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Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects

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Abstract Positron emission tomography was used to compare the pharmacokinetics of [^{11}C]methylphenidate in the human brain with the temporal course of the subjective and cardiovascular effects observed after intravenous methylphenidate (0.5 mg/kg). Four subjects were tested twice with [^{11}C]methylphenidate, at baseline and after methylphenidate. All subjects showed almost identical uptake of ^{11}C labeled drug in brain, as well as a very similar decrease in binding of [^{11}C]methylphenidate in basal ganglia, after pretreatment with methylphenidate. In contrast, the magnitude of the behavioral and cardiovascular changes induced by methylphenidate varied among the subjects. The temporal course for methylphenidate effects paralleled closely the pharmacokinetics of [^{11}C]methylphenidate in brain for the perception of "restlessness" and for changes in systolic blood pressure and heart rate. In contrast, methylphenidate induced "high", "anxiety" and changes in diastolic blood pressure decreased rapidly despite long lasting binding of the drug in brain. These results indicate that binding of methylphenidate in brain does not appear to predict individual responses to the drug and that more than one neurotransmitter and/or adaptation process are likely to be involved in the behavioral and cardiovascular effects of methylphenidate.

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Introduction

The ability of most drugs of abuse to raise dopamine concentration in the nucleus accumbens appears to be crucial to their ability to promote self administration (reinforcing properties) (Koob and Bloom 1988). Psychostimulant drugs such as cocaine and methylphenidate raise dopamine by inhibiting the dopamine (DA) transporter (Madras et al. 1989; Carroll et al. 1992). Methylphenidate (MP), which is the most commonly prescribed psychotropic medication for children in the United States (Wilens and Biederman 1992), has a higher affinity for the DA transporter than that of cocaine (Ki for inhibition of dopamine uptake correspond to 390 nM and 640 nM, respectively), which is one of the most reinforcing and addictive of the abused drugs (Fischman and Schuster 1981; Koob and Bloom 1988; Johanson and Fischman 1989). Because inhibition of the DA transporter has been shown to correlate with the reinforcing properties of cocaine and cocaine-like drugs (Ritz et al. 1987), one might predict MP to be at least as reinforcing as cocaine. However, though MP is reinforcing it is infrequently abused (Parran and Jasinski 1991). Similarly, mazindol which is more potent than cocaine in inhibiting DA uptake (Seeman 1993), does not induce consistent self-administration in all animals (Corwin et al. 1987; Bergman et al. 1989) and is not perceived as reinforcing by humans (Chait et al. 1986, 1987). One of the reasons for these discrepancies may relate to differences in their pharmacological profiles (Madras and Kaufman 1994). For example, MP and cocaine, in addition to inhibiting the DA transporter also inhibit norepinephrine uptake (Calligaro and Eldefrawi 1987; Patrick et al.

1987); whereas serotonin uptake is inhibited by cocaine (Reith et al. 1983; Richelson and Pfenning 1984) but not by MP (Schweri et al. 1985). The pharmacokinetic properties of these drugs also contribute to their unique characteristics. Specically, the rapidity of drug delivery to brain has been shown to affect their reinforcing properties. The shorter the interval between intake and perceived effects of the drug, the greater the reinforcing potential (Oldendorf 1992). Different routes of administration lead to different drug pharmacokinetics (Perez-Reyes et al. 1982). This, in turn affects their reinforcing properties (Verebey and Gold 1988). We recently postulated that the rate of clearance from brain for drugs that inhibit the DA transporter also affects their abuse liability (Volkow et al. 1995). Drugs with fast clearance kinetics, such as cocaine, would facilitate rapid frequent administration, whereas drugs with slow clearance kinetics would not (Volkow et al. 1995). Comparisons of the temporal patterns of drug effects with pharmacokinetics could provide information about the relation between these two variables.

