
In Vivo Measurement of Brain Monoamine Oxidase B Occupancy by Rasagiline, Using ^{11}C -L-Deprenyl and PET

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In recent years, monoamine oxidase B (MAO-B) inhibitors have become widely used in the treatment of early-stage Parkinson's disease. ^{11}C -L-deprenyl PET has been used by others to characterize MAO-B ligands in terms of their in vivo potency toward MAO-B and duration of action. In this study, we used ^{11}C -L-deprenyl PET to demonstrate the specific binding characteristics of the new irreversible selective MAO-B inhibitor rasagiline in 3 healthy volunteers. **Methods:** The healthy volunteers received 1 mg of rasagiline daily for 10 d. Dynamic ^{11}C -L-deprenyl PET brain scans were acquired before the first treatment (scan 1) and immediately (scan 2), 2–3 wk (scan 3), and 4–6 wk (scan 4) after the final treatment. **Results:** On scan 1, all subjects showed the highest L-deprenyl uptake in the thalamus and basal ganglia, with fairly high activity also in the cortex and cerebellum and much lower activity in the white matter. The areas of high uptake were absent from scan 2, on which activity throughout the brain was comparable to that in white matter, presumably because of blocking of MAO-B binding sites by rasagiline. Gradual recovery toward the baseline state was observed in the weeks after termination of treatment (scans 3 and 4). **Conclusion:** ^{11}C -L-deprenyl PET showed binding of rasagiline to MAO-B, confirming blocking of MAO-B sites after 10 d of treatment with 1 mg of rasagiline per day, with immediate post-rasagiline treatment tracer uptake and metabolism in the basal ganglia compatible only with nonspecific binding. Subsequent gradual recovery was also seen, with return to near-baseline uptake. This finding is compatible with the known rate of de novo synthesis of MAO-B, confirming the irreversible binding of rasagiline.

Key Words: PET brain imaging; ^{11}C -L-deprenyl; MAO-B inhibitors; rasagiline

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Monoamine oxidase B (MAO-B) inhibitors are widely used in the treatment of Parkinson's disease (PD). L-deprenyl (selegiline) is an irreversible MAO-B inhibitor that has been given as a treatment for PD for many years and has been labeled with ^{11}C and used in PET studies to image the distribution of available MAO-B in the brain. In such a study, Fowler et al. (1) demonstrated that the resulting distribution of radioactivity in the brain corresponded to the known distribution of MAO-B, with concentrations highest in the thalamus and striatum (caudate and putamen) and concentrations in the brainstem and cortex also higher than in white matter. Autoradiographic evidence confirming this pattern of distribution of MAO-B in the brain includes studies using L-deprenyl labeled with ^{11}C and with ^3H (2,3), as well as studies using other MAO-B inhibitors (4,5).

The study of Fowler et al. (1) also indicated reduced tracer uptake after pretreatment with MAO-B inhibitors, confirming that ^{11}C -L-deprenyl uptake in these brain regions is due to the MAO-B inhibitory action of the tracer. ^{11}C -L-deprenyl PET can therefore be used to study, in vivo, the effects on MAO-B occupancy of L-deprenyl itself as well as other novel MAO-B inhibitors, including assessment of recovery of MAO-B after withdrawal of medication, and clarification of effective dosage.

In studies on animals, after administration of sufficient unlabeled L-deprenyl to totally block MAO-B site occupancy, analysis of serial ^{11}C -L-deprenyl scans showed a half-life of 6.5 d for recovery of MAO-B in the pig brain (6) and 30 d in the baboon brain (7). Similar studies (8) on humans (PD patients and healthy volunteers) indicated a half-life of 40 d. Because L-deprenyl is an irreversible MAO-B inhibitor, recovery after withdrawal of medication indicates de novo synthesis of MAO-B.

Subsequently, ^{11}C -L-deprenyl PET has been used to study the duration and effectiveness of MAO-B inhibition after different doses of the reversible MAO-B inhibitor Ro 19 6327 (lazabemide) (9–11). The minimum dose of Ro 19 6327 required to achieve maximum MAO-B inhibition was estimated, as was the time for MAO-B activity to return to

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normal after treatment with Ro 19 6327. Unlike L-deprenyl, in the case of a reversible MAO-B inhibitor, recovery time reflects duration of drug action more than de novo MAO-B synthesis.

