Neurochemical Mechanisms Underlying Responses To Psychostimulants

ND Volkow, JS Fowler, R Hitzemann, GJ Wang

Brookhaven National Laboratory, Upton, New York, NY 11973 (NDV, JSF, GJW); Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, New York 11794-8101 (NDV, RH)

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Abstract

This study proposes to use positron emission tomography (PET) to investigate if there are biochemical and metabolic characteristics of the brain of individuals which could put them at risk for drug addiction. It takes advantage of the normal variability between individuals in response to psychoactive drugs to investigate the relation between mental state, brain neurochemistry and metabolism and the behavioral response to drugs. We discuss here its use to assess if there is an association between mental state and dopaminergic reactivity in response to the psychostimulant drug methylphenidate (MP). Changes in synaptic dopamine induced by MP were evaluated with PET and [¹¹C]raclopride, a D₂ receptor radioligand that is sensitive to endogenous dopamine. Methylphenidate significantly decreased striatal [¹¹C]raclopride binding. The study showed a correlation between the magnitude of the dopamine-induced changes by methylphenidate, and the mental state of the subjects. Subjects reporting high levels of anxiety and restlessness at baseline had larger changes in MP-induced dopamine changes than those that did not. Further investigations on the relation between an individual's response to a drug and his/her mental state and personality as well as his neurochemical brain composition may enable to understand better differences in drug addiction vulnerability.

Specific Aims

To use positron emission tomography (PET) to investigate if differences in dopaminergic reactivity among individuals could explain the variability in response to psychostimulants and to assess its relation to mental state and personality characteristics of individuals. Investigation of these relations may provide clues of the association between brain biochemistry and predisposition for drug abuse.

The underlying hypothesis for this experimental strategy 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 (Deminier et al 1989).

Positron Emission Tomography (PET), (Fowler et al 1990) in conjunction with [¹¹C]raclopride (Farde et al 1985), a D₂ dopamine receptor ligand, that is sensitive to endogenous dopamine (Seeman et al 1989, Young et al 1991, Inoue et al 1989) will be used to measure dopamine reactivity. Responsivity of the dopamine (DA) system will be assessed by monitoring changes in [¹¹C]raclopride binding induced by methylphenidate (MP) (Scheel Kruger 1971). Methylphenidate increases synaptic DA concentration by inhibiting the DA transporter (Schwartz et al, 1985). Changes in DA concentration induced by methylphenidate, 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 utilized 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

Cocaine is recognized as one of the more reinforcing and addictive of the drugs of abuse (Koob and Bloom, 1988). The ability of cocaine to enhance dopaminergic activity appears to be indispensable in its reinforcing properties and is probably also involved in its addictive properties (Ritz et al., 1987; Roberts et al., 1977; Woolverton and Johnson, 1992; DeWit and Wise, 1977; Galloway, 1988). With respect to addiction, it has been postulated that it is due to DA depletion induced by chronic cocaine administration (Dackis and Gold, 1985). However, the mechanisms underlying cocaine addiction are probably more complex, which may explain the inconsistencies in studies of the effects of chronic cocaine in DA brain activity (Post et al. 1987), as well as the ineffectiveness of DA agonists in the long-term treatment of the cocaine addict (Kleber and Gawin 1984, Gawin and Ellinwood, 1988). 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 consequences on the brain regions that it modulates. Alternatively, abnormalities in these brain regions prior to drug exposure could be associated with a higher vulnerability for drug addiction, and the activity of other neurotransmitters that regulate these same 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, 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 5HT, opiate peptides, and GABA, among others.

Animal studies investigating dopaminergic changes underlying drug addiction have implicated multiple mechanisms such as changes in DA concentration, D1 and D2 receptors, cyclic AMP, 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 Post et al., 1987; Woolverton and Johnson, 1992). For example, while some studies report decreases in receptor numbers, DA concentration and in 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 of them 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 DA activity. Although several investigators have reported increased prolactin levels in cocaine abusers (Cocares et al., 1986; Dackis and Gold 1985; Kransler and Wallington, 1988; Mendelson et al., 1987, 1988), others have failed to find them (Gawin et al., 1985; Swartz et al., 1990). Studies measuring plasma growth hormone in cocaine abusers have also yielded similar inconsistencies among investigators (Satel et al., 1991). Another strategy has been to evaluate plasma HVA concentration in cocaine abusers. Such studies have also been unsuccessful in delineating a consistent pattern of abnormalities among investigators (Extein et al., 1989; Satel et al., 1991; Martin et al., 1989).