Studies of drug pharmacokinetics in humans typically involve measurements of drug and/or drug metabolites in samples of blood and/or urine from which inferences are made about the kinetics of the drug in brain. With positron emission tomography (PET), which enables one to measure the concentration of positron labeled compounds at different times after their administration, one can directly monitor the regional pharmacokinetics of drugs in human brain (Fowler et al. 1990). For example, PET has been used to measure the pharmacokinetics of cocaine in the brain and body in living human subjects (Fowler et al. 1989; Volkow et al. 1992). These studies have shown fast uptake and clearance of cocaine in brain which parallels the temporal course for the "high" experienced after intravenous cocaine (Fowler et al. 1989). Because experiments are done in awake human subjects, PET can be used in conjunction with traditional measures of drug effects to investigate the relation between the pharmacokinetics of a drug in brain and the time course of its behavioral effects. PET can also be used to assess within a group of subjects the relation between the magnitude of the drug effects and the rate of uptake and binding of the drug in brain. In a previous study we used PET to investigate the relation between the pharmacokinetics of [11C]cocaine and those of [11C]methylphenidate in human brain and the subjective perception of the "high" (Volkow et al. 1995). This study showed that while the initial uptake of the drug in brain was correlated with the subjective perception of the "high", the continuous presence of the drug in brain was not.

In the current study we extend the analysis to include the relation between pharmacokinetics of [11C]methylphenidate in human brain and the temporal course for other subjective as well as for the cardiovascular effects of MP.

Materials and methods

Subjects

Subjects were four normal healthy male volunteers (ages 26, 36, 38 and 43 years), who were screened for absence of medical, neurological, or psychiatric disease. Care was taken to exclude subjects with a past or present history of alcohol or drug use (except for caffeine). Urine toxicology tests were performed to ensure absence of psychoactive drug use. Studies had been approved by the Human Studies Review Committee at the Brookhaven National Laboratory and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consents were obtained from all subjects after the nature of the procedures was explained.

Scan

PET studies were carried out with a whole-body, high-resolution positron emission tomograph (6 × 6 × 6.5 mm Full Width Half Maximum, 15 slices, Computer Technologies, Incorporated, CTI 931). To ensure accurate repositioning of subjects in the PET camera, for the repeated scans, an individually molded headholder was made for each subject. The head of the subject was positioned in the gantry with the aid of two orthogonal laser lines one of which was placed parallel to the canthomeatal line and the other parallel to the sagittal plane. A chin strap device was used to minimize movement of the head during the scan.

Subjects underwent two scanning session with [^{11}C]methylphenidate which were done 2 h apart from each other, to allow for the decay of > 95% of the radioactivity from the first injection of ^{11}C labeled drug (6 half-lives = 120 min). For each scanning session, the emission scans were started immediately after injection of 5–10 mCi of [^{11}C]methylphenidate (mass of MP injected 9 ± 2 μg) and a series of 20 scans were obtained for a total of 84 min (four 15 s, two 30 s, four 1 min, four 2 min, five 10 min and one 20 min scan). The first scanning session was done with no pharmacologic intervention and the second scanning session was done 10 min after administration of MP (0.5 mg/kg IV). The first scanning session was used to obtain a baseline for the pharmacokinetics of [^{11}C]methylphenidate and the second scanning session was used to assess the effects of pharmacological doses of MP on the binding of [^{11}C]methylphenidate. The behavioral and cardiovascular responses induced by the administration of the pharmacological doses of MP during the second scanning session were monitored at periodic intervals and were used to compare with the pharmacokinetics of [^{11}C]methylphenidate. Subjects were told they were receiving MP.

Prior to [^{11}C]methylphenidate injection, transmission scans were obtained to correct for attenuation. In preparation for the study, subjects had two catheters implanted, one in an antecubital vein for tracer injection and the other in the radial artery for blood sampling. Arterial sampling was used to quantitate total carbon-11 and unchanged [^{11}C]methylphenidate in plasma. Arterial samples were obtained using an automated blood sampling device (Ole Dick, Denmark) every 2.5 s for the first 2 min and then every minute from 2 to 5 min and then at 10, 15, 20, 30, 45, and 90 min. Details on synthesis of [^{11}C]methylphenidate, sampling procedures and quantitation of MP and of unchanged tracer in plasma have been published (Ding et al. 1994; Volkow et al. 1995).