Rasagiline is a new selective, irreversible MAO-B inhibitor with benefits that may include not only a symptomatic effect due to MAO-B inhibition but also a neuroprotective effect, potentially slowing progress of the disease (12,13). Rasagiline has demonstrated efficacy in clinical trials, both as stand-alone treatment for early PD (14–16) and as an adjunct to levodopa for treatment of more advanced PD (17,18). The impact of rasagiline on long-term progression of PD may differ from that of L-deprenyl, because the potential neurotoxic or neuroprotective effects are thought to be mediated in part by the different metabolites of each drug. Although selegiline metabolizes into amphetamines—compounds with neurotoxic potential—the major metabolite of rasagiline is aminoindan, with no known neurotoxic effects (12). In view of these indications from in vitro studies (12,13), animal studies (19), and the initial clinical trials that rasagiline may have advantages for treatment of PD, the investigation of the characteristics of rasagiline in vivo in humans is of great relevance.

In this study, we used ^{11}C -L-deprenyl PET to demonstrate the MAO-B inhibitory effect of a 10-d course of a therapeutic dose of rasagiline in healthy volunteers and to monitor recovery of brain MAO-B site availability after termination of drug treatment.

MATERIALS AND METHODS

^{11}C -L-Deprenyl Synthesis

^{11}C -L-deprenyl was prepared as described previously (20), although in a fully automated manner. Radiosyntheses were performed on a ^{11}C -CH₃I module (Nuclear Interface). Specific radioactivities were determined by high-performance liquid chromatography, using cold mass calibration curves. ^{11}C -Carbon dioxide was produced by the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ nuclear reaction on nitrogen containing 1% oxygen, using a Cyclone 18/9 cyclotron (Ion Beam Applications). Bombardment was performed for 60 min with a 26- μA beam of 16-MeV protons. At the end of bombardment, the target gas was delivered and trapped by a cryogenic trap in the ^{11}C -CH₃I module. The radiosynthesis had an average starting activity of 40.7 GBq, average synthesis time of 45 min, average radiochemical yield (end of bombardment) of 25%, and specific activity (end of bombardment) of 66.6 ± 7.4 GBq/ μmol .

Subjects

Three healthy male volunteers (ages: 30, 28, and 28 y; heights: 170, 181, and 172 cm; weights: 62, 80, and 77 kg) were screened by physical examination and biochemical and hematologic tests to rule out neurologic, psychiatric, and cardiovascular disease. The subjects were taking no regular medications and were nonsmokers, and MRI had been performed to rule out structural brain abnormality. They underwent a 10-d course of 1 mg of rasagiline per day, taken orally in the presence of one of the investigators to ensure compliance. The study was approved by the Hadassah University Hospital Ethics Committee, and all subjects gave informed written consent.

Scan Protocol

Dynamic ^{11}C -L-deprenyl PET brain scans were acquired before the first dose of rasagiline (scan 1) and immediately (scan 2), 2–3 wk (scan 3), and 4–6 wk (scan 4) after the last dose of rasagiline. Scans were acquired on an HZL/R PET scanner (Positron Corp.; axial field of view, 16.6 cm; in-plane resolution, 6.2 mm; axial resolution, 6.3 mm; slice thickness, 2.56 mm). The subjects fasted for at least 4 h before the start of each scan. For each scan, a 15-min transmission scan was acquired before intravenous bolus injection of approximately 370 MBq of ^{11}C -L-deprenyl. For scan 2, ^{11}C -L-deprenyl was injected 90–105 min after the last dose of rasagiline had been taken. All dynamic brain scans (24×5 s, 6×30 s, 5×1 min, 4×5 min, 2×10 min, and 2×20 min) were acquired from 0 to 90 min after injection. Because the first scans showed no changes in the distribution of activity in the brain after 75 min, acquisition times were reduced to 75 min in subsequent scans. Venous blood samples were obtained at 30 min after injection to measure residual activity in the blood.

