Postinjection L-Phenylalanine Increases Basal Ganglia Contrast in PET Scans of 6-^{18}F-DOPA

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The sensitivity of ^{18}F-DOPA positron emission tomography for imaging presynaptic dopamine systems is limited by the amount of specific-to-nonspecific accumulation of radioactivity in brain. In rhesus monkeys, we have been able to increase this ratio by taking advantage of the lag time between ^{18}F-DOPA injection and the formation of its main metabolite, the amino acid ^{18}F-fluoromethoxydopa, the entrance of which into brain is responsible for most of the brain's nonspecific radioactivity. By infusing an unlabeled amino acid, L-phenylalanine, starting 15 min after ^{18}F-DOPA administration, we preferentially blocked the accumulation of ^{18}F-fluoromethoxydopa by preventing its entrance into brain through competition at the large neutral amino acid transport system of the blood-brain barrier. This method appears as reliable as the original and more sensitive, as demonstrated by the comparison of normal and MPTP-treated animals under both conditions.

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Positron emission tomography (PET) with 6-^{18}F-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) is used to investigate the pre-synaptic dopaminergic (DA) uptake system. Although an exact quantitative model relating brain and plasma ^{18}F-DOPA data to precise physiologic parameters is still unavailable (*1,2*), ratios of ^{18}F accumulation in the basal ganglia to ^{18}F accumulation in DA-poor areas (posterior cortices or cerebellum) have been shown to bear a coarse relationship to striatal DA levels (*3–6*). Thus, these ratios have provided useful information on the state of the DA system.

Ratios, however, can only be accurately determined when a precise identification of the striatum can be made. This can be difficult in subjects with substantial DA depletion, in part, because of the considerable ^{18}F background in the brain. The most important component of this background is 6-^{18}F-L-3-methoxy-4-hydroxyphenylalanine (^{18}F-3-OM-DOPA), one of the major metabolites of ^{18}F-DOPA. This amino acid, primarily produced in the liver, can readily cross the blood-brain barrier (BBB), probably using the same large neutral amino acid (LNAA) transport system as L-DOPA. 3-OM-DOPA appears to have a uniform distribution throughout the brain in rodents (*7*) and in primates (*8*). Administration of ^{14}C- or ^{3}H-labeled L-DOPA or ^{18}F-DOPA to rats or primates leads to significant concentrations of 3-OM-DOPA in plasma and a substantial background of 3-OM-DOPA in brain (*9–11*). The other metabolites of L-DOPA produced in the periphery and found in plasma, mainly dopamine (DA), homovanillic acid, 3,4-dihydroxyphenylacetic acid, and their sulfated conjugates, are not likely to cross the BBB to any significant degree.

Some groups (*3,12*) have tried to increase the amount of ^{18}F-DOPA available for entrance in the brain and, thereby, striatal uptake, by pre-treating with carbidopa (α-methyldopahydrazine) (CD), a potent inhibitor of the peripheral DOPA decarboxylase (*13*). As expected, carbidopa pre-treatment induced higher levels of ^{18}F striatal activity (*12*). However, carbidopa treatment also led to an increase in ^{18}F-OM-DOPA in the plasma and brain background (*12*). Thus, the contrast in the PET images between specific and nonspecific structures and the precise localization and quantification of striatal structures did not improve. Indeed, the striatum/cortex ratios reported by different groups with and without carbidopa pre-treatment are very similar (*3,4*).

An elegant solution to the background problem in man would be to block the formation of ^{18}F-3-OM-DOPA by the liver with a peripheral catechol-O-methyl transferase (COMT) inhibitor. Studies in rats and non-human primates (*14–16*) have shown increased levodopa availability for entrance into the striatum and other structures after such blockade. Unfortunately, most specific COMT inhibitors lack selectivity and/or are toxic for human use (*17*). Recently, preliminary ^{18}F-DOPA studies have been reported in both human and non-human primates successfully using new COMT inhibitors (*18,19*). However, little data exist yet on the toxicity of the compounds. Moreover, safe and effective doses to use for ^{18}F-DOPA scans have

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yet to be established. For this determination, investigators will have to consider the effects of altering the metabolism of ^{18}F-DOPA on organ-specific radiation exposure.