Behavioral and cardiovascular evaluation

The behavioral and cardiovascular effects induced by the administration of MP (0.5 mg/kg IV) prior to the second scanning procedure were recorded in these subjects. Behavioral effects were evaluated using analog scales that assessed the subjective percep-

tion of "high", "anxiety" and "restlessness" (defined as need to move). The interviewer (G.J.W.) asked the subjects to rate their subjective experience from 0 (felt nothing) to 100 (felt intensely) (Wang et al. 1995). The scales were completed 5 min prior to and every minute for 20 min after MP administration and then at 5-min intervals thereafter (total of 70 min). We also normalized each individual's scale to its own maximum and expressed the responses as percent from this maximum.

Electrocardiographic recording, blood pressure, and pulse rate were obtained every 15 min for 30 min prior to and at 2, 4, 6, 8, 10, 15, 20, 30, 40, and 60 min after MP administration.

Analyses

Regions of interest were drawn directly on the emission images. For this purpose, an averaged image corresponding to the images obtained between 15 and 84 min was obtained. Regions for basal ganglia and for cerebellum were drawn in this averaged image as previously described (Volkow et al. 1995). Briefly, a template of geometric regions for five different planes was used. The templates were manually adjusted to each individual scan and the weighted average for each anatomical region was computed. Regions were obtained in three planes for the basal ganglia and in two planes for the cerebellum.

For comparison purposes, the concentration of [^{11}C]methylphenidate in basal ganglia was normalized to the highest value in a given individual and expressed as percent of that value, as for the behavioral measures. The cardiovascular effects were quantified with respect to the values obtained prior to MP and then normalized with respect to the maximal change and expressed as percent of that value. In this way, ^{11}C kinetics could be graphed together with temporal changes in behavioral and cardiovascular measures.

Time activity curves for tissue concentration and for unchanged tracer in plasma were used to calculate the distribution volume (DV) in basal ganglia and cerebellum using a graphical analyses technique for reversible system as previously described (Logan plots; Logan et al. 1990). The ratio of the DV in basal ganglia to that in cerebellum was used as model parameter. This ratio corresponds to $(B_{max}/K_d)+1$ and is insensitive to changes in cerebral blood flow (Logan et al. 1994).

Comparisons between baseline measures and peak effects of methylphenidate were tested using paired t-tests (double tail).

Results

Methylphenidate induced a "high" and increased "anxiety" and "restlessness" in all subjects. It also increased heart rate and systolic and diastolic blood pressure. The effects were significant for all measures and corresponded to: heart rate ($t = 5.09$, $df = 3$, $P < 0.02$), systolic blood pressure ($t = 6.63$, $df = 3$, $P < 0.007$), diastolic blood pressure ($t = 35.00$, $df = 3$, $P < 0.0001$), high ($t = 5.13$, $df = 3$, $P < 0.02$), anxiety ($t = 4.33$, $df = 3$, $P < 0.03$) and restlessness ($t = 3.3$, $df = 3$, $P < 0.05$). However, the magnitude of the effects differed among the subjects. Whereas two of the subjects showed intense behavioral effects, the other two showed only moderate effects (Table 1). The increases in heart rate were also quite variable and ranged between 28 and 83% (Table 1). Though the plasma concentration of MP differed between the subjects, it did not seem to account for the variability in the magnitude of the behavioral effects, since the subjects (2 and 3) with more intense "high" responses showed diverse MP concentrations (Table 2).

In contrast to the variability in the behavioral and cardiovascular effects of MP, the uptake and kinetics of [11C]methylphenidate in the brain at baseline as well as after MP administration were strikingly similar for the four subjects (Fig. 1). The almost identical changes in B_{max}/K_d after MP among the subjects (range 68–72%) (Table 2) suggest that the extent of DA transporter occupancy by MP was similar for these individuals.