Image Processing and Data Analysis

All images were reconstructed using filtered backprojection (Butterworth filter; order, 10; cutoff, 0.36 of Nyquist frequency). Regions of interest were drawn on the thalamus, basal ganglia, cortex, cerebellum, and white matter. For this purpose, summed images obtained 30–70 min after injection were used, except for scan 2, on which brain structures were not clearly delineated. For that scan, regions of interest were drawn on the summed images of the first 5 min after injection (showing tracer delivery), on which the brain structures were sufficiently clear. Time–activity curves were calculated for all regions of interest. MedX (Sensor Systems, Inc.) was used for drawing regions of interest and for the calculation of time–activity curves.

Modified Patlak analysis as described by Bergstrom et al. (21), using the cerebellum time–activity curve modified by a monoexponential as a reference tissue input function, was applied to the time–activity curves for all brain regions. Modification of the cerebellar time–activity curve by an exponential is intended to compensate for the MAO-B binding in this reference region. Like Bergstrom et al., we found that introduction of the exponential led to linearization of the Patlak graphs and that applying the same linearity criterion resulted in a similar value for the exponent, $\exp(-0.04t)$, where t represents time from injection, in minutes. The slopes of the resulting modified Patlak plots estimated relative tracer binding in the different brain regions. Patlak analysis was performed by a weighted linear least-squares fit using Interactive Data Language (Research Systems, Inc.).

RESULTS

Figure 1 presents images of 1 transaxial slice including thalamus and striatum for the 3 subjects 30–70 min after tracer injection. Scans 1–4 are shown for each subject. In all 3 subjects, the highest L-deprenyl uptake is seen on scan 1. The strongest labeling was in the thalamus and basal ganglia, with a high activity concentration also seen in the cortex and much lower activity in the white matter. The cerebellum, not included in these slices, had an activity concentration similar to that of the cortex. The high intensity in the thalamus and basal ganglia on scan 1 was almost absent from scan 2, on which activity in these structures was comparable to that in white matter, presumably because of

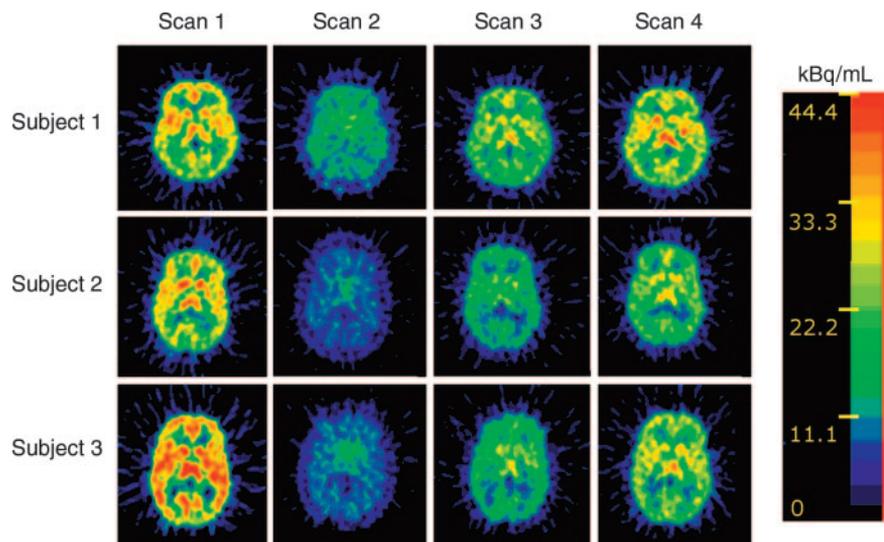


FIGURE 1. Summary of ^{11}C -L-deprenyl images: average activity distribution for all 3 subjects in 1 image slice on each of the 4 scans—before (scan 1), immediately after (scan 2), and 2–3 (scan 3) and 4–6 wk (scan 4) after treatment with rasagiline. Color on all images is adjusted to same absolute scale of intensities.

blocking of MAO-B tracer uptake sites by rasagiline. Gradual recovery toward the baseline state was observed on scans 3 and 4. These recovery scans were acquired 19, 15, and 15 d (scan 3) and 33, 40, and 35 d (scan 4) after the end of rasagiline treatment for the 3 subjects and indicated similar, but not identical, changes in activity distribution for all 3 subjects.

