Delayed L-Phenylalanine Infusion Allows for Simultaneous Kinetic Analysis and Improved Evaluation of Specific-to-Nonspecific Fluorine-18-DOPA Uptake in Brain

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The accumulation of 3-O-methyl-6-[^{18}F]fluoro-L-DOPA (^{18}F-30M-DOPA) in the brain from the circulation is responsible for most of the nonspecific background during ^{18}F-DOPA positron emission tomography scanning. To increase the sensitivity of ^{18}F-DOPA for imaging presynaptic dopamine systems, we took advantage of ^{18}F-30M-DOPA's rapid clearance from the brain ($T_{1/2}$ ~ 15–20 min). The infusion of the unlabeled amino acid L-phenylalanine, starting 75 min after ^{18}F-DOPA administration, prevents ^{18}F-30M-DOPA entrance into the brain through competition at the large amino acid transport system of the blood brain barrier. This method produces high specific-to-nonspecific contrast images of ^{18}F accumulation beginning 15–30 min after onset of amino acid infusion and better sensitivity to small changes in ^{18}F-DOPA uptake while still allowing for kinetic analysis of the data in the early time points. Kinetic and anatomical data were found to be strongly correlated.

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PET studies allow examination of certain aspects of some neurotransmitter pathways, presynaptic metabolism and/or receptor properties in vivo. One of the most widely used tracer is 6-[^{18}F]fluoro-L-3,4-dihydroxy-phenylalanine (^{18}F-DOPA). PET scans of ^{18}F regional brain accumulation following ^{18}F-DOPA injection have been used to assess central presynaptic dopaminergic (DA) function. Transported across the blood-brain barrier (BBB) into the brain through the large neutral amino acid (LNAA) transport system, ^{18}F-DOPA is mainly decarboxylated in DA nerve terminals to 6-^{18}F-dopamine (^{18}F-DA) by aromatic amino acid decarboxylase (AAAD). In turn, ^{18}F-DA is metabolized to 6-^{18}F-3,4-dihydroxy-phenylacetic acid (^{18}F-DOPAC) and 6-^{18}F-homovanillic acid (^{18}F-HVA). Retention of ^{18}F-DOPA and its metabolites is responsible for the specific accumulation of ^{18}F activity in structures known to possess rich DA-innervation such as the striatum. Fluorine-18 accumulation is reduced in the striatum of patients with Parkinson's disease and other neurodegenerative diseases (*1–7*) and in patients and animals exposed to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (*8–11*).

When ^{18}F accumulation is reduced, either because of degeneration of the DA nerve terminals or because of the small amount of DA terminals in some brain areas (e.g., in the cortex), accurate identification of the structures and positioning of the regions of interest (ROIs) becomes a critical issue. Unfortunately, precise identification and quantification of structures with poor ^{18}F-DOPA uptake is difficult because of the presence of a considerable nonspecific ^{18}F background produced by the entrance into the brain of the main peripheral metabolite of ^{18}F-DOPA, 3-O-methyl-6-[^{18}F]fluoro-L-DOPA (^{18}F-30M-DOPA) (*12, 13*). To enhance the contrast of specific-to-nonspecific ^{18}F accumulation in PET images, it is necessary to selectively prevent ^{18}F-30M-DOPA from entering the brain. This can be accomplished either by eliminating ^{18}F-30M-DOPA from the plasma or by blocking its transport through the BBB. For example, some groups (*14,15*) have reported increased contrast using newly available catechol-O-methyl transferase inhibitors to prevent peripheral ^{18}F-DOPA methylation.

We recently reported promising results using a different approach (*16*). This approach called for: (1) pretreatment with the peripheral decarboxylase inhibitor carbidopa (CD) to increase ^{18}F-DOPA plasma bioavailability and (2) the continuous infusion of the unlabeled amino acid L-phenylalanine (PH) beginning 15 min after tracer administration (i.e, when most ^{18}F-DOPA has already entered the brain and ^{18}F-30M-DOPA levels are still low). By saturating the BBB/LNAA transport system, PH infusion blocks ^{18}F-30M-DOPA entrance into the brain. An increased visual contrast was found between DA-rich and DA-poor areas and their ratios. This technique, however, presented two main disadvantages. The early infusion of

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unlabeled PH resulted in the loss of specific brain counts and a valid kinetic analysis of the data was not possible, because k_1 approaches zero shortly after the start of the amino acid infusion.