Comparisons between the time course of the normalized behavioral measures revealed similar temporal patterns for the "high" and for "anxiety". However, the pattern of "restlessness" was longer lasting (Fig. 2). The temporal pattern for MP induced changes in heart rate was similar to those in systolic blood pressure but not to those in diastolic pressure: whereas MP induced long lasting increases in heart rate and systolic blood pressure the increased diastolic blood pressure rapidly decayed to baseline levels but then increased again (Fig. 2). The temporal course for the behavioral effects and the cardiovascular response showed a similar pattern between diastolic blood pressure and "high" and "anxiety", and between systolic blood pressure and heart rate and "restlessness" (Fig. 2).

The behavioral responses to MP and the kinetics of [11C]methylphenidate in basal ganglia are compared in Fig. 3. Peak behavioral effects preceded the peak concentration of [11C]methylphenidate in basal ganglia (8–15 min), and occurred at 1–3 min for the "high" and for "anxiety" and at 1–5 min for "restlessness". Whereas the "high" and the "anxiety" declined rapidly

Table 1 Individual values for the effects of methylphenidate (*MP*) (0.5 mg/kg IV) in the behavioral and cardiovascular measures. Behavioral measures were subjectively rated by the subjects (rated from 0 to 100) and correspond to the highest values reported by a given individual. Cardiovascular effects are expressed as percent change from baseline after administration of MP (0.5 mg/kg IV) and correspond to the maximal change in a given subject

Subject	Higher scores induced by MP			Maximal change (% baseline)		
	High	Anxiety	Restlessness	Pulse	Systolic	Diastolic
1	50	40	45	67	42	28
2	90	40	75	28	23	26
3	90	10	20	39	20	30
4	40	40	20	83	38	28

Table 2 Individual values for the changes in [^{11}C]methylphenidate binding in basal ganglia after administration of methylphenidate (*MP*) 0.5 mg/kg IV and for the corresponding measures of plasma concentration of MP. Changes in binding are quantified as changes in estimates of B_{max}/K_d in basal ganglia with respect to baseline. Plasma concentration of MP was measured at 27, 67 and 107 min after MP administration

Subject	% change	Plasma MP concentration (ng/ml)		
	B_{max}/K_d	27 min	67 min	107 min
1	70.3	112	59	44
2	68.4	100	63	49
3	70.5	159	93	64
4	70.7	143	73	49

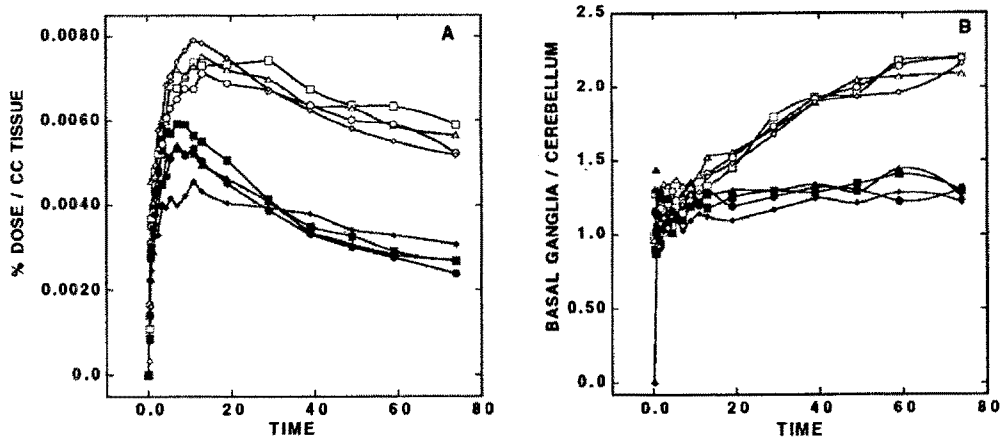

Fig. 1 Individual time activity curves for: **A** rate of uptake of [^{11}C]methylphenidate in basal ganglia (*open symbols*) and cerebellum (*closed symbols*), expressed as % injected dose per cc of tissue; **B** basal ganglia to cerebellum ratio for the studies done at baseline (*open symbols*) and the studies done after MP (0.5 mg/kg IV) (*closed symbols*). Each symbol denotes a different subject with his corresponding paired parameter (denoted as open or closed). The time activity curves for the absolute uptake of [^{11}C]methylphenidate as well as for the change in the basal ganglia to cerebellar ratios after MP administration did not differ between the subjects