Data from these images, in the form of average activity concentrations over all 3 subjects, are presented graphically in Figure 2. On scan 1, average activity concentration was highest in the thalamus and basal ganglia (mean, 37.53 kBq/mL), with the cortex also showing raised activity (mean, 29.25 kBq/mL), and mean activity in the white matter was 11.58 kBq/mL. On scan 2, mean activity concentrations in the basal ganglia and thalamus were down to about 13.23 kBq/mL; thus, these structures were barely visible relative to white matter. Activity in the cortex and cerebellum was also reduced, whereas activity in the white matter changed little from that seen on scan 1. Scans 3 and 4 indicated gradual recovery of tracer uptake in the thalamus, basal ganglia, cortex, and cerebellum, returning to

baseline levels on scan 4 in the first subject and approaching these levels in the remaining 2 subjects.

^{11}C activity concentration in blood samples at 30 min after injection reflected the opposite pattern to that seen in the brain (Fig. 3). Thus, residual activity in the blood was highest on scan 2, corresponding to the lower tracer uptake in brain structures in this immediate post-treatment scan. This pattern was marked in subjects 2 and 3, though not in subject 1.

Figure 4 presents the brain region time-activity curves for all 4 scans for 1 subject, showing an initial sharp increase in the very first minutes after tracer injection, corresponding to fast delivery of the tracer to all brain regions. On scan 1, high levels of tracer remain in all regions except white matter. On the other hand, on scan 2, the initial high concentrations of tracer do not persist, presumably because of blocking of binding sites, and only low levels of tracer are observed in the brain on later images. The pattern on scans 3 and 4 is somewhere between the extreme situations seen on scans 1 and 2. The data presented in Figures 1 and 2 reflect the portion of these curves between 30 and 70 min after tracer injection.

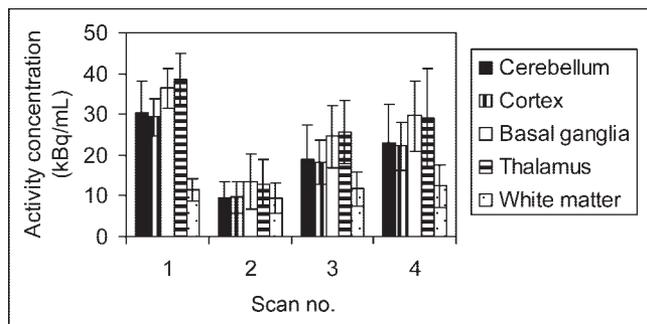


FIGURE 2. Comparison of ^{11}C -L-deprenyl activity concentrations (30–70 min after injection) in brain regions on scans 1–4 (average over 3 subjects). Cortex includes frontal, occipital, parietal, and temporal cortices. Error bars indicate ± 1 SD.

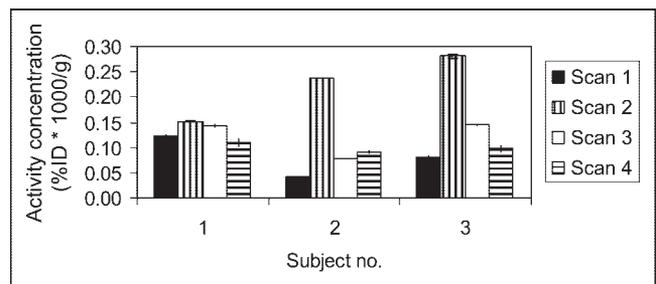


FIGURE 3. ^{11}C activity concentrations (expressed as percentage injected dose [%ID] \times 1,000/g) in whole-blood samples taken 30 min after injection during scans 1–4. Error bars indicate range of values.