In postmortem studies, investigators have reported in the brain of cocaine abusers: decreased brain DA concentration (Wilson et al., 1990; Wyatt et al., 1988;), decreases (Staley et al. 1992) and increases (Little 1992) of DA transporter sites; decreases in mRNA's for D₂ receptors (Meador-Woodruff 1992) and decreases in D₁ receptors (Toiba et al. 1992).

Pharmacological studies have reported findings suggestive of decreased and/or abnormal function of DA receptors in cocaine abusers: blunted response to DA agonists (Hollander et al., 1990; Hitzemann et al., in press) and increased sensitivity to DA antagonists (Kumor et al 1986; Choy-Kwang and Lipton 1989; Hegarty et al 1990).

Imaging studies evaluating the dopamine 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 dopamine receptor availability (Volkow et al 1990, 1993), decreased dopamine metabolism (Baxter et al 1988) and decreased metabolism in projection areas of the mesocortical dopamine system (Volkow et al 1992). However, because these studies evaluated individuals only after they have become addicted, they can not determine if these abnormalities were present prior to drug use. It is possible that the abnormalities in DA function preceded their drug use and may have contributed to a higher vulnerability for drug addiction. Because prospective studies to evaluate dopamine function prior to drug abuse would be extremely costly we have set out to investigate the association between dopamine function and response to psychostimulant in normal non addicted individuals.

Genetics And Predisposition To Psychostimulant Abuse

There is increasing evidence that genetic factors contribute to the predisposition to drug abuse (Deminere et al 1989). The investigation of the genetic differences in the function of various neurotransmitters and their relationship to drug abuse have shown that the strongest link is with the dopamine system. In animals, heightened responsivity to novel stimuli or to psychostimulants predict their vulnerability to drug self administration (Deminere et al 1989) and these behaviors in turn have 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.

Positron Emission Tomography (PET), an imaging technique for mapping neurochemical processes (Fowler et al 1990), has been used with [¹¹C]raclopride, a D₂ dopamine 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 DA D₂ receptor (K_d 1.9 nM) which makes it sensitive to synaptic DA concentration. PET brain imaging studies demonstrating the sensitivity [¹¹C]raclopride to drug induced changes in synaptic DA, were first done in baboons (Dewey et al 1993, 1992).

Human studies monitoring the response of the DA system to challenge with PET (Volkow et al 1994) used methylphenidate (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 in cocaine's reinforcing and addictive properties, 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 pleasurable. This process of intrinsic reinforcing drug effects is the one associated with increased DA in nucleus accumbens and prefrontal cortex (Ritz et al., 1987; Hurd and Ungerstedt, 1989; Goeders and Smith, 1986). The memory of the drug experience and of the circumstances and the 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 this 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, we hypothesize that other processes are also involved, since 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 is probably regulated both by DA and serotonin (Di Chiara et al., 1991; Loh and Roberts, 1991) and may involve orbito frontal, 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 from his/her 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 characteristic, in particular those relating to novelty seeking behaviors, compulsivity and impulsivity, may facilitate with drug seeking behaviors.