after MP administration, the concentration of [11C]methylphenidate declined slowly. The temporal response to MP-induced "restlessness" was longer lasting and corresponded better with the clearance rate of [11C]methylphenidate. At 90 min the responses for the "high" and for "anxiety" were ca. 15–20% those of peak; those for "restlessness" were ca. 65–70% and the concentration of [11C]methylphenidate in basal ganglia was ca. 65–70%.

The cardiovascular responses to MP and the kinetics of [^{11}C]methylphenidate in basal ganglia are compared in Fig. 3. While MP-induced changes in blood pressure peaked (diastolic 1–3 min, systolic 1–5 min) prior to the peak brain [^{11}C]methylphenidate (8–15 min), that for the heart rate peaked at the same time (8–12 min). Changes in heart rate as well as systolic blood pressure were relatively long lasting and at 90 min values were ca. 55–60% those of peak; MP-induced changes in diastolic blood pressure declined rapidly but

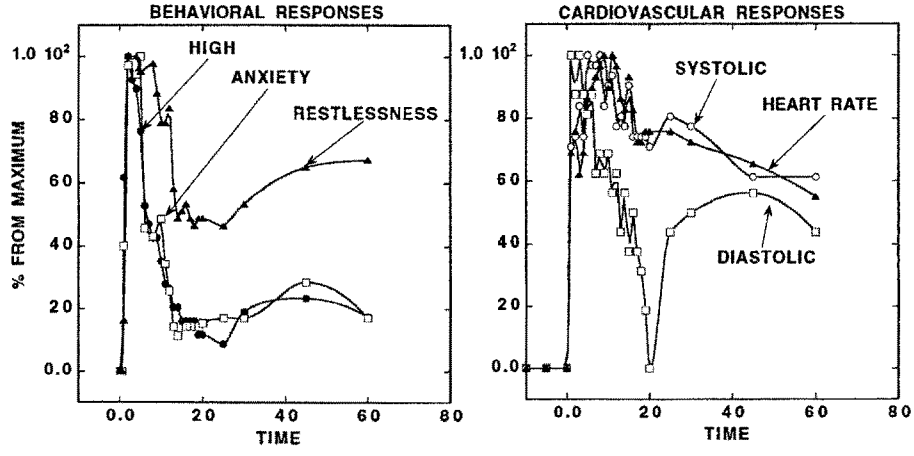

Fig. 2 Temporal course for the behavioral and cardiovascular effects of MP (average for the four subjects). Values are expressed as % change from maximum. For the cardiovascular responses this reflects maximum changes after subtracting the baseline values. MP-induced "high" and "anxiety" and the increases in diastolic blood pressure were of shorter duration than the increases in "restlessness", systolic blood pressure and heart rate