The technique described here overcomes both disadvantages while retaining the same benefits, i.e., increased differentiation of specific-to-nonspecific ^{18}F accumulation and, thereby, enhanced sensitivity to small changes in ^{18}F-DOPA uptake. By taking advantage of the fast clearance of ^{18}F-30M-DOPA from the brain, calculated from our ^{18}F-30M-DOPA data (*13*), we estimated that it should be possible to delay the PH infusion up to 70–80 min after ^{18}F-DOPA administration. By this time, nearly all the available plasma ^{18}F-DOPA should have already entered the brain. Thus, very little specific brain ^{18}F accumulation would be lost and an even greater contrast enhancement of specific-to-nonspecific areas would be obtained during the late time points. Moreover, this delay would enable kinetic analysis to be performed on the early time points.

We also investigated the relationships between the qualitative analysis yielding a ratio of specific-to-nonspecific ^{18}F activity obtained during late time points and the more quantitative kinetic approach made possible by the acquisition of both plasma and tissue activity over time.

METHODS

Twenty-two rhesus monkeys were studied. Nine normal controls (C1 to C9), four clinically asymptomatic, bilaterally MPTP-treated (total cumulative dose: 2–4.8 mg/kg in a saphenous vein) (M1 to M4) and five unilaterally MPTP-treated monkeys (total cumulative dose: 0.3–1.5 mg/kg into the right internal carotid artery) (H1 to H5) received an initial PET scan after injection of ^{18}F-DOPA alone. Then, C6, M2 and H3 in addition to four new control animals (C10 to C13), age- and size-matched to the original group, received a ^{18}F-DOPA PET scan with CD pretreatment followed by continuous infusion of cold PH 75–80 min after tracer injection. All the animals were fasted for 12–18 hr before ^{18}F-DOPA injection.

Carbidopa (a gift from Merck, Sharp and Dohme, Rahway, NJ) (5 mg/kg p.o., 60–90 min before ^{18}F-DOPA injection) and PH (in phosphate-buffered saline; pH 7.4) were prepared as previously described (*16*). Starting 75–80 min after tracer injection, 50 mg/kg of unlabeled PH was injected during a 15–20-min period, followed by a continuous infusion at 100 mg/kg/hr until the end.

Scanning Technique

Animal preparation, ^{18}F-DOPA synthesis and scanning procedure are described in detail elsewhere (*11*). Scanning (Scanditronix PC 1024-7B; in-plane resolution: 6–6.5 mm FWHM; slice thickness: 10–11 mm) began at the time of the ^{18}F-DOPA injection (1-min bolus injection, specific activity 300–700 mCi/mmol) and lasted up to 4 hr. The averaged doses were 3.12 ± 1.16 mCi for the animals injected with ^{18}F-DOPA (n = 18) and 2.04 ± 0.93 for the animals injected with ^{18}F-DOPA + CD + PH (n = 7).

Multiple arterial blood samples were drawn during the course of the study. Due to technical difficulties, arterial blood data from animals C9 and M4 were not obtained. Metabolite analysis was performed on 9–14 of the plasma samples. The metabolite analysis technique used is described in detail in a previous paper (*17*). Briefly, positively and negatively charged metabolites were separated by passage of a 0.1–0.2-cc aliquot of plasma through a cation/anion exchange column (pH 5.5). The column effluent was then extracted with alumina (pH 8.7) to separate ^{18}F-30M-DOPA from ^{18}F-DOPA.

Data Analysis

Previously described criteria (*11*) were used for the identification of striatal structures and the determination of the correction factor used to adjust for positioning errors. The averaged activity of several posterior cortical areas (occipital, occipito-parietal, temporal, parietal) was used to calculate the striatum/cortex ratio.

Brain and blood data were normalized to the amount of activity injected per kilogram of body weight. Time-activity curves of striatal, cortical, temporal muscles activity and striatum-to-cortex ratios were generated for each animal. Left and right brain time-activity curves, compared using repeated measure analysis of variance (ANOVA), were not significantly different in either the normal or bilaterally MPTP-treated monkeys and were averaged.

To compare data between animals and groups, all brain, plasma and metabolite activity curves were interpolated at standard predefined times (computed linear regression). They were then averaged by groups and conditions. Because only one of the bilaterally and unilaterally MPTP-treated animals was scanned in the experimental condition with CD + PH, only the data obtained in normal animals in the two conditions were compared. The separation of the data into two time periods, 0–80 and 90–180 min, allowed us to assess, CD (0–80 min) and PH (90–180 min) effects on ^{18}F accumulation in brain, muscle and plasma.

The areas under the curve of the time-activity curve of the striatum, cortical areas and muscle and the four classes of plasma metabolites (^{18}F-DOPA, ^{18}F-30M-DOPA, anion and cation) during the same time periods were calculated and compared using Student's t-tests.