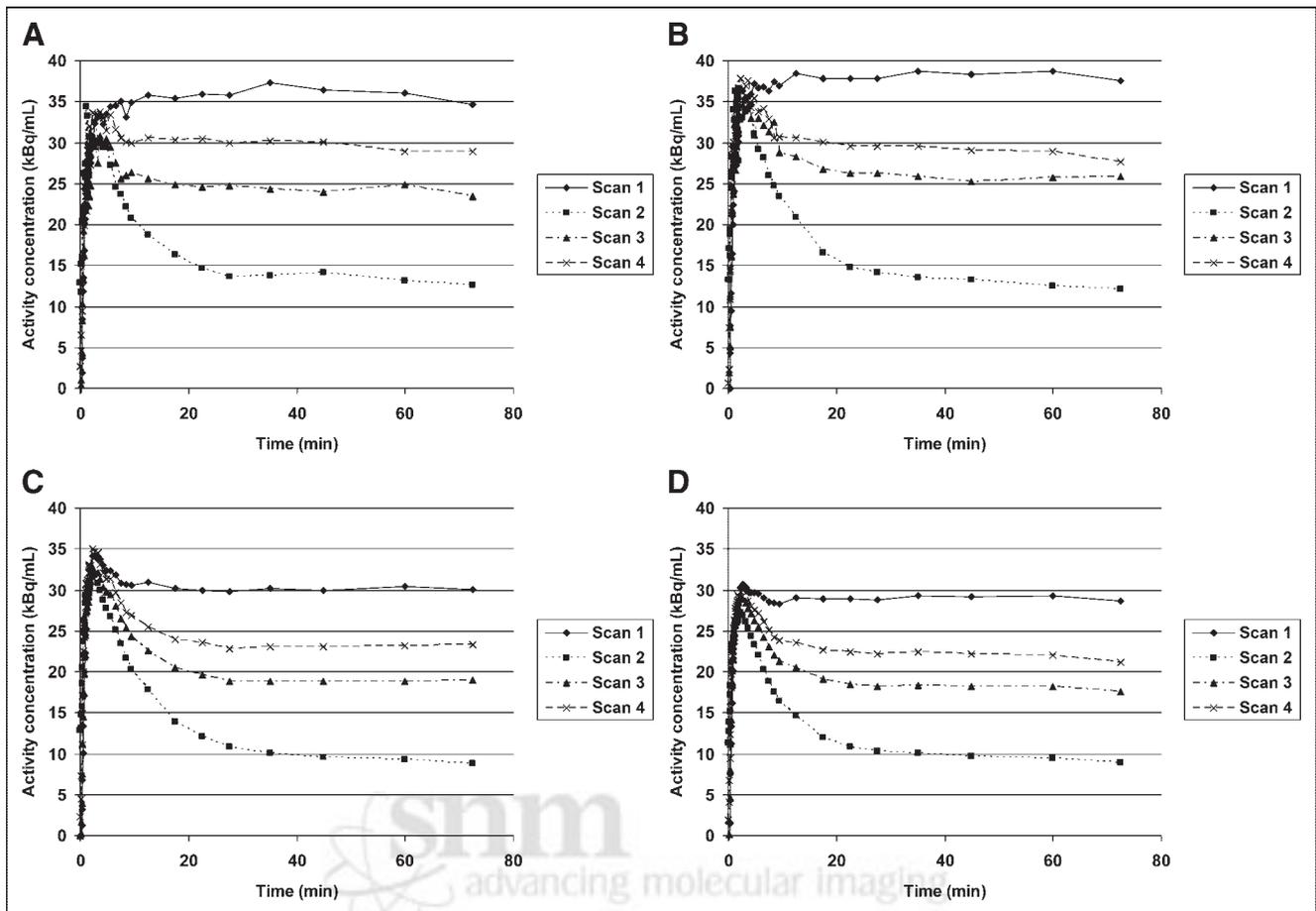


FIGURE 4. Average time-activity curves for basal ganglia (A), thalamus (B), cerebellum (C), and cortex (D) (including frontal, occipital, parietal, and temporal cortices) from 0 to 90 min after injection on scans 1-4.

Modified Patlak analysis (21) using the cerebellum as a reference region yielded slope values for each brain region. Unlike the activity concentration data obtained from the images, these slope values are a measure of MAO-B binding; however, because they use the reference tissue time-activity curve rather than an arterial input function, they give relative rather than absolute values of binding. Because their absolute values are not meaningful, ratios of the modified Patlak slopes for each brain region relative to those for white matter were calculated and are plotted in Figure 5. Although the distribution of the Patlak slope ratios does not differ much from that of the activity concentrations, it is notable that the SDs (indicated by the error bars) are much smaller, particularly for scans 2, 3, and 4, indicating less variation between the 3 subjects in the rate of return to MAO-B binding after rasagiline treatment.