Based on the following three observations, we have investigated a different solution for reducing ^{18}F-3-OM-DOPA levels in brain.

1. Metabolite analyses have shown that ^{18}F-3-OM-DOPA levels become higher in plasma than ^{18}F-DOPA levels around 20 min after ^{18}F-DOPA injection (*3,10*).
2. 3-OM-DOPA is an amino acid thought to enter the brain through the LNAA transport system.
3. Competition between amino acids exists for this transport system (*20*).

Thus, we reasoned that we could block the entrance of ^{18}F-3-OM-DOPA into the brain by saturating the LNAA transport system with an unlabeled amino acid after most of the ^{18}F-DOPA had been allowed to enter the brain. For that purpose, we administered, to a group of rhesus monkeys, the amino acid L-phenylalanine 15 min after ^{18}F-DOPA injection. By delaying the administration of L-phenylalanine from time of radioisotope injection, we hoped that sufficient ^{18}F striatal activity could be achieved while still reducing the background coming from ^{18}F-3-OM-DOPA entrance into brain. To increase the initial ^{18}F-DOPA accumulation in the striatum, we also tried pretreating a third group of animals with carbidopa, which we hoped would allow more ^{18}F-DOPA to enter the brain in the first 15 min.

MATERIALS AND METHODS

Eighteen, age-, sex-, and size-matched normal rhesus monkeys were used in this study. They were divided into three groups: nine normal controls, four neurologically asymptomatic, bilaterally MPTP-treated (total cumulative dose: 2–4.8 mg/kg i.v.) and five unilaterally MPTP-treated (total cumulative dose: 0.3–1.5 mg/kg into the internal carotid artery) monkeys. Data obtained from the normal and asymptomatic bilaterally MPTP-treated monkeys after injection of ^{18}F-DOPA alone have been previously reported (*21*). All animals initially received a PET scan after injection of ^{18}F-DOPA alone. One of the controls and two new normal animals had a PET scan after injection of ^{18}F-DOPA followed by continuous infusion of the unlabeled amino acid L-phenylalanine. Three of each of the normal controls and bilaterally and unilaterally MPTP-treated monkeys received a subsequent PET scan using ^{18}F-DOPA in combination with carbidopa and L-phenylalanine.

Chemicals

The carbidopa powder was a gift of Merck, Sharp and Dohme (Rahway, NJ). It was suspended in sterile distilled water (5 mg/cc) and 5 mg/kg were administered to the anesthetized monkey through a gastric feeding tube, 60–90 min before the injection of ^{18}F-DOPA. L-phenylalanine (Sigma Chemical Co, St. Louis, MO) was dissolved in phosphate-buffered saline (pH 7.4) and sterilized through a 0.22-μm millipore filter. The unlabeled amino acid was infused continuously through the intravenous line, beginning 12–15 min after ^{18}F-DOPA administration and continuing for the duration of the PET study. The rate of L-phenylalanine administration was 50 mg/kg during the initial 15–20 min, then 100 mg/kg/hr until the end of the scanning period.

Scanning Procedures

Fluorine-18 DOPA synthesis, scanning procedures and, data analysis are described in detail elsewhere (*21*). Briefly, the animal was immobilized with ketamine (10 mg/kg i.m.) and anesthetized with sodium pentobarbital (10–15 mg/kg i.v.). An endotracheal tube and intravenous and arterial indwelling catheters were inserted. Additional low doses of sodium pentobarbital were given as needed throughout the course of the procedure. The animal was positioned in the scanner (Scanditronix PC 1024-7B with an inplane resolution of 6–6.5 mm FWHM and a slice thickness of 10–11 mm) in the horizontal stereotaxic plane.