Striatum-to-cortex ratios between 120 and 180 min were calculated for each monkey. They were averaged by groups and conditions and compared using a Student's t-test.

As described by Patlak et al. (*18,19*) and Martin et al. (*20*), a multiple-time-graphical analysis of the ^{18}F-DOPA data was done for the eight normal controls, three MPTP-treated and five hemi MPTP-treated animals that received ^{18}F-DOPA alone and for each animal that received ^{18}F-DOPA + CD + PH. The main result of the graphical analysis, K, can be considered equal to the rate constant for net uptake of ^{18}F-DOPA from blood to striatum. In this paper, K is also referred to as the influx constant. Because: (1) PH infusion blocks the entrance of ^{18}F-DOPA as well as of ^{18}F-30M-DOPA into the brain, making the assumptions of the Patlak analysis incorrect, and (2) the amount of ^{18}F-DOPA present in plasma in the later time points is very small and therefore difficult to quantitate, the graphical analysis was restricted to the first 80 min after isotope injection. In the hemi-lesioned animals, both left and right influx constants, K, were calculated. The K values were compared using a Student's t-test. K (0–80 min) and the striatum-to-cortex ratios (120–180 min) were compared to one another using Pearson's correlation.

RESULTS

The visual contrast between DA-rich and DA-poor areas from 100 to 180 min was increased in the animals in the

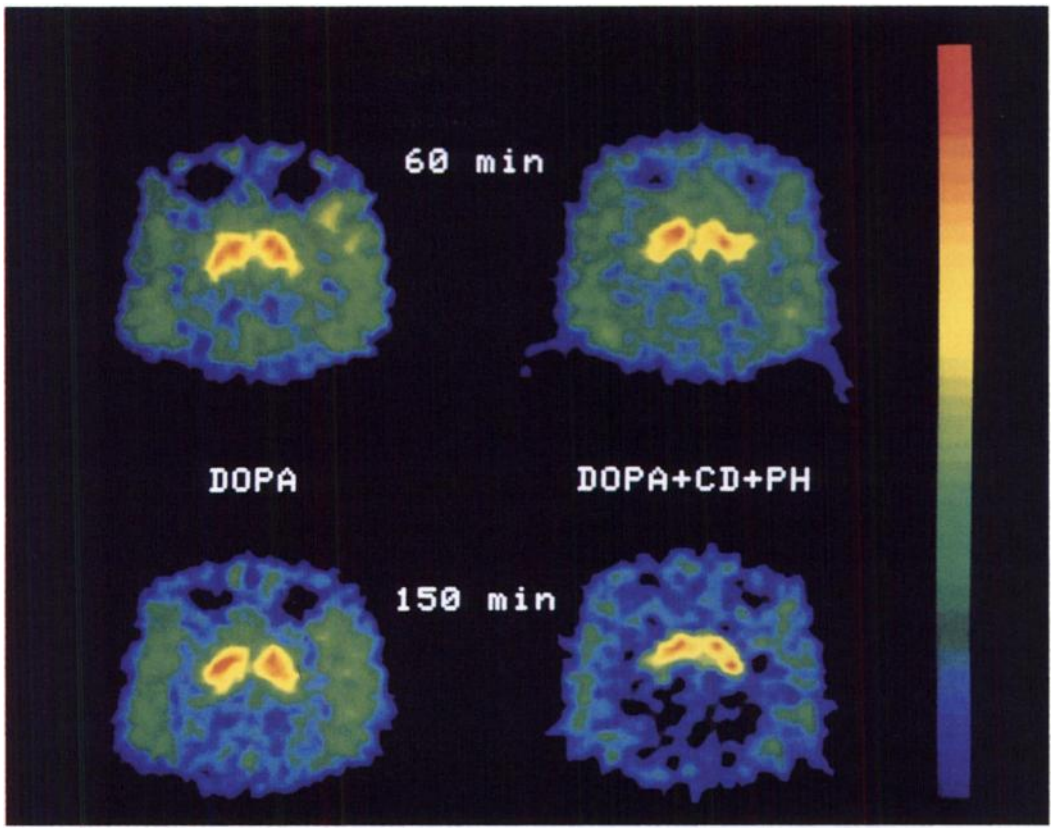

FIGURE 1. Images from the ^{18}F-DOPA kinetic set taken at 60 (top) and 150 min (bottom) after injection of ^{18}F-DOPA alone (DOPA) (left) or with carbidopa pretreatment and followed by PH infusion (DOPA + CD + PH) (right) in two normal monkeys, matched for age and weight. The 60-min images, obtained before the start of the L-phenylalanine infusion, show no significant difference in brain ^{18}F accumulation. The 150-min images, obtained 75 min after the beginning of the amino acid infusion, show the increase contrast between specific (striatum) and nonspecific (posterior cortical areas) ^{18}F accumulation in the DOPA + CD + PH condition. For easier comparison of the two sets, the images have been corrected for the number of millicuries injected and are normalized to their own maximum.

