A New PET Ligand for the Dopamine Transporter: Studies in the Human Brain

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Carbon-11-*d-threo*-methylphenidate, the active enantiomer of methylphenidate (ritalin), has been shown to bind uniquely to the dopamine transporter in the baboon brain. This study characterizes its binding in the human brain and measures its test-retest reproducibility. **Methods:** Studies were done in seven normal controls, each of whom was scanned with [^{11}C]*d-threo*-methylphenidate on two different occasions. Six subjects were scanned twice 3–5 wk apart without intervention to assess reproducibility. One subject was scanned sequentially before and after treatment with methylphenidate to assess binding saturability. Graphical analysis was used to obtain tissue distribution volumes (DV). The ratio of the DV in the basal ganglia (BG) to that in cerebellum (CB) (DV_{BG}/DV_{CB}), which corresponds to (B_{max}/Kd) + 1 was used to estimate dopamine transporter availability. **Results:** Highest tracer uptake occurred in the basal ganglia, where activity peaked 7–11 min postinjection. The half-clearance time for the tracer in brain regions other than the basal ganglia was 74 min. In the basal ganglia, only 10%–15% of the activity had cleared at 74 min. Time-activity curves for [^{11}C]*d-threo*-methylphenidate in the basal ganglia and cerebellum were highly reproducible. The average percent change for the absolute value for DV_{BG}/DV_{CB} was 6.5% ± 4% (range 0–12%). Methylphenidate pretreatment decreased basal ganglia uptake but not cortical or cerebellar binding and reduced DV_{BG}/DV_{CB} by 62% and B_{max}/Kd by 91%. **Conclusion:** These studies demonstrate that [^{11}C]*d-threo*-methylphenidate binding in the human brain is reversible, highly reproducible and saturable. Thus, it is an appropriate PET ligand to measure dopamine transporter availability.

Key Words: carbon-11-*d-threo*-methylphenidate; dopamine transporter; cocaine; dopamine neurons

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The dopamine system appears to play a major role in movement, motivation and reward (*1–4*). Disruption of dopamine activity has been implicated in the pathogenesis of schizophrenia (*5*) and Parkinson's disease (*6,7*), as well as in some of the cognitive and behavioral changes associated with aging (*8*). It is crucial in the reinforcing properties of drugs of abuse (*4,9*). Therapeutically, it is a molecular target for antipsychotic drugs (*10,11*), antiparkinsonian agents (*12,13*) and for drugs used to treat narcolepsy (*14*) and attention deficit disorder (*15*).

Imaging technologies such as PET and SPECT are uniquely suited to measure parameters that relate to neurotransmitter activity. Of particular interest has been the use of PET to assess the dopamine system. Different elements from the dopamine synapse have been investigated with PET. The postsynaptic elements have been investigated with tracers that measure dopamine D2 (*16–19*) and D1 receptors (*20*). The presynaptic element (dopamine neurons) has been investigated using tracers to measure dopamine metabolism (*21,22*), transporter sites (*23–27*) and vesicular transporters (*28*). Recently, PET has also been used to assess the responsivity of the dopamine system to pharmacological challenge (*29–31*).

Several PET radioligands that bind to the neuronal dopamine transporter have been reported, including [^{11}C]nomifensine (*23,32*), [^{11}C]cocaine (*25*), [^{18}F]GBR 13119 (*24*), [^{18}F]GBR 12909 (*27*), [^{11}C]WIN 35428 (*26,33*) and [^{11}C]methylphenidate (*34,35*) and [^{11}C]NNC 12-0722 (*36*).