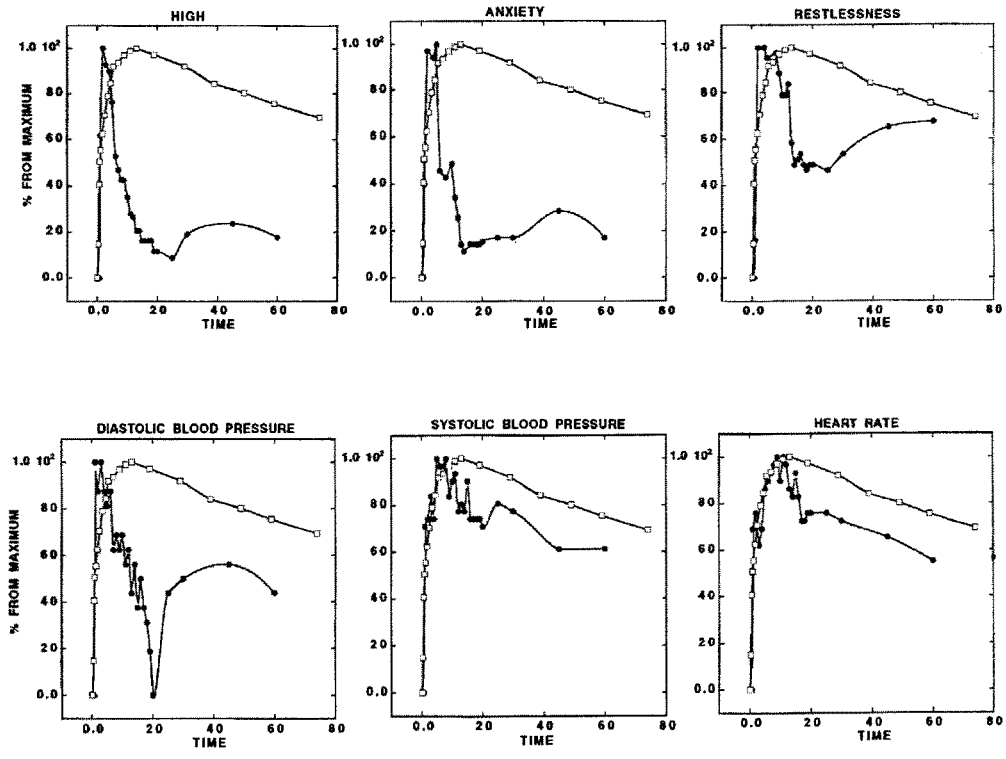

Fig. 3 Relation between the pharmacokinetics of [^{11}C]methylphenidate in basal ganglia (*open squares*) and the temporal course for the various behavioral and cardiovascular effects of MP (*closed circles*) (average for the four subjects). The peak of the behavioral effects and the blood pressure changes precedes the peak for the maximal concentration of the drug in brain. The "high", "anxiety" and diastolic blood pressure are dissociated from the rate of clearance of [^{11}C]methylphenidate from brain

increased again at 20 min and at 90 min were 40–45% those of peak.

Discussion

Methylphenidate consistently induced a "high" and increased "anxiety", "restlessness", heart rate and systolic and diastolic blood pressure in all four subjects investigated. The temporal course for these effects showed two distinct temporal patterns. Though all of the measured drug effects showed a fast onset (between 1 and 15 min), they differed markedly in the rate to which they returned to baseline. For the "high", "anxiety" and diastolic blood pressure (fast recovery), there was a rapid decline in the intensity of the effects from peak values (values close to baseline at 20 min post-injection), followed by a second rise of smaller intensity. For the changes in heart rate and systolic blood pressure (slow recovery), there was a slow decline in intensity from peak values with significant heart rate and systolic elevations still present at 90 min. The drug effects with a slow recovery pattern showed a better correspondence with the pharmacokinetics of [11C]methylphenidate in basal ganglia than the drug effects with a fast recovery pattern. This parallelism would seem to implicate a dopaminergic contribution to the effects of MP on heart rate and systolic blood pressure. Though the role of dopaminergic mechanisms in cardiovascular responses to psychostimulants is controversial (Schindler et al. 1995), there is evidence in humans that the dopaminergic antagonist haloperidol attenuates the cardiovascular effects of cocaine (Sherer et al. 1989) and of amphetamine (Angrist et al. 1974). For those effects of MP with a fast recovery, the correspondence with the pharmacokinetics of [11C]methylphenidate occurred only during its initial uptake. This could indicate that while the initial rise of MP in brain is associated with the experience of the "high" and the increased "anxiety", the persistence of the drug in brain is not. On the other hand, "restlessness", which persisted for a long time, followed a similar temporal course to that of MP in basal ganglia, indicating that it may reflect the persistent presence of the drug in brain. These two distinct temporal patterns for the recovery of MP effects could theoretically reflect differences in adaptation processes leading to acute tolerance for the "high" but not for the "restlessness". For example, acute tolerance to the "high" but not to the cardiovascular effects of cocaine has been documented (Foltin and Fischman 1991). However, they could also reflect involvement of different synaptic and extrasynaptic regulation elements (Grace 1995) as well as different neurochemical mechanisms.