experimental condition compared to ^{18}F-DOPA injection without PH infusion (Fig. 1). The striatum-to-cortex ratios obtained between 120 and 180 min in the animals that received CD pretreatment (−60 min) with PH infusion (+75 min) were significantly higher than in the animals that received ^{18}F-DOPA alone (Table 1). Both observations appear to be the result of a decrease in ^{18}F accumulation in the DA-poor areas.

ANOVA between 0 and 80 min after tracer injection (i.e., before PH infusion) showed no significant difference in striatal and posterior cortices ^{18}F time-activity curves when ^{18}F-DOPA was injected alone or preceded by CD

TABLE 1
Averaged Striatum-to-Cortex Ratios (120–180 min) and Rate Constant for Net Uptake of ^{18}F-DOPA from Blood to Striatum (0–80 min) in the Two Experimental Conditions: DOPA Alone or with Carbidopa Pretreatment and L-phenylalanine Infusion (DOPA+CD+PH)

	Normal control	MPTP-treated	HEMI-MPTP-contralateral	Treated ipsilateral
Striatum/cortex DOPA alone	2.75 ± 0.29 (n = 9)	1.74 ± 0.07 (n = 4)	2.61 ± 0.44 (n = 5)	1.48 ± 0.12 (n = 5)
Rate constant K DOPA alone	0.0142 ± 0.0021 (n = 8)	0.0051 ± 0.0011 (n = 3)	0.0143 ± 0.0012 (n = 5)	0.0053 ± 0.0016 (n = 5)
Striatum/cortex DOPA+CD+PH	4.36 ± 0.32* (n = 5)	2.11 (n = 1)	3.56 (n = 1)	1.19 (n = 1)
Rate constant K DOPA+CD+PH	0.0139 ± 0.0026 (n = 5)	0.0047 (n = 1)	0.0094 (n = 1)	0.0013 (n = 1)

* A significant difference ($p < 0.001$) with the normal controls in the DOPA condition. Data are given ± s.d. and the number of animals (n).

pretreatment (Fig. 2). Striatal and cortical areas under curves were not significantly different during the same time period (Fig. 3). However, the ANOVA between 90 and 180 min (i.e., 15 min after the beginning of PH infusion until the end of the experiment) showed a significantly lower ^{18}F accumulation ($p = 0.003$) in the cortical nonspecific area (Fig. 2). The ANOVA comparison of striatal time-activity curves showed a significant interaction ($p = 0.008$) for time × condition. Only the 180-min time point significantly differed ($p = 0.038$) between the two conditions. Area under curve comparisons yielded similar results (Fig. 3). Ratio striatum-to-cortex time-activity curves were not significantly different between 0–80 min, while they were highly significantly different between 90–180 min (Fig. 4). As analyzed by ANOVA or comparison of the areas under curves by Student's t-test, there was no significant CD or PH effects on muscle ^{18}F accumulation.

The plasma ^{18}F-DOPA and ^{18}F-30M-DOPA areas under the curve from 0 to 80 min were increased slightly but nonsignificantly with CD pretreatment (Fig. 5). The small number of animals studied in the CD condition may have contributed to this observation. The anion and cation metabolite areas under the curve were nonsignificantly decreased when CD was administered prior to ^{18}F-DOPA. Between 90 and 180 min, there was no significant differences between ^{18}F-DOPA, ^{18}F-30M-DOPA and anion metabolites in the two conditions, but there was a significant decrease in the cation metabolites ($p = 0.04$) (Fig. 5).

There was no significant change in the rate constant K (0–80 min) when ^{18}F-DOPA was administered with or without CD pretreatment (Table 1 and Fig. 6).

A strong correlation existed between the striatum-to-cortex ratio from 120 to 180 min (i.e., when contrast between specific and nonspecific accumulation areas is the highest) and the K values between 0 and 80 min (i.e., before L-phenylalanine infusion) in both experimental conditions, DOPA alone ($r = 0.932$ $p < 0.0001$) and DOPA + CD + PH ($r = 0.924$ $p < 0.001$) (Fig. 7).