Summary

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 (orbito frontal, cingulate and prefrontal cortices) in reinforcing properties of drugs (Dworkin and Smith 1992). We believe 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 restrain from using cocaine. The extent to which these changes represent normal variability that predisposes an individual to drug addiction needs to be investigated. In this proposal we take advantage of the normal variability in response to psychostimulants to determine if we can identify characteristics of the DA system associated with "drug liking", "loss of control during drug intoxication" and "desire for more drug"

Preliminary Studies

(1) Studies supporting the use of ^{11}C raclopride with MP to assess the functional activity of the presynaptic DA neuron

To support the feasibility of using ^{11}C -raclopride and FDG (with and without MP challenge) to evaluate the function of PDN in humans, we present the following preliminary results:

Reproducibility of ^{11}C raclopride binding studies in humans,
Pharmacokinetics and regional distribution of MP in the brain
Effects of MP on ^{11}C raclopride binding,

Reproducibility of ^{11}C raclopride binding:

^{11}C -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 ^{11}C raclopride measurements need to be reproducible. Reproducibility of ^{11}C -raclopride binding in the human brain was evaluated in 5 normal controls who were scanned with ^{11}C -raclopride twice, with no intervention, 24 hours apart. After injection of 3.8-12.5 mCi of ^{11}C -raclopride (specific activity 0.5-1.5 Ci/ μM at EOB; 2-24 μg injected dose) a series of 20 emission scans were obtained from time of injection through 60 minutes. Arterial sampling was used to quantitate total ^{11}C and unchanged ^{11}C -raclopride in plasma. Time-activity (% dose/cc) curves for ^{11}C -raclopride in the striatum and cerebellum were highly reproducible with an average difference in peak uptake for repeated studies in the same individual of 4%.

The striatum/cerebellar ratios for the average activity concentration between 30 and 60 minutes showed differences that ranged from -7% to 8% 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 (DV) in basal ganglia (BG) to that in cerebellum (CB) and revealed intrasubject values that ranged from -11% to 5%. There were no significant differences in total plasma activity nor in percent non-metabolized ^{11}C -raclopride between repeated studies.

This study showed that measurements of ^{11}C -raclopride in the human brain under conditions of no intervention are highly reproducible in the same individual (Volkow et al 1993b).

Figure 1 about here

Distribution And Pharmacokinetics Of [^{11}C]Methylphenidate In Human Brain

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

Peak uptake of [^{11}C]methylphenidate in whole brain corresponded to 7-10% of the injected dose. Binding of MP was heterogeneous, the highest concentration was in basal ganglia (BG) and relatively low levels were detected in cortex and cerebellum (CB). Binding in BG was to the DA transporter since it was inhibited by pretreatment of drugs that inhibit the DA transporter but not by drugs that inhibit the serotonin or the norepinephrine transporter (Ding et al in press).

The regional distribution of [^{11}C]methylphenidate in human brain was almost identical to that of [^{11}C]cocaine (Fowler et al 1989). The time to reach peak uptake in brain was 4-10 minutes. Peak concentration of [^{11}C]methylphenidate in brain were maintained for 15-20 minutes. In the BG the half peak clearance for MP corresponded to 90 min.

Methylphenidate pretreatment significantly decreased [^{11}C]methylphenidate binding in basal ganglia but not in other brain regions. Values for the distribution volumes (DV) (Logan et al 1990) in BG, and CB before and after MP, as well as the ratios for the DV to that in CB are shown in Table 1 along with the values obtained for the test-retest measures.

Table 1 Distribution volumes (DV) for BG and CB and for the ratio of the DV in BG/CB for [^{11}C]methylphenidate. Values represent average for 4 normals tested twice to assess reproducibility and of 4 subjects tested with and without pretreatment with MP (0.5 mg/kg iv)

Test/Retest				Methylphenidate Pretreatment			
DV BG	DV CB	DV BG/CB	% Change	DV BG	DV CB	DV BG/CB	% Change
20.3 ± 1.5	10.5 ± 0.9	1.9 ± 0.7	-2.5 ± 4	16.9 ± 1.6	8.0 ± 0.5	2.12 ± 0.10	-37 ± 1
19.8 ± 1.1	10.2 ± 0.8	1.9 ± 0.8		11.7 ± 1.2	8.7 ± 0.7	1.33 ± 0.04	

Effects of MP on [^{11}C]Raclopride binding:

The relatively lower affinity of raclopride for the D₂ DA receptor (K_d = 1.1 nM) 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 et al., 1989; Inoue et al., 1991). [11C]Raclopride has been used successfully with PET to assess 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, we measured the effects of 0.5 mg/Kg iv MP in normal human subjects.