MP-induced "high", and blood pressure changes which occurred faster than the peak uptake of [11C]methylphenidate in brain could reflect involvement of peripheral mechanisms. The plasma concentration of norepinephrine has been shown to rise sharply and return to baseline levels 10 min after administration of MP (Joyce et al. 1986), MP-induced sympatho-adrenal release of catecholamines may

account for the sharp and short lasting changes in diastolic blood pressure and may also contribute to the "high" and the rise in "anxiety". Our drug naive subjects did not distinguish between the "high" and the "rush" which are reported as separate subjective phenomena by experienced psychostimulant abusers. In a recent paper, peripheral responses were discussed as one of the possible mechanisms involved in the generation of the "rush" (Stathis et al. 1995). Future studies in cocaine abusers may enable distinction of the components due to the "rush" from those due to the "high". Such studies are necessary to ascertain the extent to which the temporal response to the "high" differs from that of the "rush" and to determine the possible contribution of peripheral mechanisms to these drug effects. The possible role of noradrenergic mechanisms in the rise in "anxiety" after MP has support from the literature documenting noradrenergic involvement in anxiety (Redmond and Huang 1979; Charney et al. 1992) as well as from the effectiveness of clonidine, an alpha2 adrenergic agonist that decreases norepinephrine release, in reducing anxiety from drug withdrawal (Glassman et al. 1988). It is also possible that the differences in the time at which peak effects are observed after MP administration represent differences in the extent of transporter inhibition required to induce maximal effects for the various actions of MP.

The cardiovascular effects of MP are similar, though not identical, to those reported for intravenous cocaine (Cook et al. 1984; Foltin and Fischman 1991). Cocaine induced increases in diastolic blood pressure also returned to baseline values faster than those for systolic blood pressure and showed a second peak of smaller magnitude than the first one (Cook et al. 1984). Similarly, for the studies reported by Foltin and Fischman (1991), increases in diastolic blood pressure after 32 mg intravenous cocaine return to baseline by 60 min, whereas systolic blood pressure remained significantly elevated. We do not have an explanation for the mechanisms underlying this dissociation.

The magnitude of MP-induced effects varied among the subjects. This agrees with previous reports of marked variability in the responses to MP (Joyce et al. 1986; Chait 1994; Wang et al. 1995). In contrast to the variable responses, the rates of uptake and distribution and the pharmacokinetics of [^{11}C]methylphenidate in brain among individuals were similar. Furthermore, the inhibition of binding of [^{11}C]methylphenidate in basal ganglia by pretreatment with MP, which is an indicator of DA transporter occupancy by MP, did not differ between the subjects. This suggests that the variability among individuals in their response to MP is not due to variable brain uptake or binding of the drug. Rather, it appears to be predominantly due to differences in the responsivity of the DA and/or norepinephrine systems and/or differences in responsivity of circuits that respond to changes in dopaminergic or noradrenergic input. Mechanisms underlying the variability in individual responses to psychostimulants remain largely unknown. In rodents, the magnitude of the responses to psychostimulant drugs can be predicted on the basis of spontaneous behaviors such as locomotor activity at baseline and responses to novel stimuli (Deminiere et al. 1989; Deutch et al. 1990). In humans an association between characteristics of subjects and their response to psychostimulants has been noted for personality traits (De Wit et al. 1986; Kavoussi and Coccaro 1993; Depue et al. 1994; Von Felsinger et al. 1995) as well as for psychopathology (Janowsky et al. 1973; Angrist et al. 1980; Van Kammen et al. 1982; Lieberman et al. 1994). We have also reported an association between the magnitude of the changes in synaptic DA assessed in PET experiments and the mental state of the subjects at baseline. Subjects who reported high scores on "anxiety" and negative mood at the time of drug administration showed the most robust responses to MP (Volkow et al. 1994).