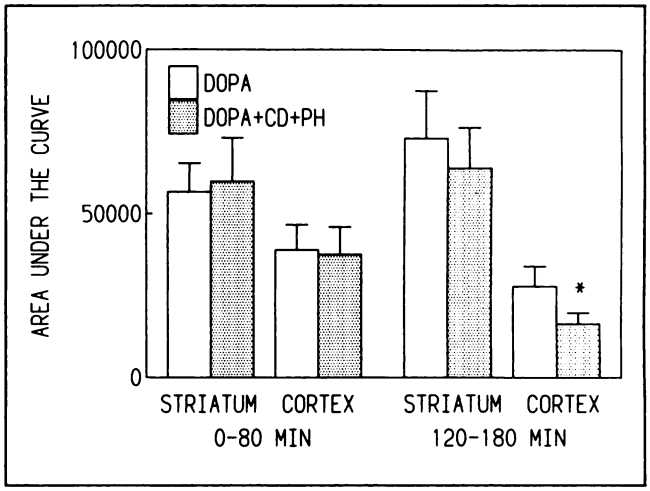

FIGURE 3. Averaged areas under the curve showing the effects of carbidopa (0–80 min) and L-phenylalanine (90–180 min) on ^{18}F accumulation in the striatum and cortex in the DOPA + CD + PH condition compared to ^{18}F accumulation in the DOPA condition in normal monkeys. Data are represented with the standard deviation. The asterisk indicates a significant difference ($p = 0.003$).

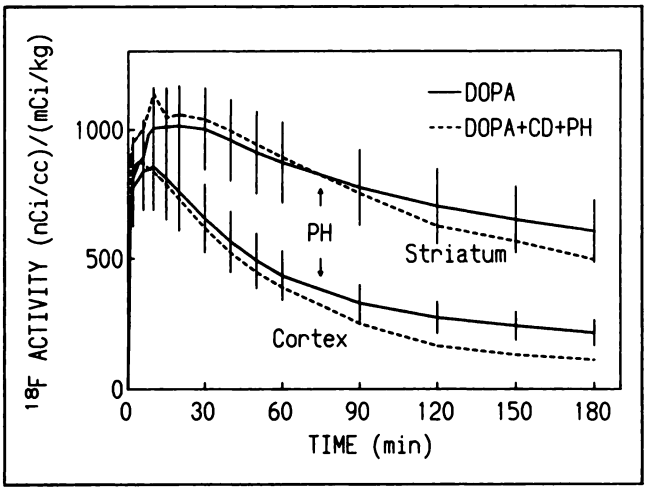

FIGURE 2. Averaged striatal and cortical ^{18}F time-activity curves obtained in normal control monkeys after injection of ^{18}F-DOPA alone (DOPA) and ^{18}F-DOPA preceded by carbidopa (−60 min) and followed by L-phenylalanine infusion (+75 min) (DOPA + CD + PH). The arrow indicates the onset of amino acid infusion (PH). For image clarity, only the standard deviation of the ^{18}F-DOPA alone condition has been represented.

DISCUSSION

This paper confirms earlier findings obtained with constant infusion of unlabeled PH beginning 15 min after ^{18}F-DOPA injection (*16*). In both situations, PH infusion beginning either at 15 or 75 min after tracer administra-

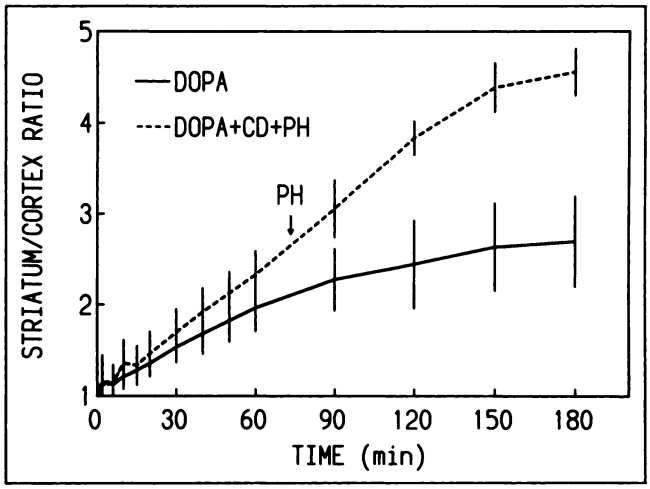

FIGURE 4. Averaged striatum-to-cortex ratio curves in normal controls in the two experimental conditions, DOPA and DOPA + CD + PH. The arrow indicates the onset of amino acid infusion (PH).

