that increases synaptic DA concentration by inhibiting the DA transporter (Scheel-Kruger 1971). Such studies measured the responsiveness of the DA system to MP by evaluating changes in striatal 11C-raclopride binding. Because uptake of 11C-raclopride in the human brain is highly reproducible (Volkow et al. 1993b), it can be used to probe changes induced by pharmacological interventions.

Addiction: More Than One Behavior

With all the research documenting the relevance of the DA system to the reinforcing and addictive properties of cocaine, one is left to explain why DA-enhancing drugs have not been effective in the long-term treatment of the cocaine abuser. A plausible explanation is the multiplicity of behaviors associated with cocaine addiction. For example, one can distinguish an initial process by which the intake of the drug is experienced as pleasur-able. This process of intrinsic reinforcing drug effects is the one associated with increased DA in NACC and prefrontal cortex (Goeders and Smith 1986; Hurd and Ungerstedt 1989; Ritz et al. 1987). The memory of the drug experience and of the circumstances and behaviors associated with the experience have also been shown to contribute to repeated cocaine intake (Wise 1990). With repeated administration, the ability of this memory to elicit a desire or craving for cocaine becomes more frequent and serves to perpetuate the use of cocaine (Johanson and Fischman 1989).

The neurochemical and neuroanatomical substrates for consolidation of the cocaine experience memory and for eliciting cocaine craving are not well understood, but probably involve the hippocampus among other brain regions. While the memory and intrinsic reinforcing properties of cocaine are important, it is hypothesized that other processes are involved as well. One reason is that compulsive cocaine administration in the addicted individuals occurs despite rapid

tolerance to the subjective effects of cocaine (Fischman et al. 1985) and even in the presence of adverse physical reactions. The drive and loss of control leading to compulsive self-administration of cocaine are probably regulated both by DA and serotonin (Di Chiara et al. 1991; Loh and Roberts 1988) and may involve orbitofrontal, prefrontal, and cingulate cortices. Other processes, such as sensitization, have also been reported to occur with repeated cocaine administration (Post et al. 1987) and may also participate in triggering and/or perpetuating compulsive drug self-administration.

Another contributor invoked in the facilitation of repeated cocaine use is the emotional reaction of the individual to the losses experienced due to cocaine addiction (Johanson and Fischman 1989). In particular, dysphoria during withdrawal has been associated with a higher relapse rate in the cocaine abuser (Johanson and Fischman 1989). One could postulate that because the mesolimbic DA system is involved with reward processes, its dysfunction in the cocaine abuser could intensify depressive symptoms such as anhedonia and loss of drive (Willner et al. 1992). Because of the multiplicity of variables involved in drug addiction, it is highly likely that an individual's unique characteristics, in particular those relating to novelty-seeking behaviors, compulsivity, and impulsivity, may facilitate drug-seeking behaviors.

Preliminary methodological studies support the feasibility of using 11C-raclopride and [18F] fluorodeoxyglucose (FDG) (with and without MPchallenge) to evaluate the function of presynaptic dopamine neurons (PDNs) in humans. Another study provides preliminary data on the correlation between the responsivity to the psychostimulant drug MP and behavioral measures.

Reproducibility of 11C-Raclopride Binding

11C-raclopride has been successfully utilized with PET to assess changes in endogenous DA concentration after pharmacological intervention in the living baboon brain (Dewey et al. 1992, 1993). For similar studies to be feasible in humans, 11C-raclopride measurements need to be reproducible. Reproducibility of 11C-raclopride binding in the human brain was evaluated in five normal controls who were scanned with 11C-raclopride twice, with no intervention, 24 hours apart. After injection of 3.8 to 12.5 millicuries (mCi) of 11C-raclopride (specific activity 0.5 to 1.5 Ci/μM at end of bombardment (EOB); 2 to 24 micrograms (μg) injected dose), a series of20emission scans were obtained from time of injection through 60-minutes. Arterial sampling was used to quantitate total 11C and unchanged

11C-raclopride in plasma. Time-activity (percentage of dose percc) curves for 11C-raclopride in the striatum and cerebellum were highly reproducible with an average difference of 4percent in peak uptake for repeated studies in the same individual. Figure 1 shows the time-activity curves for 11C-raclopride in striatum and in cerebellum for a subject tested twice.