The lack of correlation between plasma concentration of MP and binding inhibition by MP could reflect a number of factors. These include: the small sample size; the fact that we did not separately measure the active and the inactive enantiomers of MP (Srinivas et al. 1991) (only the active enantiomer would block the binding of [^{11}C]methylphenidate to the DA transporter); that we did not measure the free fraction of MP in plasma (our measures correspond to total concentration of drug in plasma), and the possibility that a saturating dose of MP was given. Though the dose of MP given to the subjects only reduced calculated B_{max}/K_d to 70% of control values, this may underestimate transporter occupancy if there are differences in non-specific binding between cerebellum and striatum and/or if conditions of equilibrium required for valid tracer kinetic modeling are not met. Preliminary calculations, using PET data on uptake of [^{11}C]methylphenidate in human brain (Volkow et al. 1995) and assuming "free" and DA transporter-bound drug are in equilibrium 2 min after intravenous administration, indicate that a transient occupancy level of 97% would require a dose of MP of about 1.4 mg/kg IV. Studies at lower doses in larger samples are required to assess better the relation between variability in drug effects and uptake of drug in brain.

Limitations of the present study are: (1) the analysis of the pharmacokinetics of MP in brain were done at tracer doses which may differ from those at pharmacological doses; (2) small sample size; (3) lack of a placebo condition and, (4) difficulties in standardizing subjective measures between subjects. Though the analysis of the pharmacokinetics of MP was done at tracer doses, the similarities between the pharmacokinetics of [^{11}C]methylphenidate in brain as assessed with PET and the temporal course for the concentration of MP in rodent brain measured after administration of pharmacological doses (Aoyama et al. 1994), indicates

that it adequately estimates the pharmacokinetics of MP at pharmacological doses. The small number of subjects limits the generalizability of the findings. Despite this, the temporal patterns for the effects of MP are similar to those we had previously documented for MP in a study done in 20 normals and 10 cocaine abusers (Wang et al. 1995). Lack of a placebo condition limits our ability to differentiate drug effects from condition effects. MP was given while the subjects were lying in the PET scanner and hence their responses may have been confounded by their reaction to the PET procedure as well as their expectations of receiving a drug as part of an experimental protocol. Nonetheless, it is unlikely that both the behavioral and cardiovascular effects reflect only the conditions of the PET experiment, since in a previous study also done under PET conditions, where we compared the effects of placebo with those of MP we found increases in cardiovascular and subjective effects similar to those reported in this study, for the MP condition but not for placebo (Wang et al. 1995).

The importance of drug pharmacokinetics to the reinforcing properties of drugs of abuse have long been recognized (Balster and Schuster 1973; Oldendorf 1992). Specifically, the rapidity of drug delivery to brain has been shown to affect reinforcement. The shorter the interval between intake and perceived effects of the drug, the greater the reinforcing potential (Oldendorf 1992). However, the role of drug pharmacokinetics in other central or peripheral effects of abused drugs has received less attention despite the fact that such an investigation could provide clues about the mechanisms of drug action. Also, the relationship of drug clearance to phenomena such as tolerance and sensitization has been poorly investigated. This study reports mainly on the use of PET to measure the pharmacokinetics of MP in basal ganglia which predominantly reflects its kinetics at the DA transporter (Ding et al. 1994). However, with appropriate drug pretreatment interventions it may be possible to measure the kinetics of MP at the norepinephrine transporter. Also needed are studies on the relation between doses of MP, the extent of DA and NE transporter inhibition, and drug effects.

In conclusion, this study documents two temporal patterns for the behavioral and cardiovascular effects of MP, one of which follows the kinetics of the drug in brain and another one which does not. Studies on the pharmacokinetics of MP in central and peripheral monoamine transporters may allow determination of the differential contributions of DA and norepinephrine transporters in these two temporal patterns of MP effects.

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