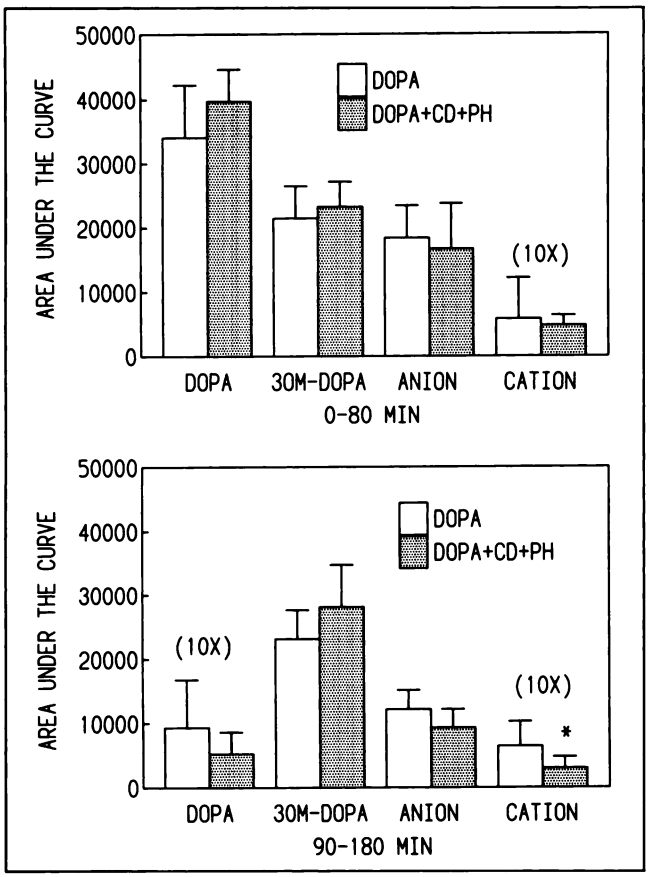

FIGURE 5. Averaged areas under the curve for ^{18}F-DOPA 0–80 min and 90–180 min postinjection showing the effects of carbidopa (top) and L-phenylalanine (bottom) on ^{18}F-DOPA metabolism in the plasma. Data are shown with standard deviation.

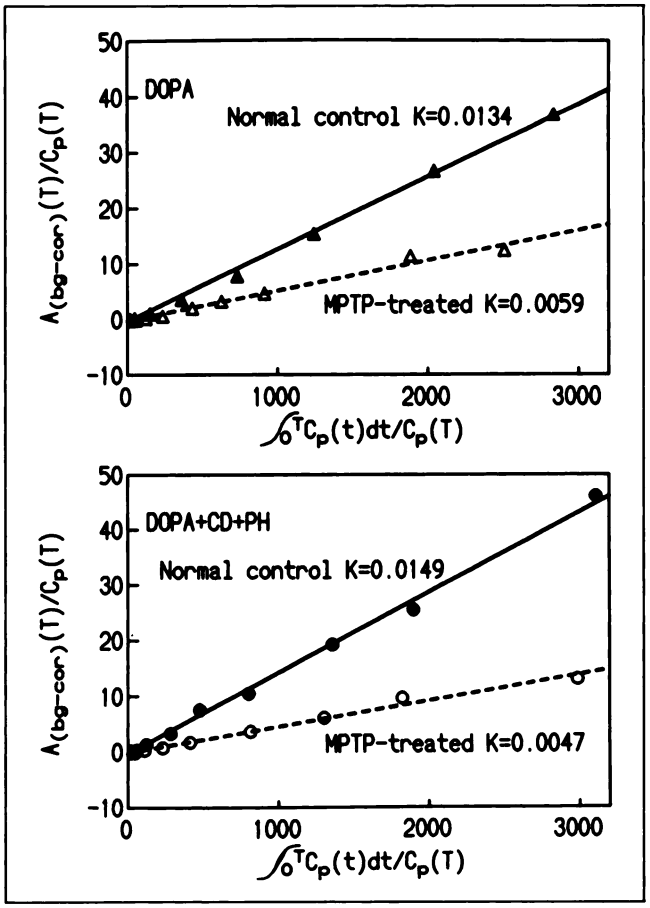

FIGURE 6. Plots of the Patlak equation as described in the text showing the relationship between specific striatal radioactivity (striatal activity minus reference cortical area activity) and integrated plasma ^{18}F-DOPA activity for the first 80-min postinjection. The slope of the regression line equals the rate constant for net uptake of ^{18}F-DOPA from blood to striatum, K. Data are shown in two representative normal controls (filled symbols) and the same MPTP-treated animal (unfilled symbols) when injected with ^{18}F-DOPA alone (DOPA) or with carbidopa pretreatment (DOPA + CD + PH).

tion, successfully prevents ^{18}F-30M-DOPA entrance into the brain, by competing with the radioactive amino acid for the LNAA transport system at the BBB.