The striatum/cerebellar ratios for the average activity concentration between 30 and 60 minutes showed differences that ranged from -7percent to 8 percent between the repeated studies. Logan plots (graphical analysis for reversible system (Logan et al. 1990)) were used to obtain the ratio of the distribution volume of basal ganglia to cerebellum. These revealed intrasubject values that ranged from -11percent to 5 percent. There were no significant differences between repeated studies in total plasma activity or in percent nonmetabolized 11C-raclopride. Therefore, measurements of 11C-raclopride in the human brain under conditions of no intervention are highly reproducible in the same individual (Volkow et al. 1993b).

Distribution and Pharmacokinetics of 11C-Methylphenidate in Human Brain

In order to determine the time at which MP reached peak concentration in the human brain, brain uptake and pharmacokinetics of 11C-methyl-phenidate were measured. Eight normal healthy male volunteers (20 to 74-years) were scanned twice, 2 hours apart, using 5 to 10 mCi of 11C-methylphenidate. Four subjects had two repeated scans to assess test/retest reproducibility. Four subjects had one scan as baseline and the second scan 10 minutes after intravenous (IV) administration of 0.5milli-grams per kilogram (mg/kg) MP to assess specific to nonspecific binding.

Peak uptake of 11C-methylphenidate in whole brain corresponded to 7 to 10 percent of the injected dose. Binding of MP was heterogeneous, the highest concentration was in basal ganglia, and relatively low levels were detected in cortex and cerebellum. In basal ganglia, MP bound to the DA transporter molecule; binding was inhibited by pretreatment with drugs that inhibit the DA transporter but not by drugs that inhibit the serotonin or the norepinephrine transporter (Ding et al. 1994).

The regional distribution of 11C-methylphenidate in the human brain was almost identical to that of 11C-cocaine (Fowler et al. 1989). The time to reach peak uptake in the brain was 4 to 10 minutes. Peak concentration of 11C-methylphenidate in the brain was maintained for 15 to 20 minutes. In the basal ganglia, the half peak clearance for MP was 90 minutes.

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MP pretreatment significantly decreased 11C-methylphenidate binding in basal ganglia but not in other brain regions. Values for the distribution volumes (Logan et al. 1990) in basal ganglia and cerebellum before and after MP, as well as the ratios for the distribution volume to that in cerebellum, are shown in table 1 along with the values obtained for the test-retest measures.

Effects of Methylphenidate on 11C-Raclopride Binding

The relatively lower affinity of raclopride for the D2 receptor (Kd=-1.1nM) makes it sensitive to competition with endogenous DA (Seeman et al. 1989; Young et al. 1991). Studies in rodents have demonstrated that raclopride binding is increased by pretreatment with drugs that deplete DA and decreased by drugs that increase DA (Ross and Jackson 1989; Inoue et al. 1989). 11C-Raclopride has been used successfully with PET to assess

TABLE 1. Distribution volumes for basal ganglia and cerebellum and for the ratio of the distribution volume of basal ganglia/cerebellum for 11C-methylphenidate.

Test/Retest			
Basal ganglia	Cerebellum	Basal ganglia/ cerebellum	% Change
20.3±1.5	10.5±0.9	1.9±.07	-2.5±4
19.8±1.1	10.2±0.8	1.9±.08	
Methylphenidate Pretreatment			
Basal ganglia	Cerebellum	Basal ganglia/ cerebellum	% Change
16.9±1.6	8.0±0.5	2.12±.10	-37±1
11.7±1.2	8.7±0.7	1.33±.04	

NOTE: Values represent the average for four normal subjects tested twice to assess reproducibility and of four subjects tested with and without pretreatment with MP (0.5 mg/kg IV).

relative changes in DA concentration in the baboon brain (Dewey et al. 1992, 1993). To assess the feasibility of measuring relative changes in DA concentration using 11C-raclopride in humans, the effects of 0.5 mg/kg IV MP in normal human subjects were measured.