We recently synthesized [^{11}C]*d-threo*-methylphenidate, the more active enantiomer of methylphenidate (*37,38*), as a new ligand for the dopamine transporter (*39*). The [^{11}C]*d-threo* enantiomer is advantageous over [^{11}C]methylphenidate (racemic mixture) in that its quantification is not confounded by the presence of *l-threo* methylphenidate (less active enantiomer). Characterization of the binding of [^{11}C]*d-threo* methylphenidate in the baboon brain with PET has shown that its specific binding is predominantly to the dopamine transporter and that pretreatment with drugs that bind to the dopamine transporter can completely inhibit its specific binding (*40*). Also, its kinetics are ideally suited to the relatively short half-life of ^{11}C. This study evaluates the behavior of [^{11}C]*d-threo*-methylphenidate in the human brain to assess its suitability as a PET tracer to measure dopamine transporter availability.

METHODS

Subjects

Seven healthy human controls (5 men, 2 women; 23–74 yr) screened for absence of medical, neurological or psychiatric dis-

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ease were investigated. 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 twice in the week that imaging was performed to ensure absence of psychoactive drug use. Informed consent was obtained from the subjects following the guidelines of the Human Studies Review Committee at Brookhaven National Laboratory.

Six of these subjects were tested with [^{11}C]*d-threo*-methylphenidate twice, 3 to 5 wk apart, with no pharmacological intervention to assess test-retest reproducibility. One of the subjects was tested twice, 2 hr apart, with and without pretreatment with methylphenidate to assess binding saturability. Methylphenidate (0.5 mg/kg i.v.) was given 7 min prior to [^{11}C]*d-threo*-methylphenidate.

PET

PET studies were carried out with a whole-body, high-resolution positron emission tomograph (6 × 6 × 6.5 mm FWHM, 15 slices). To ensure accurate repositioning of subjects in the PET camera for the repeat imaging, an individually molded headholder was made for each subject. The subject's head was then 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 head movement during imaging. Prior to [^{11}C]*d-threo*-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. Dynamic scans were obtained immediately after injection of 4–8 mCi [^{11}C]*d-threo*-methylphenidate (specific activity >0.4 Ci/μmole at time of injection). A series of 20 emission scans were obtained from time of injection up to 84 min (four 15-sec, two 30-sec, four 1-min, four 2-min, five 10-min and one 20-min scans).

Arterial Input Function

Total ^{11}C and unchanged [^{11}C]*d-threo*-methylphenidate in plasma were quantified in arterial plasma samples. Arterial blood was obtained using an automated blood sampling device every 2.5 sec for the first 2 min and then drawn manually every minute from 2 to 5 min and then at 10, 15, 20, 30, 45 and 90 min.

A solid-phase extraction system, developed and implemented robotically in our laboratory, was used to quantify [^{11}C]*d-threo*-methylphenidate in plasma samples taken at 1, 5, 10 and 30 min. Briefly, whole blood was collected in centrifuge tubes containing sodium fluoride (1 mg/ml) to inhibit plasma esterases. After centrifugation, aliquots of plasma were counted for total radioactivity. Plasma (0.05–0.4 ml) was mixed with 5 ml water and applied to activated Varian BondElut cyanopropyl cartridges (500 mg). A series of four solvent rinses were used to remove the metabolite fractions (2 × 5 ml deionized water followed by 2 × 50% methanol). The radioactivity remaining on the cartridge represented unchanged tracer. The solid-phase analysis was validated by HPLC plasma analysis. The stability of [^{11}C]*d-threo*-methylphenidate to racemization was assessed using a chiral HPLC system described previously (*39*).

Image Analyses

Regions of interest (ROIs) were drawn on averaged emission scans representing the activity from 10 to 84 min after tracer injection. ROIs for the basal ganglia (caudate and putamen), thalamus, prefrontal cortex, temporal cortex, occipital cortex and cerebellum from averaged images were projected to the dynamic emission scans. ROIs were obtained in five different planes for the cortical regions and in two planes for subcortical and cerebellar regions. In a given plane, left and right regions were averaged. In addition, a global measure was obtained by averaging activity in the five central planes. A detailed description for the procedure, as well as the template for the ROIs, has been published elsewhere (*25*).

Binding of [^{11}C]*d-threo*-methylphenidate was quantified using distribution volumes calculated with a graphical analyses technique for reversible systems (*41*). The ratio of the distribution volume in the ROI to that in the cerebellum was used to assess reproducibility of the measurements.