The similar reduction in striatal and cortical ^{18}F accumulation suggests that ^{18}F-30M-DOPA is cleared equally from both specific and nonspecific accumulation areas, which is consistent with our previous data showing an homogenous distribution of this compound in the brain (*13*). In the brain, this results in an increased contrast between areas of specific and nonspecific ^{18}F accumulation. The increased contrast was demonstrated by the finding of increased striatum-to-cortex ratios observed between 120 and 180 min in animals that received ^{18}F-DOPA + CD + PH compared to animals that received ^{18}F-DOPA alone (Table 1).

Striatum-to-cortex data obtained with +75 min PH infusion closely parallel the data obtained with +15 min infusion (*16*). However, identification of the DA areas was improved by the conservation of specific brain counts afforded by the delay of amino acid infusion until 75 min post ^{18}F-DOPA injection.

Both PH procedures show enhanced sensitivity for detecting subtle changes in ^{18}F-DOPA uptake. The "normal" side of the hemi-MPTP-treated monkey scanned with the +75 min infusion method revealed a decrease in striatum-to-cortex ratio similar to the decreased ratio already reported in the noninjected side of the three different hemi-lesioned animals scanned with the +15 min infusion method compared to normal controls. The combined data from these four animals suggest that reduction of brain nonspecific background by amino acid infusion enhances the sensitivity of ^{18}F-DOPA scanning to small changes in DA function. When ^{18}F-DOPA was injected alone, the noninjected side of the hemi-parkinsonian animals was not distinguishable from normal (*21*).

A delay in the amino acid infusion presents several advantages over the early infusion technique. The amount of amino acid to be administered is reduced. There is no significant reduction in brain ^{18}F activity. Patlak graphical analysis or compartment model analysis can be applied to the early time points of the PET kinetic data. The higher visual contrast generated by the decreased ^{18}F-30M-DOPA

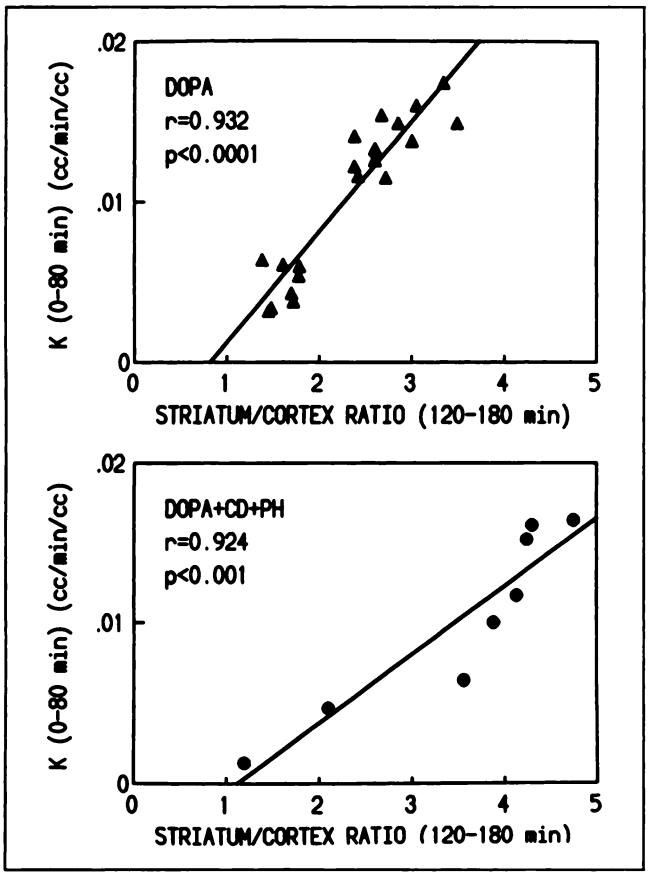

FIGURE 7. Scatter plots of the averaged striatum-to-cortex ratio between 120 and 180 min and the influx constant K obtained between 0 and 80 min in the DOPA and DOPA + CD + PH conditions. The fitted line was determined by least squares analysis of the data. The mean left-to-right value for K and the striatum-to-cortex ratio was used for the normal and bilaterally lesioned MPTP-treated animals. For the hemi-parkinsonian animals, both left and right ratios and K values are represented. The correlations remain even when the left and right values of the hemi-lesioned animals are pooled.

during the late time points, permits to position the ROIs with greater reliability, especially on anatomical structures with low ^{18}F-DOPA uptake, such as frontal cortical areas.