Fifteen normal healthy male volunteers (age range 22 to 45) were scanned using a whole-body, high-resolution PET. Description of positioning, preparation, and transmission scans have been published (Volkow et al. 1994). Subjects had two scans done after injection of 4 to 10 mCi of 11C-raclopride. The first scan was done after placebo and the second scan on a different day after 0.5 mg/kg IV MP; the subjects were blind as to which was administered. Either placebo (3 ml saline) or MP was injected 6 to 9 minutes prior to 11C-raclopride. 11C-raclopride binding was quantified using the ratio of the distribution volume in basal ganglia to that in cerebellum, which corresponds to Bmax/Kd-1 (Logan et

al. 1990). Changes in 11C-raclopride binding with MP were quantified as percentage of change from baseline:

(Bmax/Kd (baseline) - Bmax/Kd (MP)/ Bmax (baseline).

Except for one subject, MP consistently and significantly decreased 11C-raclopride binding in excess of the test-retest variability for 11C-raclopride ($F = 44.9$, $p < 0.0001$). Figure 2 shows the time-activity curves for 11C-raclopride after placebo and after MP for one of the subjects. The magnitude of the changes in 11C-raclopride with MP were quite variable, ranging from 10 to 47 percent.

Correlation Studies Between Behavioral Measures and Responsivity to Methylphenidate

Prior to placebo and/or MP administration and every 20 minutes thereafter, subjects recorded their subjective emotional experience for high (defined as euphoria), anxiety, restlessness (defined as the need to

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move), distrust (perception that others are trying to cause harm), and mood (defined as a contrast between being depressed and being happy) using analog scales that were rated from 0 to 10 (Ekman 1967). Baseline behavioral scores were quantified by averaging the measurements obtained during the placebo study.

To quantify the behavioral changes caused by MP, average scores were collected during the MP scan and subtracted from those obtained during placebo. Correlation analyses were performed between the changes in 11C-raclopride binding with MP and the subjective evaluations for mood, anxiety, high, distrust, and restlessness during baseline and MP-induced changes in the behavioral measures. Significant changes in the behavioral measures after MP administration were tested with analysis of variance (ANOVA). To correct for multiple comparisons, the level of significance was set at $p < 0.01$; values smaller than 0.05 are reported as trends.

The behavioral response to MP was quite variable among individuals (table 2). While some subjects reported effects of the drug to be pleasurable and described feelings of high, euphoria, increased sexual desire, and a need to talk, others reported the experience to be unpleasant and described very high levels of anxiety, restlessness, suspicion, and perceptual distortions.

Correlation analyses revealed significant positive correlations with anxiety ($r = 0.82$; $p < 0.0002$) (figure 3) and restlessness ($r = 0.65$; $p < 0.008$) (figure 4). Subjects who reported high levels of anxiety and restlessness during the placebo scan were the ones who showed the largest changes in 11C-raclopride binding with MP.

Similar to previous reports, this study documents a widespread variability in the behavioral response of subjects to the psychostimulant MP. The variability in the response was also observed for MP-induced DA changes. The study documents a correlation between MP-induced DA changes and the baseline mental state of the subjects. The positive correlation observed between response to MP and anxiety and restlessness could be considered analogous to the association observed in animals between sensitivity to psychostimulants, their response to novel stimuli, and their locomotor activity (Hooks et al. 1991; Jones et al. 1990; Piazza et al. 1989; Rouge-Pont et al. 1993). Because the measurement of anxiety was obtained during the placebo scan, it reflects the subject's response to the PET experience. Restlessness was the only measure that could be obtained for motor behavior since subjects are asked to refrain from moving during the PET procedure. In animal studies, behaviors

TABLE 2. Effects of 0.5 mg/kg IV methylphenidate on behavior.