The distribution volume provides a measure of binding that is a linear function of receptor availability given by:

$$DV = K_1/k_2'(1 + NS + B_{max}/Kd'), \qquad \text{Eq. 1}$$

for regions containing receptors characterized by an equilibrium dissociation constant Kd′ and free receptor concentration, B_{max}. For nonreceptor regions the distribution volume is given by:

$$DV = K_1/k_2'(1 + NS). \qquad \text{Eq. 2}$$

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 B_{max} can be obtained from Equations 1 and 2 giving:

$$\frac{B_{max}/K_d'}{1 + NS} = \frac{DV_{ROI}}{DV_{CB}} - 1. \qquad \text{Eq. 3}$$

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 K_1 and k_2'. The advantages of the distribution volume are that it is easily determined by a graphical technique derived from classical compartmental equations, it is not a function of blood flow (*42*) and it is a more stable measure than individual kinetic constants determined directly by compartmental analysis which are sensitive to noise and statistical fluctuations in the data (*43*). The ratio of the distribution volume for the ROI to cerebellum eliminates possible differences in the K_1/k_2 ratio between experiments. The assumption that the ratio of the transport constants is the same for the basal ganglia and cerebellum is one that is commonly made (*44*).

Reproducibility in the values for the ratio of the distribution volume in ROI to that in the cerebellum was estimated as the percent change for the regional mean values of the two scans. To assess intrasubject change in the distribution volume ratios, the mean for the absolute measures was used. Differences between the measures obtained during the first and second studies were assessed with paired t-tests (double-tail). Changes in the distribution volume for the ROI to that in the cerebellum after methylphenidate were considered significant if they were greater than three s.d. from the changes in test-retest measures.

RESULTS

Mean value for peak uptake of [^{11}C]*d-threo*-methylphenidate in whole brain corresponded to 9% ± 1.2% of the injected dose (range 8%–11%). Uptake of [^{11}C]*d-threo*-methylphenidate in the brain was heterogeneous, with the highest concentration in the basal ganglia (caudate, putamen). Relatively low concentrations were observed in thalamus, cortex and cerebellum. Figure 1 shows the brain

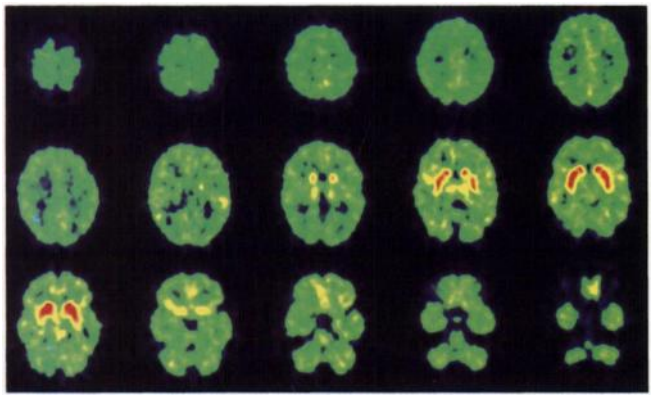

FIGURE 1. Brain images obtained with [^{11}C]*d-threo*-methylphenidate in a normal volunteer.

images obtained with [^{11}C]*d-threo*-methylphenidate from one of the subjects.

Uptake of [^{11}C]*d-threo*-methylphenidate in the brain was fast and peaked between 7 and 11 min in the cortical and subcortical regions and between 5 and 7 min in the cerebellum. Clearance of [^{11}C]*d-threo*-methylphenidate was slower in the basal ganglia than in other brain regions. Whereas for most brain regions 50% clearance from peak activity occurred approximately 74 min post-tracer injection, in the basal ganglia, only 10%–15% clearance had occurred at 74 min.