Effects of CD and PH on Brain and Plasma

Figures 2 and 4 show that CD effects on brain ^{18}F accumulation and plasma ^{18}F-DOPA were modest. There were no significant increases in total brain radioactivity. The nonsignificant increase in plasma ^{18}F-DOPA is consistent with an earlier report by Melega et al. (*22*), but somewhat smaller than what we reported in a previous paper (*17*) in a larger group of animals. It is likely that the lack of significant CD effect on ^{18}F-DOPA metabolism in nonhuman primate studies such as ours and Melega et al. (*22*), compared to the massive effects reported in human (*22*) results from absorption and/or metabolism difference between human and nonhuman primates. We did not measure the concentration of CD in the plasma and so cannot be sure of the amount that was actually absorbed in the blood. However, the changes in peripheral metabolism are consistent with expected CD effects.

CD pretreatment did not significantly alter the rate constant for net uptake of ^{18}F-DOPA from blood to striatum. This suggests that: (1) the transport rate constant for ^{18}F-DOPA at the level of the BBB may not be affected at the doses of CD used and (2) that the increase in striatal ^{18}F activity was due to an increase in plasma ^{18}F-DOPA bioavailability.

Neither CD pretreatment or amino acid infusion appear to modify ^{18}F peripheral storage in the muscles or significantly modify organ dosimetry (unpublished data). As previously shown in earlier studies, the administration of large amount of neutral amino acid has no effect on plasma metabolite levels (*17,23,24*).

Practical Considerations for Clinical Use

The infusion of any combination of neutral amino acids available for human use would probably be as safe and effective as an infusion of PH alone. In this study, we used a PH infusion for simplicity of the preparation and to investigate the possible side-effects of administering a large dose of an amino acid to a subject. None of the 28 animals (normal, lesioned or under various drug treatment, 3–13 yr old) that received up to 300 mg/kg of PH, have exhibited any indications that these doses of amino acid produced any side-effects or toxicity. Furthermore, no adverse effects at these doses are known, except in phenylketonuric patients. Bremer and Neuman (*25*) and Potkin et al. (*23*) administered, without complications, doses of 50 to 100 mg/kg (oral or i.v.) to normal controls, schizophrenics, phenylketonuric heterozygotes and phenylketonuric patients.

One can also note that the amino acid infusion method provides consistent data and does not appear to produce a significant increase in the variability of the PET data compared to ^{18}F-DOPA alone, as shown by the standard deviation of the striatum-to-cortex ratio of the normal control group in the two conditions (Table 1). Similar observations were made when the amino acid infusion began 15 min after tracer injection. This suggests that the blockade of ^{18}F-30M-DOPA entrance at the BBB was equally effective across all the animals studied.

Practically, it is always of interest to reduce the time that a patient has to be in the scanner. In most institutions, for a ^{18}F-DOPA scan, subjects are required to remain in the scanner for about 2 hr. Our animals are scanned for at least 3 hr and the ratios of specific-to-nonspecific ^{18}F accumulation are obtained between 120 and 180 min. However, for clinical purposes, the scan length can be shortened to 2 hr. Because the clearance half-life of ^{18}F-30M-DOPA is short ($T_{1/2}$ ~15 min), it is probably possible to begin the amino acid infusion 45–60 min after the ^{18}F-DOPA injection and still obtain good anatomical data between 90 and 120 min. However, it may still be difficult for some patients to spend 2 hr in the scanner. Thus, we

became interested in the possibility of comparing kinetic data (i.e., the influx constant K) and the purely anatomical data (the ratio, DA-rich-to-DA-poor areas) in order to shorten the scan time to solely the time necessary to obtain good anatomical images.

As shown in Figure 6, a strong correlation exists between the data obtained by kinetic and anatomical analysis, in both conditions, when ^{18}F-DOPA is injected alone or with CD + PH infusion. The correlation shown here combines data from both normal and MPTP-lesioned animals. This correlation, or a trend to it, also exists within the normal control group alone as well (DOPA: $r = 0.83$ $p = 0.01$ $n = 8$; DOPA + CD + PH: $r = 0.84$ $p = 0.07$ $n = 5$). Such correlation is probably made possible by the lack of extreme changes in plasma ^{18}F-DOPA metabolism seen in our animals and the relatively small variability in our brain data. Obviously, these correlations need to be verified and duplicated in human subjects. Nevertheless, they provide a heuristic basis for the investigation of alternative techniques for the acquisition of relevant data in patients that are incapable of withstanding a long scanning period and/or in patients in whom metabolite analysis cannot be obtained. For example, scanning between 90 and 120 min to obtain anatomically appropriate PET images and the striatum-to-cortex ratio may still yield clinically significant data, while providing the patient with a reduced scanning time.

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