DISCUSSION

As in other ^{11}C -L-deprenyl PET studies (1,6-11), high tracer uptake was observed on scan 1 in the basal ganglia and thalamus, the brain structures with the highest concentration of MAO-B, indicating high specific binding of the tracer to MAO-B in these regions. In the cortex and cere-

bellum at baseline, uptake was slightly less than in the basal ganglia and thalamus but still much higher than in white matter. On scan 2, uptake was low throughout the brain. The time-activity curves indicated that although tracer arrived in the brain during this scan as in the pretreatment scan, it was not bound there, presumably because of blocking of specific binding by rasagiline, and instead was quickly washed out. The observed higher residual activity in 30-min blood sam-

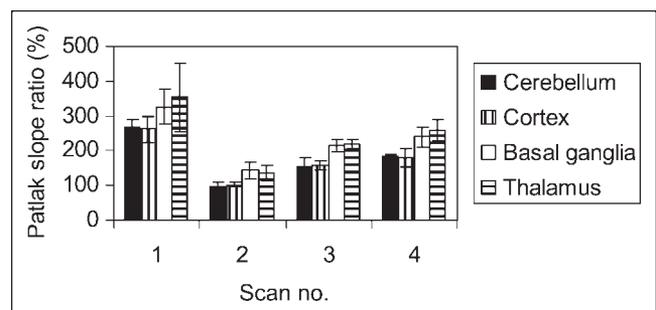


FIGURE 5. Comparison of modified Patlak slope ratios (relative to white matter) for brain regions on scans 1-4 (average over 3 subjects). Cortex includes frontal, occipital, parietal, and temporal cortices. Error bars indicate ± 1 SD.

ples taken during scan 2 was in concordance with this reduced brain uptake, reflecting activity due to ^{11}C -L-deprenyl and its labeled metabolites that was not taken up and therefore remained in the blood. The images in scans 3 and 4, as well as the corresponding semiquantitative measures, showed uptake intermediate to that on scans 1 and 2, indicating gradual return of tracer binding.

Our study was designed to monitor the MAO-B inhibitory effects of rasagiline in the brain *in vivo*. The clinical effects of rasagiline have now been studied in several clinical trials, with rasagiline given as a once-daily dose. Each study included a patient group taking 1 mg/d, the dose used in our study. Rasagiline has been shown to have a beneficial effect, compared with placebo, on symptoms of PD as measured by the Unified Parkinson's Disease Rating Scale in patients with early PD (14–16). The effect of rasagiline as adjunct therapy in levodopa-treated patients with more advanced PD, with or without motor fluctuations, has also been demonstrated in placebo-controlled trials, in which rasagiline improved both motor fluctuations and PD symptoms (17,18). In all these studies, rasagiline was given once daily, and its effect was observed throughout the 24 h, in keeping with the irreversible MAO-B inhibition. Rabey et al. (18) found that the clinical effect of rasagiline treatment was still apparent 6 wk after its termination, suggesting persistence of MAO-B–blocking effects during the relatively slow *de novo* synthesis of MAO-B, as well as a neuroprotective effect not directly related to MAO-B inhibition. Such a neuroprotective effect has also been suggested by the results of a delayed-start trial (14).

The pharmacokinetic and pharmacodynamic properties of clinical doses of rasagiline have also been investigated in humans and showed rasagiline to be an irreversible MAO-B inhibitor, giving rise to full saturation of MAO-B occupancy after 7 d, as measured by platelet MAO-B inhibition in healthy volunteers, and indicating that blocking would already be essentially complete after a 10-d course of treatment (22). This study also indicated that the time to reach the maximum plasma concentration of rasagiline after oral administration was about 0.5 h and that the corresponding time for its major metabolite, 1(R)-aminoindan, was 1.42 h. Thus, at the time of our scan 2, 90–105 min after the last rasagiline dose, plasma concentrations of rasagiline would be past their peak, whereas the concentration of 1(R)-aminoindan should be high, suggesting that absence of ^{11}C -L-deprenyl uptake in this scan is due to prior blocking rather than competition with rasagiline in plasma.