Fifteen normal healthy male volunteers (age range 22-45), were scanned using a whole-body, high-resolution positron emission tomograph (6x6x6.5 mm Full Width Half Maximum, 15 slices, Computer Technologies, Incorporated, CTI 931). Description of positioning, preparation and transmission scans have been published (Volkow et al 1994). Subjects had two scans done after injection of 4-10 mCi of [11C]raclopride. The first scan was done after placebo and the second scan on a separate day after 0.5 mg/kg iv methylphenidate (MP). Subjects were blind to whether placebo (3 ml saline) or MP was administered which were injected 6-9 minutes prior to [11C]raclopride. Prior to placebo and/or MP and every 20 minutes thereafter, subjects recorded their subjective emotional experience using analog scales which were rated from 0-10 (high, anxiety, distrust, restlessness, and mood).

[11C]raclopride binding was quantified using the ratio of the distribution volume (DV) in basal ganglia to that in cerebellum which corresponds to $B_{max}/K_d - 1$ (Logan et al 1989). Changes in [11C]raclopride binding with MP were quantified as percent change from baseline (B_{max}/K_d (baseline) - B_{max}/K_d (MP) / B_{max} (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%.

Figure 2 About Here

(2) Correlation Studies Between Behavioral Measures And Responsivity To MP

Prior to placebo and/or MP and every 20 minutes thereafter, subjects recorded their subjective emotional experience for high (defined as euphoria), anxiety, restlessness (defined as the need to 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 which 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 with MP we averaged scores collected during the MP scan and subtracted them from those obtained during placebo. Correlation analysis were performed between the changes in [^{11}C]raclopride binding with MP and the subjective evaluation for mood, anxiety, high, distrust and restlessness during baseline and MP-induced changes in the behavioral measures. Significant changes of MP in the behavioral measures were tested with ANOVA. To correct for multiple comparisons we set the level of significance to $p > 0.01$, values smaller than 0.05 are reported as trends.

The behavioral response to methylphenidate was quite variable among individuals. While some subjects reported 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, suspiciousness, and perceptual distortions. Table 2 summarizes the behavioral effects of MP

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

Table 2 Effects of 0.5 mg/kg iv methylphenidate (MP) on behavior. Subjects ($n = 15$) score the behavioral measures on a scale of 0-10. Significant differences (repeated measure ANOVA), between placebo and MP are indicated with superscripts ($a = p < 0.0005$ $b = p < 0.0001$).

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 [^{11}C]raclopride binding with MP.

Figure 3, about here

Figure 4, about here

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 dopamine changes. The study also documents a correlation between MP induced dopamine 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 and their response to novel stimuli and their locomotor activity (Hooks et al 1991, Jones et al 1990, Rouge Pont et al 1993, Piazza et al 1989). Because the measurements of anxiety were obtained during the placebo scan, it reflects the subject's response to the PET experience. Restlessness was the only measure we could obtain for motor behavior since subjects are asked to refrain from moving during the PET procedure. In the animal studies behaviors associated with responsivity to psychostimulant are associated with dopaminergic tone (Le Moal and Simon 1991, Deminiere et al 1989, 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 and in humans they may also increase the risk for drug self administration.

Further work is required to determine if the variability in MP induce dopaminergic changes represents differences in dopaminergic reactivity, to evaluate if these differences are genetically or environmentally controlled and to assess if they are associated with a higher vulnerability for drug abuse.

Methods

Subjects:

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

Inclusion criteria:

- (1) Right handed, 24-50 years;

Exclusion criteria:

- 1) History of neurological or psychiatric disease;
- 2) History of alcohol or drug abuse in themselves or in first-degree relatives;
- 3) Medical illnesses, vascular or metabolic disorders;
- 4) Those requiring medication;
- 5) History of head trauma or loss of consciousness.
- 6) Cardiac arrhythmia's apart from sinus bradycardia.

Subject Evaluation:

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 : CBC, urine analysis, SMA6, LFT's, T3-T4, and urine and plasma tests to identify intoxication.