A blood flow study using ^{15}O-labeled water (10–20 mCi) was performed before all ^{18}F-DOPA injections. Rapid online reconstruction of the blood flow data insured accurate positioning of the monkey in the scanner. Cerebral blood flow was determined using Alpert et al.'s method (*22*). The striatal and cortical regions of interest (ROIs) used for the determination of blood flow and ^{18}F-DOPA accumulation were identical. Blood flow data were normalized to whole brain average and compared using Student's t-test.

The ^{18}F-DOPA (1–4.9 mCi) diluted in 3–5 cc of saline was injected into the animal and scanning was performed for 200 min. Metabolite analysis performed from arterial blood samples collected throughout the course of the study will be described in detail elsewhere.

Method of Analysis

Fluorine-18 accumulation data (in nCi/cc) were divided by the amount of millicurie injected. Time-activity curves of striatum (DA-rich structure), occipito-parietal cortex (DA-poor area), surrounding muscles (temporalis muscles), and the striatum/cortex ratio were obtained from the kinetic set. Values obtained from left and right ROIs were averaged except for the hemilesioned animals. All curves were interpolated at pre-defined times to permit the calculation of averaged curves for each of the three conditions. Repeated measure analysis of variance (ANOVAR) was used to compare: (1) the kinetics of ^{18}F accumulation in the striatum, cortex, and muscles, and (2) the kinetics of striatum/cortex ratios between (3) treatment groups (i.e., in the ^{18}F-DOPA and L-phenylalanine infusion with and without carbidopa pretreatment conditions to the ^{18}F-DOPA alone condition) and between (4) animal groups (i.e., normal monkeys and monkeys with a DA lesion over time).

Striatum/cortex ratios between 90 and 200 min were calculated for both individual animals and each of the three groups and the three conditions. Striatum/cortex ratios between normal and lesioned animals and between the three experimental conditions were compared using independent t-tests.

RESULTS

Comparison of normalized blood flow values with and without carbidopa pre-treatment using independent t-test showed no significant differences between the two conditions in both striatal and cortical areas.

As depicted in the images in Figure 1, the contrast between DA-rich and DA-poor areas was increased in the

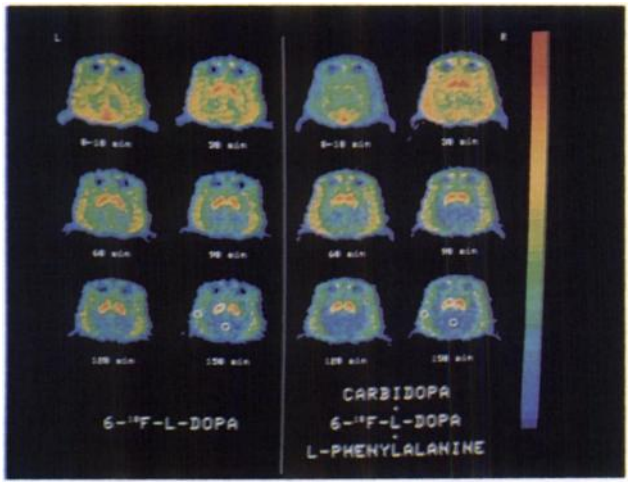

FIGURE 1. Portions of the ^{18}F-DOPA kinetic set after ^{18}F-DOPA injection alone (left) and in association with carbidopa and L-phenylalanine (right) in a normal monkey. The position of the ROIs used to obtain the TACs (striatum, occipito-parietal cortex, and temporal muscles) is displayed on the left side of the last picture in the two experimental conditions, but both left and right structures were analyzed at each time point. For comparison of the two sets, the images have been corrected for the number of millicuries injected.