Scans with [^{11}C]*d-threo*-methylphenidate were highly reproducible in a given subject. Figure 2 gives the individual time-activity curves for the basal ganglia and cerebellum for the six subjects undergoing repeated measures. Except for Subject 2 and, to a lesser extent, Subject 7, the rest of the subjects showed almost superimposable curves on retest. Quantitative estimates for the uptake parameters (K_1) as well as the distribution volume measures were also highly reproducible. Table 1 shows the results for the test-retest reproducibility data for K_1 and distribution volume values in the various brain regions as well as for the ratios of the distribution volume in the ROI to that in cerebellum. The distribution volume plots for the basal ganglia from the test-retest studies for one of the subjects is shown in Figure 3. The individual measures for the distribution volume values in the basal ganglia and cerebellum as well as for the ratio of these volumes are given in Table 2. The test-retest reproducibility for the distribution volume in the basal ganglia to that in cerebellum (DV_{BG}/DV_{CB}) in a given subject averaged 6.5% (mean of absolute value), with a range of values for the percent change between 0% to 12%.

Methylphenidate pretreatment significantly reduced [^{11}C]*d-threo*-methylphenidate binding in the basal ganglia. Apart from the basal ganglia, the only other brain region which showed some evidence of change with methylphenidate pretreatment was the thalamus (Table 3). Since the test-retest variability for percent change in this region was large (Table 1), it was not considered significant. Figure 4 shows the time-activity curves for the basal ganglia and cerebellum at baseline and after methylphenidate pretreatment. Methylphenidate decreased binding in the basal ganglia to values comparable to those in the cerebellum. Pretreatment with methylphenidate significantly decreased the ratio of the distribution volume in the basal ganglia to that in the cerebellum from 3.11 to 1.19 (Table 3). Estimating B_{max}/Kd ($DV_{BG}/DV_{CB^{-1}}$) showed that methylphenidate decreased B_{max}/Kd by 91%.