3) Personality evaluation:

To assess personality structure we will use the Minnesota Multiphasic Personality Inventory. We will use this inventory to extract factor scores for impulsivity, novelty seeking behavior and extroversion.

4) Evaluation prior to and during PET procedure:

- a) **Cardiovascular response:** methylphenidate has been shown to increase blood pressure and heart rate. In rare circumstance it has also been shown to favor the

occurrence of extraventricular contraction. To ensure maximal safety during this study we are proposing to carefully monitor the cardiovascular response to MP. Cardiovascular response to MP will be monitored by recording heart rate, blood pressure and EKG. For this purpose subjects are attached to an automatic device that enables us to continuously monitor heart rate and EKG throughout the study. Blood pressure is monitored every 15 minutes starting 30 minutes prior to drug administration. Recordings of these measures are obtained at 15 minute intervals until the end of the study. At that point measures are only recorded every 30 minutes until the subject returns to baseline (values $\pm 10\%$ those recorded prior to MP administration) at which time he is allowed to leave the PET facility.

b) Behavioral measures include measures that are rated by an outside observer and subjective evaluation using analog scales.

Measures rated by an outside observer are obtained prior to placebo or MP, 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 which are known to be induced by psychostimulants. and the Scales for the assessment of positive and negative symptoms (SANS and SAPS) (Andreasen, 1982, 1984). The scales are designed to differential measure the negative and positive symptoms. Although they are specifically designed for schizophrenia, psychostimulants can induce some of the symptoms and have therefore even been proposed as models for schizophrenic symptomatology.

Measures rated by the individual include subjective analog scales scored from 1-10 for anxiety, restlessness, high, depression, happiness, mood, suspiciousness, tiredness, desire for more MP, control over the desire for more MP. The analog scales are obtained prior to administration of MP or placebo and periodically every 20 minutes until the end of the study (100 minutes).

PET Scanning:

Each subject will be tested twice with ^{11}C raclopride: during placebo and during MP. 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 6-9 minutes prior to ^{11}C -raclopride administration.

The PET studies will be done using a whole-body, high-resolution positron emission tomograph (6x6x6.5 mm Full Width Half Maximum, 15 slices, Computer Technologies, Incorporated, CTI 931). . Subjects will be positioned in the PET camera using the individual head

holder utilized for the MRI. The MRI are obtained for neuroanatomical with the PET scans. The fiducial marker which is placed 2 cm above the CM line is used as reference to align the position of the gantry. An external chin-strap 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: one venous for tracer injection, and the other arterial for measurement of total plasma concentration of radioactivity. Blood samples are also obtained to measure blood gases and plasma MP concentration.

Emission scans are will be performed after injection of 6-10 mCi of [^{11}C]raclopride. Scanning is started immediately after injection for a total of 60 minutes. During this period, sequential scans are obtained at 1-min. intervals until 10 min and at 5 min thereafter.

During scans, lights are dimly illuminated and noise is kept to a minimum. The only interaction maintained with the patient is the periodic evaluation of subjects for their behavioral response to MP or placebo. In order to assess the plasma concentration of MP and metabolites we will obtain blood samples prior to and at 15, 45, 75, 105 and 125 min 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:

The MRI will be obtained prior to the PET scans and are used for coregistration with the PET scans. MRIs will be performed using a General Electric 1.5 Tesla MRI instrument. The patient will be positioned supine on the scanning table with an individually molded headholder which will also be used for the PET scanner. A fiducial marker is inserted into the headholder and is placed 2 cm above and parallel to the canthomeatal (CM) line. This marker will serve as reference to locate the angle of the 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 us to position the PET gantry parallel to it using as a reference the CM line. The CM marker is filled with gadolinium, 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 T1-weighted axial slices (Spin Echo TR=60 msec, TE=20 msec) and T2-weighted axial slices (Spin Echo TR=2500msec, TE=70msec) will be obtained. The T1 axial MRI images will be used for coregistration with the PET images. For this purpose we have developed an automated computer program that locates the centroid axis of the volume of the brain for both sets of images (Levy et al 1989)

Data Analysis:

Image Analysis: Regions of interest (ROI) will be outlined in the individual's MRI scan. To ensure that the volume of the regions is consistent across subjects we have developed a template. The template separately identifies in the basal ganglia regions in the right and the left: 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 ROI's in 2 contiguous planes. The template is adjusted for each individual subject's MRI and the ROI's 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 biochemical characteristics of an individual. We predict that individuals with increased dopaminergic reactivity will be more sensitive to MP and vice versa. To test this hypothesis we will perform correlation analysis between the changes in ¹¹C raclopride binding and the behavioral effects of MP. Significance will be set as per Bonferroni .