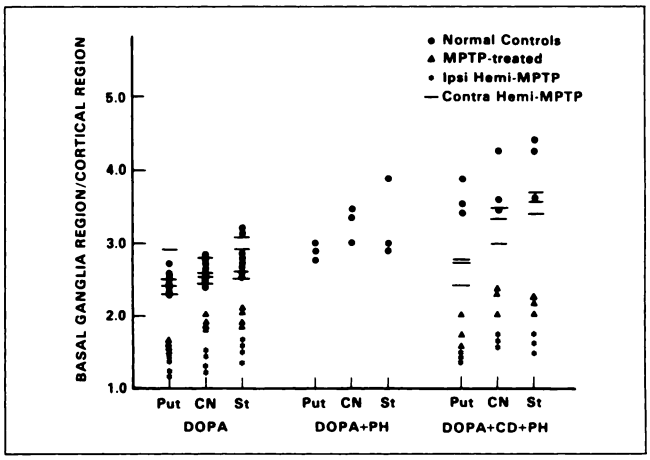

FIGURE 2. The putamen/cortex (Put) ratios and caudate nucleus/cortex (CN) ratios at 120 min after tracer injection and averaged striatum/cortex ratio (St) between 90 and 200 min after ^{18}F-DOPA injection in the three conditions: ^{18}F-DOPA alone (DOPA), ^{18}F-DOPA followed by L-phenylalanine infusion (DOPA+PH), and ^{18}F-DOPA followed by L-phenylalanine infusion with pre-treatment by carbidopa (DOPA + CD + PH). Left and right striatum/cortex, putamen/cortex, and caudate nucleus/cortex ratios have been averaged in normal and bilaterally MPTP-treated animals, but ratios from both the MPTP-injected sides (Ipsi Hemi-MPTP) and noninjected sides (Contra Hemi-MPTP) are represented for the unilaterally lesioned animals.

animals who received carbidopa pre-treatment (−60 min) with unlabeled L-phenylalanine infusion 15 min (+15) following ^{18}F-DOPA injection. A smaller increase in contrast also was observed in the animals receiving L-phenylalanine infusion without carbidopa pre-treatment. This increased contrast is reflected in the significantly higher striatum/cortex ratios in the animals receiving both ^{18}F-DOPA with carbidopa and L-phenylalanine compared to the animals receiving ^{18}F-DOPA only (Figs. 2–4 and Table 1) using both ANOVAR to compare the ratio time-activity curves and independent t-test to compare the 90–200-min ratios. Comparison of the time-activity curves of the striatum/cortex ratios obtained in the ^{18}F-DOPA with L-phenylalanine infusion with or without carbidopa conditions with those obtained in the ^{18}F-DOPA alone using ANOVAR showed strong group × time and group effects (Fig. 4). Furthermore, the independent t-tests used to compare the striatum/cortex ratios values between 90 and 200 min showed that: (1) the striatum/cortex ratios of the bilaterally MPTP-treated animals and of the lesioned striatum of the hemi-MPTP-treated monkeys were significantly lower than those of the normal controls in both conditions; (2) however, although the noninjected side of the hemi-MPTP-treated animals appeared unaffected compared to normals when ^{18}F-DOPA was given alone, a significant difference existed in the striatum/cortex ratios between these two groups when ^{18}F-DOPA was injected with carbidopa and L-phenylalanine (Fig. 3 and Table 1). Table 1 clearly expresses the superior sensitivity of the ^{18}F-DOPA scanning with carbidopa and L-phenylalanine to subtle changes in striatal ^{18}F accumulation.