The findings of our study were similar to those of others using ^{11}C -L-deprenyl to demonstrate the action of MAO-B inhibitors in blocking tracer uptake in the brain and consequently increasing the activity remaining in blood (10). The time–activity curves (Fig. 4) indicate that initial uptake in the brain is rapid, occurring within minutes after injection, when almost all the activity is still in the form of ^{11}C -L-deprenyl (9,10), whereas later, after the first 15–20 min, labeled metabolites of L-deprenyl may predominate. The

time–activity curves of the baseline study also confirm that L-deprenyl is an irreversible MAO-B inhibitor, with activity in the brain remaining at a high level and not declining during imaging, because of the irreversible binding. This has been demonstrated previously by others (1,9,11). Lammertsma et al. (11), in their study with full kinetic analysis using metabolite-corrected arterial input functions, were able to further confirm the irreversibility of ^{11}C -L-deprenyl binding by showing the linearity of a Patlak fit, and to show, using a 2-tissue-compartment model, that inclusion of a parameter to allow for reversibility did not improve the quality of the fit.

Because we did not perform the frequent arterial blood sampling, activity concentration measurements, and metabolite corrections required to obtain an accurate arterial input function, we used the reference tissue method—as applied by Bergstrom et al. (21) to analysis of ^{11}C -L-deuterium-deprenyl PET data—for quantitation of tracer uptake. Bergstrom et al. demonstrated that the resulting modified Patlak slope values, although not representing absolute values of tracer uptake, accurately estimated relative levels of MAO-B binding within different brain tissues. These relative uptake values, expressed here as ratios of uptake in tissue relative to that in white matter, eliminate some of the confounding factors in simple measurements of activity concentration and thus provide greater confidence in the results of our study. Although these relative uptake rates have not been validated for interpatient comparison, the smaller error bars showed less variation between our 3 subjects in their response to rasagiline treatment (and subsequent recovery) when monitored by relative tracer uptake than by simpler activity concentrations.

In this study, images of activity distribution were obtained and relative quantitation was performed, but absolute tracer metabolic uptake was not calculated. Although the areas of high and low activity concentration in these ^{11}C -L-deprenyl scans do indeed correspond to brain regions of high and low L-deprenyl uptake, respectively, activity distribution is not equivalent to tracer uptake because the activity in the body includes tracer remaining in blood and vascular space at the time of the scan, as well as the metabolized tracer that reflects uptake. In addition, tracer uptake calculations take into account the amount of available tracer, a factor that may differ between subjects and even between studies of the same subject under different conditions (e.g., before and after treatment). Although the semiquantitative method avoids some of these concerns, it does not permit intersubject comparisons between slope values because of possible differences in reference region metabolism between subjects. Fowler et al. (8) found that although reduction of activity concentration in the brain after blocking of MAO-B with L-deprenyl was about 20%–30%, ^{11}C -L-deprenyl uptake was reduced to <5% of pretreatment levels. In our study, too, activity concentration in the basal ganglia was reduced after blocking by rasagiline, to about 30% of its baseline value; this presumably corre-

sponds to much less than 30% of baseline ^{11}C -L-deprenyl uptake in these regions. Using uptake ratios, we showed that uptake of ^{11}C -L-deprenyl in the cerebellum and cortex was reduced to that in white matter after rasagiline blocking, whereas in the basal ganglia and thalamus, uptake remained at levels of 43% and 36%, respectively, above that in white matter. Because uptake in white matter may also be affected by rasagiline blocking, we have no absolute measure of residual uptake after blocking. However, as in the work of Fowler et al. (8), it is likely that tracer uptake was not zero on the immediate post-treatment scan. Although it could be that the dose of rasagiline was not sufficient to cause 100% blocking, a more likely explanation that has been suggested for such findings (7) and is equally applicable to our study is that the residual uptake corresponded to very low levels of nonspecific binding of L-deprenyl or some of its labeled metabolites.