Hypothesis 2: Personality and mental state of an individual reflect in part his/her unique metabolic and biochemical brain composition . We predict that individuals who prior to the PET scan report high levels of anxiety and restlessness will have a larger response to MP than those than do not. We also predict that factor scores in the personality inventory 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 we will apply factor analyses techniques to simplify the data into a few vectors that optimize the information and minimize redundancy. Person product correlation analyses will be used to assess the significance of these correlations and we will correct with Bonferroni for the number of tests performed.

Hypothesis 3: Increased dopaminergic reactivity is associated with increased vulnerability for drug addiction. Because this studies are not longitudinal it is difficult to test his hypothesis. As an approximate solution to address this hypothesis we will use the measures of their response to MP to determine whether their behavioral response indicates a reinforcing experience with MP. We predict that subjects who show large changes in ¹¹C raclopride will be the one that will 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 we will correct with Bonferroni for the number of tests performed.

Modeling: To quantitate ^{11}C raclopride we will obtain the DV (BG)/DV (CB) using the Logan plot (Logan et al 1990). The analysis of ^{11}C -raclopride binding in terms of the DV provides a measure of binding that is a linear function of receptor availability given by

$$\text{DV} = K_1/k_2' (1 + \text{NS} + \text{Bmax} / K_d') \quad (1)$$

for regions containing receptors characterized by an equilibrium dissociation constant K_d' and free receptor concentration, Bmax. For non receptor regions the DV is given by

$$\text{DV} = K_1/k_2' (1 + \text{NS})$$

(2)

In both equations NS represents the ratio of transfer constants for nonspecific binding, K_1 and k_2' are the plasma to tissue and the tissue to plasma transport constant respectively. A parameter proportional to Bmax can be obtained from Eq. (1) and (2) giving

$$\text{Bmax}/K_d' (1/1 + \text{NS}) = [\text{DV (BG)}/\text{DV (CB)}] - 1 \quad (3)$$

Eq. (1) and Eq. (2) are based on classical compartmental analysis in which the effects of CBF and capillary permeability are implicitly included in the parameters K_1 and k_2' .

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Figure Legends

Figure 1. Time activity curves for ^{11}C raclopride in striatum (circle) and in cerebellum (rhombi) for a normal control tested twice with no intervention (First study = Closed symbols; Second study = open symbols).

Figure 2 Time activity curves for $[^{11}\text{C}]\text{raclopride}$ in BG (circles) and CB (rhombi) without (closed symbols) and with MP (open symbols).

Figure 3. Correlation between levels of anxiety during baseline and methylphenidate-induced changes in $[^{11}\text{C}]\text{raclopride}$ (expressed as % change in B_{max}/K_d from baseline).

Figure 4. Correlation between subjective evaluation for restlessness during baseline and methylphenidate-induced changes in $[^{11}\text{C}]\text{raclopride}$ (expressed as % change in B_{max}/K_d from baseline).

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Contributors

Nora D Volkow MD. Director, Nuclear Medicine, Associate Chief of Staff, Clinical Research Center, Medical Department Brookhaven National Laboratory, Upton New York 11973, Associate Professor, Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, New York 11794-8101

Joanna S Fowler PhD. Director, PET Program, Chemistry Department Brookhaven National Laboratory, Upton New York 11973

Robert Hitzemann PhD. Professor, Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, New York 11794-8101

Gene-Jack Wang MD. Associate Scientist Medical Department Brookhaven National Laboratory, Upton New York 11973

Figure 1

Figure 2

Figure 3

figure 4