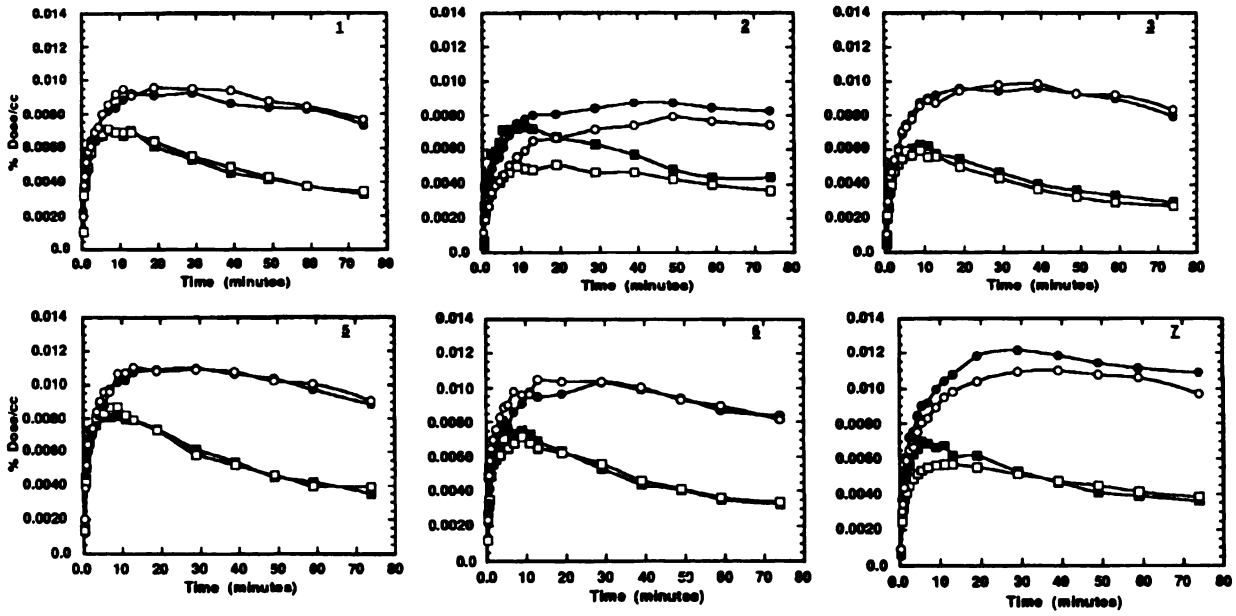

FIGURE 2. Individual time-activity curves for [^{11}C]*d-threo*-methylphenidate in the basal ganglia and cerebellum for Studies 1 and 2. Activity is expressed as percent dose per cubic centimeter of tissue. For Study 1, the striatum and cerebellum are presented as solid circles and solid squares, respectively. For Study 2, these regions are represented by the corresponding open symbols.

TABLE 1
Reproducibility for Measurements of Carbon-11-*d-threo*-Methylphenidate in Different Regions of the Human Brain

Region	Study	K_1	DV	DV_{ROI}/DV_{CB}	*%Change DV_{ROI}/DV_{CB}
Global	Test	0.40 ± 0.06	12.3 ± 0.4	1.05 ± 0.08	
	Retest	0.40 ± 0.07	12.4 ± 0.4	1.04 ± 0.06	5.8 ± 5
Basal ganglia	Test	0.60 ± 0.10	30.9 ± 2.8	2.59 ± 0.28	
	Retest	0.60 ± 0.10	31.2 ± 1.8	2.65 ± 0.33	6.5 ± 4
Thalamus	Test	0.61 ± 0.09	13.9 ± 0.9	1.18 ± 0.11	
	Retest	0.62 ± 0.93	14.0 ± 1.5	1.18 ± 0.09	8.6 ± 4
Prefrontal	Test	0.52 ± 0.10	12.0 ± 1.0	1.02 ± 0.11	
	Retest	0.50 ± 0.11	11.4 ± 0.6	0.96 ± 0.04	10.3 ± 8
Temporal	Test	0.50 ± 0.08	12.7 ± 1.2	1.08 ± 0.11	
	Retest	0.51 ± 0.09	13.0 ± 1.6	1.10 ± 0.14	10.0 ± 9
Occipital	Test	0.51 ± 0.07	10.7 ± 1.2	0.91 ± 0.11	
	Retest	0.51 ± 0.10	10.7 ± 1.5	0.90 ± 0.09	6.6 ± 6
Cerebellum	Test	0.54 ± 0.05	12.0 ± 1.1		
	Retest	0.53 ± 0.07	11.9 ± 1.0		

*Percent change reflects absolute values and is expressed with respect to the mean value of the two studies.
Data represent average from six subjects tested twice 3–5 wk apart. DV = distribution volume.

The average values for the integrated plasma concentration for unchanged [^{11}C]*d-threo*-methylphenidate for the test-retest studies are shown in Table 4. There were no significant differences in the concentration of unchanged [^{11}C]*d-threo*-methylphenidate between the first and the second studies.

DISCUSSION

These results in humans document that [^{11}C]*d-threo*-methylphenidate measurements in a given subject are highly reproducible and that binding of [^{11}C]*d-threo*-methylphenidate in the basal ganglia is saturable and almost completely blocked by pretreatment with methylphenidate. The stability of [^{11}C]*d-threo*-methylphenidate measurements, as assessed using the ratio of the distribution volume in the basal ganglia to that in the cerebellum, show individual variations that averaged less than 7% (mean of absolute values). The range of values for test-retest intrasubject variability is similar to that observed for [^{11}C]raclopride (*45*), a dopamine D2 receptor ligand.