	Placebo	MP	p <
Anxiety	2.5±1.9	2.9±2.7	NS
High	1.4±1.3	4.1±3.9	
Mood	5.4±1.6	6.3±1.8	NS
Restlessness	2.8±1.7	6.1±1.8	
Distrust	0.4±0.7	1.2±2.1	NS

NOTE: Subjects (N = 15) rated the behavioral measures on a scale of 0to 10.

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associated with responsivity to psychostimulant are associated with dopaminergic tone (Deminiere et al. 1989; Le Moal and Simon 1991; Piazza et al. 1991). One could postulate that anxious and restless individuals may have increased dopaminergic reactivity and are more sensitive to stimulant drugs. In animals, these characteristics have been associated with proneness to self-administer psychostimulants; in humans, they may also increase the risk for drug self-administration.

DESIGN AND EXPERIMENTAL METHODS

Subjects

Selection Criteria. This proposed study involves evaluation of normal healthy male and female volunteers with the following inclusion and exclusion criteria:

- Inclusion criteria: right handed, 24 to 50 years of age.

• Exclusion criteria: history of neurological or psychiatric disease; history of alcohol or drug abuse by subject or first-degree relatives; medical illnesses, vascular or metabolic disorders; those requiring medication; history of head trauma or loss of consciousness; and cardiac arrhythmia apart from sinus bradycardia.

Subject Evaluation. Each subject will be evaluated based on the following methods:

1. Diagnostic interview. A diagnostic interview will be performed to ensure absence of psychiatric or neurological disease and to record a mental state examination.

2. Medical examination. All of the subjects will be given a complete physical and a neurological examination. The following laboratory tests will be obtained: cerebellumC, urine analysis, SMA6, LFTs, T3-T4, and urine and plasma tests to identify intoxication.

3. Personality evaluation. To assess personality structure, subjects will be administered the Minnesota Multiphasic Personality Inventory (MMPI). This inventory will be used to extract factor scores for impulsivity, novelty-seeking behavior, and extroversion.

4. The following evaluations will be performed prior to and during the PET procedure.

• Cardiovascular response. MP has been shown to increase blood pressure and heart rate. In rare circumstances it has also been shown to favor the occurrence of extraventricular contraction. To ensure maximal safety during this study, it is proposed to carefully monitor the cardiovascular response to MP by record-ing heart rate, blood pressure, and EKG. For this purpose, subjects are attached to an automatic device that enables continuous monitoring of heart rate and EKG throughout the study. Blood pressure is monitored every 15-minutes starting 30minutes prior to drug administration. Recordings of these measures are obtained at 15-minute intervals until the end of thestudy. At that point measures are only recorded every 30minutes until the subject returns to baseline (values±10percent those recorded prior to MP administration).

• Behavioral measures. Behavioral measures are rated by an outside observer, and subjective evaluation is obtained using analog scales. Measures rated by an outside observer are obtained prior to placebo or MP administration and at 20, 50, and 80 minutes after MP

administration. These measures include the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). This scale provides a broad overview of symptoms known to be induced by psychostimulants. Scales for the assessment of positive and negative symptoms (SAPS and SANS) will also be administered (Andreasen 1982, 1984). Although these scales are specifically designed for use with schizophrenic patients, psychostimulants can induce some of the same symptoms and have therefore been proposed as models for schizophrenic symptomatology. Measures rated by the individual include subjective analog scales scored from 1to 10 for anxiety, restlessness, high, depression, happiness, mood, suspiciousness, tiredness, desire for more MP, and control over the desire for more MP. The analog scales are obtained prior toadministration of MP or placebo and periodically every 20minutes until the end of the study (100 minutes).