The gradual recovery of tracer uptake during the 6 wk after the end of treatment indicates a return of specific binding to MAO-B. Because rasagiline is an irreversible MAO-B inhibitor, this increased binding-site availability is attributable to new MAO-B biosynthesis. Fowler et al. (8) found the half-life for de novo synthesis of MAO-B in the human brain to be 40 d. Because our study did not calculate absolute ^{11}C -L-deprenyl uptake rates, we could not estimate the half-life for de novo MAO-B synthesis. The methods used by others (7,8) rely on absolute measures of MAO-B binding; with our small number of time points and the lack of absolute quantitation, recovery time could not be reliably estimated. However, the recovery of much, but by no means all, of the L-deprenyl binding by 4–6 wk after treatment would be compatible with a half-life of about 40 d, confirming that rasagiline is an irreversible MAO-B inhibitor and that recovery is due to de novo synthesis of the enzyme. Unlike the subjects in Fowler's study, who were elderly, the subjects in our study were young (28–30 y old). MAO-B concentration in the brain has been shown to increase with age (23); it is not known whether the rate of MAO-B synthesis also changes with age.

In our study, there was some diversity between the 3 subjects, with more complete recovery of L-deprenyl uptake in subject 1 by the time of the last scan than in subjects 2 and 3. This difference was not due to differences in scan timing, patient weight, or dose and was therefore assumed to result from slight variations in individual response. Differences in uptake of ^{11}C -L-deprenyl between 4 healthy subjects were also reported by Fowler et al. (1).

One limitation of ^{11}C -L-deprenyl PET for estimating MAO-B uptake in the brain is that under some conditions, tracer uptake in regions of high MAO-B concentration is comparable to the rate of transport. As a result, uptake may be flow limited, leading to underestimation of true uptake (24). To overcome this problem, several recent PET ^{11}C -L-deprenyl brain studies (23–26) have used a deuterium-substituted version of ^{11}C -L-deprenyl, which has slower uptake and therefore is not flow limited. Because in our

study the subjects were young and the objective was to study conditions of reduced uptake, the problem of underestimating tracer uptake was not as relevant as it would be when studying subjects with high MAO-B and lower blood flow, such as elderly patients with PD or other neurologic diseases.

Simple qualitative assessment of the images yielded a clear interpretation of ^{11}C -L-deprenyl metabolism in the brain in this study, further supported by semiquantitative analysis to give relative quantitation; however, the absence of calculation of absolute metabolic uptake rates of L-deprenyl is a limitation. Calculation of absolute tracer uptake involves application of a compartmental model, which requires an accurate arterial input function, presenting many technical difficulties. Introduction of an arterial line is an invasive procedure, with a risk, albeit small, of complications. In addition, finely spaced, accurately timed blood sampling is needed to follow the rapid changes in input function in the first minutes after injection, and achieving this accuracy requires automated equipment. A further difficulty occurs with L-deprenyl, because the accuracy of estimating activity in blood samples may be compromised by the tendency of L-deprenyl to stick to tubing (9). The semiquantitative modified Patlak analysis method that we used in the absence of an arterial input function has the disadvantage of providing only relative quantitation. Thus, we could not make direct quantitative comparisons between patients or between studies acquired before and after rasagiline treatment. An alternative approach that avoids many of the difficulties of arterial sampling and the complications of a reference tissue input function is to extract a true image-based input function from the dynamic image sequence. This approach, although frequently applied in whole-body imaging when the heart or a major blood vessel is in the field of view, is more difficult to apply in brain imaging. Liptrot et al. (27) have applied cluster analysis to extract input functions in dynamic brain imaging. Factor analysis has been applied to extract an input function from cardiac studies (28,29) and to extract a vascular component from dynamic brain images (30). Future application of these techniques to our data may enable us to extract an input function and thus to estimate the ^{11}C -L-deprenyl metabolic rate in the brain after treatment with rasagiline.

CONCLUSION

This work used ^{11}C -L-deprenyl PET to monitor the blocking of MAO-B by rasagiline and the subsequent gradual recovery. PET ^{11}C -L-deprenyl brain imaging using semiquantitative analysis demonstrated the specific binding characteristics of rasagiline to MAO-B, confirming blocking of MAO-B sites, with immediate post-rasagiline treatment tracer uptake and metabolism in the basal ganglia down to levels compatible with only non-specific binding. Recovery was gradual, compatible with the known rate of de novo synthesis of MAO-B, thus confirming the irrevers-

ible binding of rasagiline. Although not including a dose-ranging study, this work showed the potential of PET to supply information that could otherwise be achieved only in much more lengthy and costly clinical trials. Such studies could be used for the new MAO-B inhibitor drugs currently under clinical investigation.

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