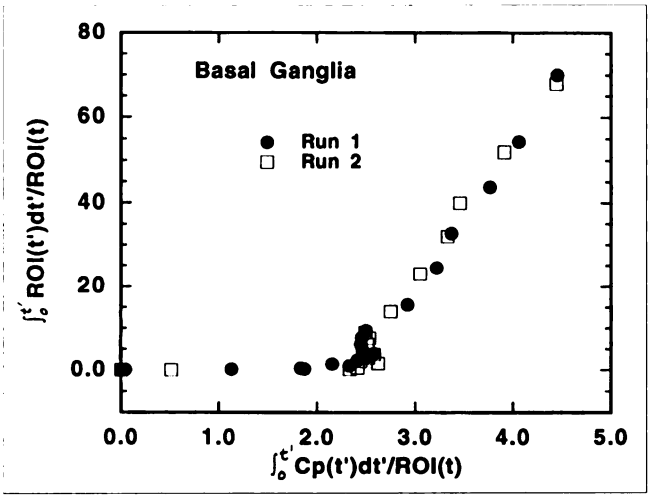

FIGURE 3. Graphical analysis (*41*) for the test-retest measures for one of the normal controls.

As previously mentioned, several ligands have been proposed to map dopamine transporter sites with PET and SPECT. Therefore, one could question the necessity of proposing still another PET ligand. Although ligands such as [^{18}F]GBR 13119 or [^{11}C]WIN 35428 have unique properties that may make them desirable for particular studies, [^{11}C]*d-threo*-methylphenidate appears to be better suited to measure dopamine transporter availability. For example, the specific binding of [^{11}C]cocaine as calculated from Equation 3 is 60%–65% lower than that of [^{11}C]*d-threo*-methylphenidate. Cocaine also has affinity for norepinephrine and serotonin reuptake sites as well as to a cytochrome P450 site (*46*). The uptake rates of [^{11}C]cocaine and [^{11}C]*d-threo*-methylphenidate in the brain are similar, but the clearance is slower for [^{11}C]*d-threo*-methylphenidate. This gives [^{11}C]*d-threo*-methylphenidate an advantage for kinetic analysis in that it is fast enough to allow application of reversible ligand models but is slow enough to obtain adequate counting statistics. Also, while binding of [^{11}C]cocaine in the brain is sensitive to drugs that change synaptic dopamine (*47*), binding of [^{11}C]*d-threo*-methylphenidate is not (*48*). This is advantageous when measuring dopamine transporters in patients with changes in synaptic dopamine concentration as a result of the disease process or as a consequence of medication.

The binding of [^{11}C]nomifensine is associated both with norepinephrine as well as the dopamine transporter (*32*), whereas specific binding of [^{11}C]*d-threo*-methylphenidate in the brain, as measured with PET, is mainly to dopamine transporters (*49*). Although *d-threo*-methylphenidate is known to have a relatively high affinity for the norepineph-

TABLE 2
Individual Values for the Basal Ganglia-to-Cerebellum (BG/CB) Ratio for Carbon-11-*d-threo*-Methylphenidate for Studies 1 and 2

Subject no.	Study	BG/CB ratio	*% Change	Distribution volume			*% Change DV_{BG}/DV_{CB}
				BG	CB	DV_{BG}/DV_{CB}	
1	1	2.08	1.0	26.8	11.2	2.41	8.2
	2	2.10		28.8	13.0	2.22	
2	1	1.77	3.9	32.9	13.9	2.37	5.7
	2	1.84		32.8	13.1	2.51	
3	1	2.69	7.9	31.2	11.2	2.78	12.4
	2	2.91		32.9	10.4	3.15	
5	1	2.27	0	28.5	11.7	2.44	6.3
	2	2.27		30.0	11.5	2.60	
6	1	2.40	3.4	30.4	12.3	2.48	0
	2	2.32		29.8	12.0	2.48	
7	1	2.80	13.3	33.6	10.9	3.09	5.7
	2	2.45		32.8	11.2	2.92	
Mean	1	2.33 ± 0.4	4.9 ± 4.9	30.9 ± 2.8	11.5 ± 1.4	2.62 ± 0.3	6.5 ± 4.0
Mean	2	2.32 ± 0.4		31.2 ± 1.8	11.9 ± 1.0	2.65 ± 0.3	

*Percent change reflects absolute values and is expressed with respect to the mean value of the two studies.