PET Scanning

Each subject will be tested twice with 11C-raclopride: during placebo administration and during MP administration. The order of administration will be randomly assigned for placebo or MP and will be double blind. The studies will be done 1 week apart. Placebo or MP will be administered 6 to 9 minutes prior to 11C-raclopride administration.

The PET studies will be done using a whole-body, high-resolution PET scanner. Subjects will be positioned in the PET camera with the indi-vidual headholder used for magnetic resonance imaging (MRI). The MRI scans are obtained for neuroanatomical coregistration with the PET scans. The fiducial marker that is placed 2 centimeters (cm) above the cantho-meatal (CM) line is used as reference to align the position of the gantry. An external chinstrap device is used in addition to the individual head-holder to minimize head motion during the scan. Before the emission scan, a transmission image will be obtained using gallium-68 to correct for attenuation. In preparation for the initial scans, two catheters are placed into the subject: a venous catheter for tracer injection and an arterial catheter for measurement of total plasma radioactivity concentration. Blood samples are also obtained to measure blood gases and plasma MP concentration.

Emission scans will be performed after injection of 6 to 10 mCi of 11C-raclopride. Scanning is started immediately after injection for a total of 60 minutes. During this period, sequential scans are obtained

at 1-minute intervals for 10 minutes and every 5 minutes thereafter. During scans, lights are dim and noise is kept to a minimum. The only inter-action maintained with patients is the periodic evaluation of their behavioral response to MP or placebo. In order to assess the plasma concentration of MP and metabolites, blood samples will be obtained prior to administration and at 15, 45, 75, 105, and 125 minutes after the injection of the first dose of MP. After completion of the scan, subjects are asked to void to minimize radiation exposure to the bladder.

Magnetic Resonance Imaging

MRI scans will be obtained prior to the PET scans and used for coregis-tration with the PET scans. The patient will be positioned supine on the scanning table with an individually molded headholder that will also be used for the PET scan. A fiducial marker is inserted into the headholder and is placed 2 cm above and parallel to the CM line. This marker will serve as reference to locate the angle of the anterior commissure-posterior commissure (AC-PC) line, which has been found to be a reliable internal indicator of position of structures. Individual determination of the location of the AC-PC angle with respect to the CM line will allow parallel position of the PET gantry using the CM line as a reference. The CM marker is filled with gadolinium and diethylenetriamine-pentaacetic acid (DTPA). Sagittal sections are initially done to locate the angle between the CM (determined with the fiducial marker) and the AC-PC line. Axial planes are then collected parallel to the AC-PC line. Contiguous 5mm thick longitudinal relaxation time (T1)-weighted axial slices (spin echo repetition time (TR) = 60 milliseconds (ms), echo time (TE) = 20 ms) and transverse relaxation time (T2)-weighted axial slices (spin echo TR = 2,500 ms, TE=70ms) will be obtained. The T1 axial MRI images will be used for coregistration with the PET images. For this purpose, an automated computer program has been developed that locates the centroid axis of the volume of the brain for both sets of images (Levy et al. 1989).

Analysis

Image Analysis. Regions of interest (ROIs) will be outlined in the individual's MRI scan. To ensure that the volume of the regions is consistent across subjects, a template has been developed. The template separately identifies regions in the right and the left in the basal ganglia: head of the caudate (2 planes), dorsal striatum (2 planes), and ventral striatum (1 plane). For the cerebellum, only one value is obtained by averaging left and right cerebellar ROIs in 2 contiguous planes The template is adjusted for each individual subject's MRI, and the ROIs are then superimposed on the PET scan.

Statistical Analysis. The primary hypotheses will be rigorously tested. Other analyses will be more exploratory in nature.

- Hypothesis 1: Behavioral response to a drug is not only a function of the chemical composition of the drug but also of the unique bio-chemical characteristics of an individual. It is predicted that indi-viduals with increased dopaminergic reactivity will be more sensitive to MP and vice versa. To test this hypothesis correlation analysis will be performed between the changes in 11C-raclopride binding and the behavioral effects of MP. Significance will be set as per Bonferroni calculations.