As shown by the time-activity curves in Figure 4, the ^{18}F activity in striatum, cerebral cortex, or muscle, although somewhat lower in the animals that received ^{18}F-DOPA and L-phenylalanine with or without carbidopa compared to the animals that received ^{18}F-DOPA alone, were not statistically significantly different. ANOVAR performed on striatal and cortical time-activity curves between the L-phenylalanine with or without carbidopa conditions and ^{18}F-DOPA alone revealed a strong group × time effect reflecting the different shapes of the curves (Fig. 4). However, individual ANOVAs at each time point

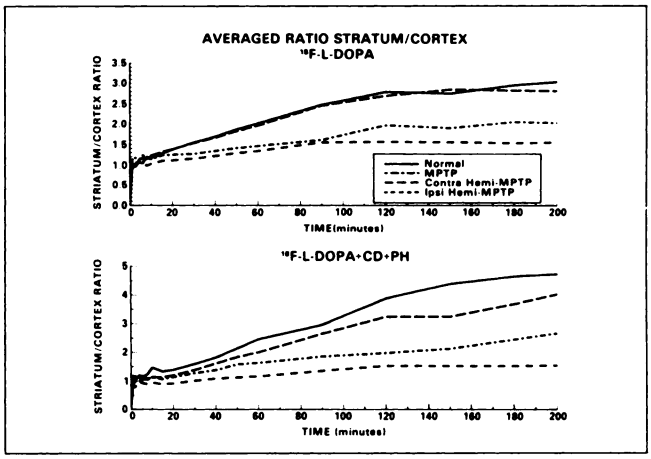

FIGURE 3. Averaged striatum/cortex ratio curves in normals, asymptomatic MPTP-treated, and ipsilateral and contralateral sides of the unilaterally MPTP-treated monkeys after ^{18}F-DOPA alone (top) and ^{18}F-DOPA with carbidopa and L-phenylalanine. Left and right striatum/cortex ratios have been averaged in normal and bilaterally MPTP-treated animals.

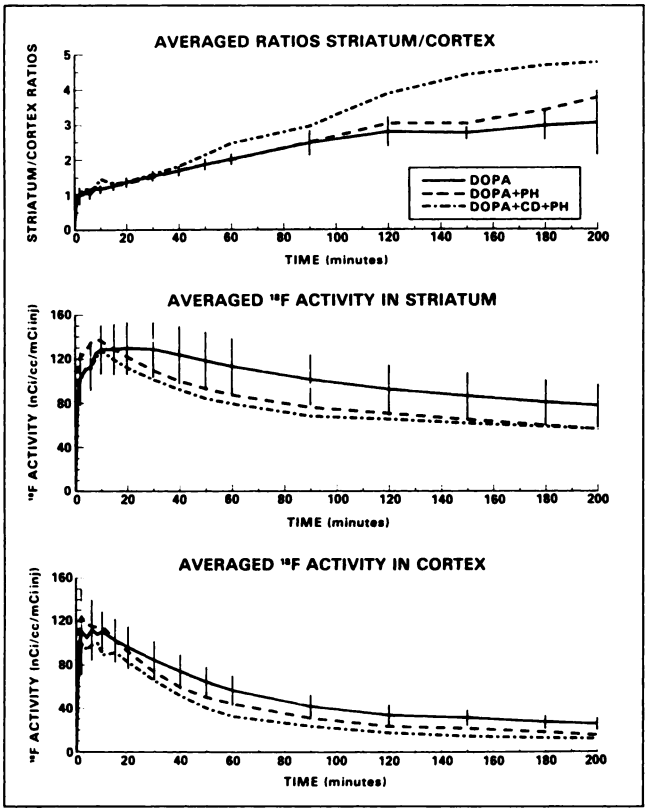

FIGURE 4. Averaged striatum/cortex ratio curves (top) and averaged ^{18}F time-activity curves in the striatum (middle) and the occipitoparietal cortex (bottom) obtained in normal control monkeys in the three experimental conditions, ^{18}F-DOPA alone (DOPA), ^{18}F-DOPA followed by L-phenylalanine infusion (DOPA + PH), and ^{18}F-DOPA followed by L-phenylalanine infusion with pre-treatment by carbidopa (DOPA + CD + PH). For image clarity, only the standard deviation of the ^{18}F-DOPA alone condition has been represented.

showed no significant difference except at time 60 and 90 min and a global no-group effect between the ^{18}F-DOPA alone condition and the L-phenylalanine conditions with or without carbidopa pre-treatment (Fig. 4). No group × time or group effects existed between the muscle time-activity curves when the L-phenylalanine conditions were compared to the ^{18}F-DOPA alone condition.