Ratios represent the average radioactivity concentration between 35 and 84 min. Values are given for the distribution volume (DV) in the BG and CB and for the ratio of the DV and BG to that of CB.

rine transporter (Kd 1860 nM) (*3*) the characterization studies in baboons failed to show an effect of pretreatment with norepinephrine transporter blockers on [^{11}C]*d-threo*-methylphenidate binding in the brain, including the thalamus, an area with a high concentration of norepinephrine transporters. Furthermore, the fact that thalamic binding was uniquely affected by drugs that inhibit the dopamine transporter but not by drugs that inhibit the norepinephrine transporter suggests that the relatively high binding of [^{11}C]*d-threo*-methylphenidate in the thalamus reflects binding to dopamine transporters. Although the effect of methylphenidate pretreatment on thalamic binding of [^{11}C]*d-threo*-methylphenidate in the human brain was larger than its effects in other brain regions, except for the basal ganglia, it was not significant. The fact that methylphenidate induced decrements in thalamic binding were of the same magnitude as those observed in the baboon brain indicates that failure to demonstrate significance may be related to the lack of power with a sample size of one. Studies in larger samples will enable researchers to determine if [^{11}C]*d-threo*-methylphenidate can be used to measure binding to extrastriatal dopamine transporters. Failure to demonstrate binding of [^{11}C]*d-threo*-methylphenidate to the norepinephrine transporters could be explained if the binding of *d-threo*-methylphenidate to the norepinephrine transporter dissociates at a much faster rate than that to the dopamine transporter so that it cannot be assessed with the relatively slow temporal resolution of PET. Another possibility is that the relative regional concentration of the nor-

TABLE 3
Values for Distribution Volume in Various ROIs and for the $DV_{ROI}DV_{CB}$ at Baseline and after Pretreatment with Methylphenidate (0.5 mg/kg i.v.)

Region	DV BSL	DV MP	$DV_{ROI}DV_{CB}$ BSL	$DV_{ROI}DV_{CB}$ MP	% Change $DV_{ROI}DV_{CB}$
Basal ganglia	34.1	13.7	3.11	1.19	−62
Thalamus	13.2	12.4	1.20	1.07	−11
Prefrontal	11.6	12.0	1.05	1.03	−2
Temporal	11.8	11.7	1.07	1.00	−6
Occipital	10.6	10.9	0.96	0.94	−2
Cerebellum	11.0	11.6			

$DV_{ROI}DV_{CB}$ = ratio of the distribution volume in the ROI to that in the cerebellum; BSL = baseline; MP = methylphenidate.

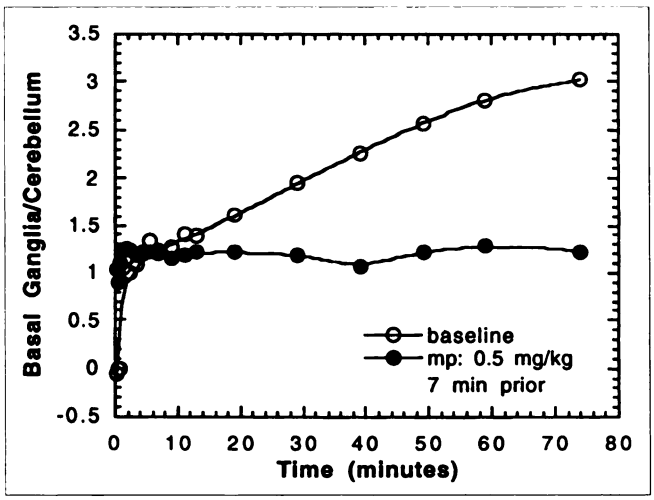

FIGURE 4. Effects of methylphenidate pretreatment on the time-activity curve for the basal ganglia-to-cerebellum ratio for [^{11}C]*d-threo*-methylphenidate. With methylphenidate pretreatment, the basal ganglia-to-cerebellum ratio approached unity.