- Hypothesis 2: The personality and mental state of an individual reflect in part a unique metabolic and biochemical brain composition. It is predicted that individuals who report high levels of anxiety and restlessness prior to the PET scan will have a larger response to MP than those who do not. It is also predicted that factor scores in the MMPI that relate to novelty seeking will be associated with dopaminergic reactivity.

To investigate possible correlations between personality and mental state variables and the magnitude of the changes in raclopride binding in response to MP, factor analyses techniques will be used to simplify the data into a few vectors that optimize the information and minimize redundancy. Pearson product correlation analyses will be used to assess the significance of these correlations and will be corrected with Bonferroni calculations for the number of tests performed.

- Hypothesis 3: Increased dopaminergic reactivity is associated with increased vulnerability to drug addiction. Because these studies are not longitudinal, it is difficult to test this hypothesis. As an approxi-mate solution, measures of physiological response to MP will be used

to determine whether the behavioral response indicates a reinforcing experience. It is predicted that subjects who show large changes in response to 11C-raclopride will be those who also report desire for more drug as well as loss of control over their desire. Pearson product correlation analyses will be used to assess the significance of these correlations and Bonferroni calculations will correct for the number of tests performed.

Modeling. To quantitate 11C-raclopride, the distribution volume (basal ganglia)and distribution volume (cerebellum) will be calculated using the Logan plot (Logan et al. 1990). The analysis of 11C-raclopride binding in terms of the distribution volume provides a measure of binding that is a linear function of receptor availability as determined by the following:

distribution volume = K1/k2 (1+NS+Bmax /Kd) (equation 1)

for regions containing receptors characterized by an equilibrium dissociation constant Kd and free receptor concentration, Bmax. For non-receptor regions the distribution volume is calculated as follows:

distribution volume = K1/k2 (1+NS) (equation 2)

In both equations, NS represents the ratio of transfer constants for nonspecific binding; K1 and k2 are the plasma-to-tissue and tissue-to-plasma transport constant, respectively. A parameter proportional to Bmax can be obtained from equations 1 and 2 giving

Bmax/Kd (1/1+NS) = [distr vol (basal ganglia)/ distr vol (cerebellum)] -1

(equation 3)

Equations 1 and 2 are based on classical compartmental analysis in which the effects of cerebral blood flow and capillary permeability are implicitly included in the parameters K1 and k2.

PUBLIC HEALTH SIGNIFICANCE

PET studies have documented DA changes in cocaine abusers that appear to be correlated with decreased metabolism in orbitofrontal cortex, cingulate gyrus, and prefrontal cortex. Animal studies have documented a central role of frontal regions (orbitofrontal, cingulate,

and prefrontal cortices) in reinforcing properties of drugs (Dworkin and Smith 1992). It is believed that DA abnormalities in the cocaine abuser lead to dysregulation of these frontal regions, favoring the emergence of behaviors associated with addiction such as impulsivity, compulsion to self-administer cocaine, dysphoria, and inability to refrain from using cocaine. The extent to which these changes represent normal variability that predisposes an individual to drug addiction needs to be investigated in order to better understand mechanisms related to addiction.

Further work is required to determine if the variability in psychostimulant-induced dopaminergic changes represents differences in dopaminergic reactivity, to evaluate if these differences are genetically or environ-mentally controlled, and to assess if they are associated with a higher vulnerability for drug abuse. Future work is required to determine the extent to which specific neurochemical characteristics associated with "liking of psychostimulant drugs" can be generalizable to other drugs of abuse. If they are specific, then future work should also be done to determine if there are specific neurochemical patterns associated with the other abused drugs such as alcohol, tetrahydrocannabinol, or heroin. If patterns can be identified that are associated with proness to addictive behaviors, this knowledge could be used to target therapeutic intervention in the addicted subject.

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