Because this technique was primarily developed for application to human subjects, the behavior of the animals that received the large doses of L-phenylalanine was closely observed after recovery from the anesthesia. No behavioral side effects were noticed in any of the animals, either normals or those with DA lesions.

DISCUSSION

This paper presents evidence for an improved method of evaluating the pre-synaptic DA system with ^{18}F-DOPA and PET. The blockade of ^{18}F-3-OM-DOPA entrance into the brain through the administration of high doses of an unlabeled amino acid not only visually improves the radiocontrast between specific and nonspecific DA areas, but also improves the activity ratios between these structures. Thus, this technique could serve either to obtain better images using the standard dose of the radioactive isotope ^{18}F-DOPA or to reduce radiation exposure by allowing the administration of a lower than standard dose while achieving equivalent quantification.

This increased striatum/cortex ratio does not appear to result from a change in blood flow distribution due to carbidopa pre-treatment, since there is no significant change in striatal and cortical blood flow with carbidopa pretreatment. The possible effects of L-phenylalanine on cerebral blood flow could not be investigated in our experimental setup, but they are unlikely to be responsible for the changes found, since L-phenylalanine is only infused after most of the ^{18}F-DOPA has already entered the brain.

The effects of carbidopa and L-phenylalanine are presently under investigation in our laboratory. Preliminary results suggest that carbidopa pre-treatment, apart from increasing ^{18}F-DOPA plasma availability to the brain in

TABLE 1
Averaged Striatum/Cortex Ratios (Between 90 and 180 Minutes) in the Three Groups of Monkeys in the Different Experimental Conditions

	Normal control	Bilateral MPTP-treated	Contra hemi-MPTP	Ipsi hemi-MPTP
DOPA	2.85 ± 0.23 (n = 7)	1.95 ± 0.18* (n = 4)	2.74 ± 0.28 (n = 5)	1.54 ± 0.12* (n = 5)
DOPA + PH	3.12 ± 0.35 (n = 3)	—	—	—
DOPA + CD + PH	4.22 ± 0.38‡ (n = 3)	2.21 ± 0.09*‡ (n = 3)	3.57 ± 0.12†‡ (n = 3)	1.69 ± 0.12* (n = 3)

Independent t-tests were used for all comparisons.

* A significant difference ($p < 0.001$) between the normal and lesioned monkeys in the DOPA alone or DOPA + PH + CD conditions.

† A significant difference ($p < 0.05$) between the non-treated side of the hemi-lesioned monkey with the normal controls in the condition DOPA + CD + PH.

‡ A significant difference ($p < 0.05$) between the DOPA + CD + PH condition and the DOPA alone condition.

n = the number of animals studied.

the early times after tracer injection, has little effect on the DA kinetics. L-phenylalanine, however, does have an effect on the entrance of ^{18}F-DOPA into the brain, blocking it almost completely and simultaneously with ^{18}F-3-OM-DOPA entrance. It may also affect the decarboxylation of ^{18}F-DOPA into ^{18}F-DA and the clearance rates of ^{18}F-DOPA and its metabolites from the brain. However, these effects are probably minimal, because L-phenylalanine is infused only after most of the ^{18}F-DOPA has already been taken up into the brain. Furthermore, our preliminary data suggest that L-phenylalanine could be infused later after tracer infusion (see below) and thus, these effects are reduced even more. Rather, its effect appears to result from an almost total blockade of ^{18}F-3-OM-DOPA entrance into the brain and a major decrease in brain nonspecific background. In conclusion, the major enhancing effects of carbidopa and L-phenylalanine are not likely to result from effects on the plasma ^{18}F-DOPA kinetics or from modification of cerebral blood flow.