TABLE 4
Mean Values for Integrated Plasma Concentration of Unchanged Tracer

Time p.i.	Plasma integral unmetabolized [^{11}C]*d-threo*-methylphenidate (nCi cc^{-1} min mCi^{-1}) Study 1	Study 2	% Unmetabolized [^{11}C]*d-threo*-methylphenidate
5 min	150 ± 20	134 ± 28	81.2 ± 6.1
10 min	194 ± 19	173 ± 33	65.7 ± 7.3
30 min	289 ± 26	264 ± 40	33.4 ± 4.7
60 min	370 ± 31	342 ± 42	18.7 ± 2.9
90 min	399 ± 34	371 ± 40	15.2 ± 2.4

epinephrine transporter is low for the limited sensitivity of PET. It is also possible that binding of *d-threo*-methylphenidate to norepinephrine transporters occurred at a different site in the transporter than the norepinephrine transporter drug (tomoxetine) used to prevent its binding (*49*).

The binding of [^{18}F]GBR 13119 and 12909 has been associated both with dopamine transporters as well as with cytochrome P450 (*50*), and its high affinity for the dopamine transporter and its consequent high rate of trapping in tissue may make it sensitive to delivery at low blood flows. Although WIN 35428 has a high selectivity for the dopamine transporter and a higher specific-to-nonspecific ratio than [^{11}C]*d-threo*-methylphenidate, its high affinity (*51*) and striatal uptake, which is still increasing after more than five half-lives of ^{11}C, may also make [^{11}C]WIN 35428 (*26*) sensitive to cerebral blood flow. The same argument may hold for [^{11}C]β-CIT (*52*), which has a high affinity for the dopamine and serotonin transporters (*53*), but for which the basal ganglia-to-cerebellum ratio is still rising over the useful experimental period for ^{11}C and appears to be suitable for ^{123}I labeling and SPECT (*54*). The use of these radiotracers could therefore lead to an underestimation of dopamine transporter availability in areas of high concentration. This is not predicted to be a problem with [^{11}C]*d-threo*-methylphenidate, whose reversibility facilitates its modeling and quantitation. Also, while [^{11}C]WIN 35428 binds to the serotonin transporter, [^{11}C]*d-threo*-methylphenidate does not. Methylphenidate's affinity for the serotonin transporter is low (Kd 15000 n*M*) (*3*). Lack of binding of [^{11}C]*d-threo*-methylphenidate to serotonin transporters is corroborated by the failure of citalopram to inhibit binding of [^{11}C]*d-threo*-methylphenidate in the brain, including the mesencephalon (an area with a relatively high concentration of serotonin transporters) (*49*). This contrasts with the results obtained with ^{123}I β-CIT, for which activity in the mesencephalon was significantly displaced by citalopram.

Although one could argue the use of one tracer versus the other, it will ultimately be the results from PET studies that demonstrate whether one tracer is better than another to monitor dopamine transporters. It is also likely that one tracer may be more feasible for certain experiments than others. For example, under conditions of decreased dopamine transporter availability, [^{11}C]WIN 35428 may be more sensitive than [^{11}C]*d-threo*-methylphenidate. For quantification in normal subjects and in patients with decreased cerebral blood flow, [^{11}C]*d-threo*-methylphenidate may be more sensitive than [^{11}C]WIN 35428. Another advantage for [^{11}C]*d-threo*-methylphenidate is that, as an approved drug, unlabeled methylphenidate can be given to humans to assess nonspecific binding. This also facilitates the approval of the labeled drug for human research PET studies through the Radioactive Drug Research Committee (RDRC) route. Some of the problems and pitfalls associated with assessing the utility of a variety of different radiotracers for the dopamine transporter have been discussed recently (*55*).

CONCLUSION

Carbon-11-*d-threo*-methylphenidate has a unique set of properties, including a high uptake rate (8%–10% injected dose), high specific-to-nonspecific binding ratio, specific binding to dopamine transporters, good reproducibility and reversible binding which facilitates its quantitation. It is also insensitive to competition by endogenous dopamine concentration (*48*). These characteristics make [^{11}C]*d-threo*-methylphenidate a particularly promising PET ligand to measure dopamine transporter availability in humans.

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