The carbidopa (−60 min) plus L-phenylalanine (+15 min) technique also provides enhanced sensitivity for detecting subtle functional abnormalities of the DA system. For instance, as depicted in Figure 3, a greater difference exists between the striatum/cortex ratio between normal controls and MPTP-treated animals. This is also observed for the differences between the neurologically normal MPTP-treated animals and the lesioned side of the unilateral MPTP-treated animals. However, the most striking evidence is given in the unilaterally MPTP-injected animals. We expected that, at the dose used for the intracarotid injections, MPTP would have induced striatal ^{18}F accumulation in the noninjected side of the hemi-lesioned animals to decrease. Indeed, it appears unlikely that MPTP is trapped in the striatum or totally peripherally metabolized at its first pass in quantities significant enough to restrict its neurotoxic effects purely to the one injected side only. However, after injection of ^{18}F-DOPA alone, the striatum/cortex ratios of the non-lesioned side appear normal compared to the striatum/cortex ratios obtained in controls, suggesting that the side contralateral to the injection side is untouched by MPTP. Nevertheless, this ratio is significantly reduced (see Table 1 and Fig. 3) when scanning of the same animals is done with ^{18}F-DOPA combined with carbidopa and L-phenylalanine revealing a lowered ^{18}F striatal accumulation and, thus, demonstrating a dysfunction of the DA striatal system in the "noninjected side" of the hemi-MPTP-treated animals. This suggests that the technique described here is more sensitive to small changes in ^{18}F accumulation and may be useful in detecting subtle modifications in DA systems as well as facilitating the identification of small DA structures.

Such a method could easily and readily be applied to ^{18}F-DOPA scans in man. Indeed, no side effects or toxicity due to the L-phenylalanine injections have been observed in the 15 monkeys, normals as well as MPTP-treated, which, to date, received up to 300 mg/kg of L-phenylalanine during the ^{18}F-DOPA studies. Except in phenylketonuric patients, no serious adverse effects of acute L-phenylalanine or natural amino acids administration at these doses are known. However, it would be of interest to reduce the amount of L-phenylalanine to concentrations closer to the doses of 50 mg/kg administered without complications by Bremer and Neuman (*23*) to normal controls and phenylketonuric patients.

However, the small and statistically nonsignificant reduction in brain ^{18}F activity (Fig. 4) represents a disadvantage of this method and suggests that beginning L-phenylalanine infusion 15 min after ^{18}F injection may be too early. If scanning were done primarily to obtain ratios of ^{18}F-DOPA specific/nonspecific uptake (i.e., between 90–120 and 180 min postinjection, when contrast is highest), one could wait a longer period between radioactive isotope injection and L-phenylalanine infusion, since ^{18}F-3-OM-DOPA should wash out rapidly. An analysis of our own ^{18}F-3-OM-DOPA data along with the curves of plasma ^{18}F-DOPA provides a theoretical basis for optimizing striatal accumulation while keeping background low through the judicious choice of the time of L-phenylalanine infusion (work in progress.).

Delaying the injection of L-phenylalanine may have several advantages. Initially, scanning could be done throughout the usual extent of ^{18}F-DOPA studies, permitting a typical Patlak analysis on the early time points to yield the rate constant for uptake of ^{18}F-DOPA. At the same time, one could benefit from the increased visual contrast afforded by the reduced ^{18}F-3-OM-DOPA background, the latter effect allowing better positioning of the ROIs and ratios of the DA-rich/DA-poor areas, particularly during the late time points. Delay of L-phenylalanine infusion could also lead to a reduction in the amount of amino acid necessary for administering to subjects.

In conclusion, an easy and safe method of improving ^{18}F-DOPA PET scanning is described in this paper. In addition to improving striatum identification and striatum/cortex ratios, the improvement in contrast might allow for the identification of more discrete DA areas and, thus, possibly provide information on the presynaptic function of the mesocortical and mesolimbic systems in a variety of disorders in man.

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