Carbon-11-FLB 457: A Radioligand for Extrastriatal D2 Dopamine Receptors

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D2 dopamine receptors in extrastriatal brain regions are of central interest for research in schizophrenia and antipsychotic drugs. This article reports the development of [^{11}C]FLB 457 for PET examination of extrastriatal D2 dopamine receptors. **Methods:** Carbon-11-FLB 457 was prepared by O-methylation of FLB 604 (2-hydroxy precursor) with [^{11}C]methyl iodide. Total radiochemical yield was 25%–35% within a total synthesis time of 30 min. The specific radioactivity at the end of synthesis was about 1300 Ci/mmole (48 GBq/μmole). **Results:** FLB 457 bound with high affinity to D2 and D3 dopamine receptors, whereas binding to other putative central receptors was negligible. PET studies in Cynomolgus monkeys demonstrated 15 times higher accumulation of radioactivity in the striatum than in the cerebellum after 60 min. Uptake in the thalamus and neocortex, extrastriatal regions with a low density of D2 dopamine receptors, was, respectively, 4 and 2.5 times higher than in the cerebellum. Radioactivity was displaced by raclopride and haloperidol which confirms the selectivity and reversibility of [^{11}C]FLB 457 binding to D2 dopamine receptors in vivo in the striatum, thalamus and neocortex. **Conclusion:** Carbon-11-FLB 457 should be a useful PET ligand for quantitative examination of D2 dopamine receptors in extrastriatal regions in the human brain.

Key Words: brain; D2 dopamine receptors; extrastriatal; carbon-11-FLB 457; positron emission tomography

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Studies on brain biochemistry, morphology and physiology indicate that the function of extrastriatal brain regions may be disturbed in patients with schizophrenia. PET has hitherto been used for quantitative determination of D2 dopamine receptors in the major basal ganglia, which are large brain structures with a high dopamine receptor density. In extrastriatal regions, the potential for PET examination is limited by the low D2 dopamine receptor densities, which are 10–100 times lower than in the basal ganglia (*1*).

Several substituted benzamides and salicylamides have high affinity and selectivity for D2 dopamine receptors. These properties and a low level of nonspecific binding are reasons for their suitability as radioligands for PET (*2,3*). The salicylamide raclopride (Table 1) is used most extensively. Raclopride has been labeled routinely with ^{11}C (*4*) and applied for the quantitative examination of D2 dopamine receptors by PET (*5*).

Carbon-11-raclopride has been used to search for extrastriatal D2 dopamine receptors in the human brain in vivo (*6,7*). However, low signal-to-background ratios in the extrastriatal regions limit the use of [^{11}C]raclopride for this purpose. Two benzamides with very high affinity and selectivity are NCQ 219 (epidepride) and NCQ 298 (Table 1). Iodine-125-epidepride has been used to identify extrastriatal D2 dopamine receptors in the postmortem human brain (*8*). SPECT using [^{123}I]epidepride allowed visualization of extrastriatal D2 dopamine receptors in humans (*9*). With [^{125}I]NCQ 298, low densities of D2 dopamine receptors were demonstrated by autoradiography in the neocortex, hippocampus and entorhinal cortex (*10,11*).

A suitable PET radioligand for extrastriatal dopamine receptors should have very high affinity to provide high specific binding at low free radioligand concentration in brain. FLB 457 ((S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide) is a substituted benzamide which has very high affinity (K_i-18 pmole) for D2 dopamine receptors in vitro (*12–14*).

In this article, we report on the preparation of [^{11}C]FLB 457 by O-methylation of FLB 604 (2-hydroxy precursor) with [^{11}C]methyl iodide (Fig. 1). The receptor binding characteristics of FLB 457 in vitro to putative central neuroreceptors were studied using various rat brain receptors and cloned human D3 dopamine receptors. Preliminary PET examinations of [^{11}C]FLB 457 were performed in Cynomolgus monkeys. Unchanged [^{11}C]FLB 457 was measured in monkey plasma by gradient HPLC. This work has been presented in part as a symposium abstract elsewhere (*15*).

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TABLE 1
Inhibition of Tritium-Raclopride Binding to Rat Striatal D2 Dopamine Receptors In Vitro of Substituted Benzamides*

Name	X	Y	Z	R^1	R^2	Stereochem.	K_i (nM)
Raclopride	OH	Cl	Cl	CH_3	C_2H_5	S	1.30
Eticlopride	OH	C_2H_5	Cl	CH_3	C_2H_5	S	0.121
NCQ 258	OH	Cl	Cl	CH_3	CH_2CH_2F	S	6.95
NCQ 134	OH	C_2H_5	Cl	CH_3	CH_2CH_2F	S	0.667
NCQ 135	OH	C_2H_5	Cl	CH_3	$CH_2CH_2CH_2F$	S	0.155
FLB 457	H	Br	OCH_3	CH_3	C_2H_5	S	0.018
NCQ 616	H	Br	OCH_3	CH_2CH_2F	C_2H_5	S	0.123
NCQ 115	H	Br	OCH_3	CH_3	$CH_2C_6H_4F$	R	0.147
NCQ 298	OH	I	OCH_3	CH_3	C_2H_5	S	0.015
Epidepride (NCQ 219)	H	I	OCH_3	CH_3	C_2H_5	S	0.024

*From Ref. 14 and references therein.

MATERIAL AND METHODS

General Chemistry

Dimethyl sulfoxide (DMSO) was obtained from Merck (Darmstadt, Germany) and distilled and dried over molecular sieves (4Å) before use and (S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-3-methoxysalicylamide (FLB 604) and (S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide (FLB 457) were prepared as previously described (*12–14*). Other chemicals were obtained from commercial sources and were of analytical grade wherever possible. Carbon-11-methyl iodide was synthesized from [^{11}C]carbon dioxide utilizing a one-pot reaction set-up similar to that reported previously (*16*).

Semipreparative reversed-phase HPLC was performed using a Kontron 420 pump, an automatic sample injector (Type VICI with a 1-ml loop), a Waters μ-Bondapak-C18 column (300 × 7.8 mm, 10 μm, Milford, MA) and a Kontron 432 UV-detector (wavelength = 254 nm) in series with a GM tube for radiation detection. Carbon-11-FLB 457 was purified using acetonitrile and 0.01 *M* phosphoric acid (22/78) as the mobile phase with a flow rate of 6.0 ml/min. The radiochemical purity of [^{11}C]FLB 457 was analyzed by reversed-phase HPLC using a Kontron 420 pump, a Rheodyne injector (7125 with a 50-μl loop) equipped with a Waters μ-Bondapak-C18 column (300 × 3.9 mm, 10 μm) and an LDC-Milton Roy 300-UV spectrophotometer (254 nm) in series with a Beckman 170 radioactivity detector (Fullerton, CA). Acetonitrile and 0.01 *M* of phosphoric acid (25/75) were used as the mobile phase with a flow rate of 2.0 ml/min.

Preparation of Carbon-11-FLB 457

Carbon-11-methyl iodide was trapped at room temperature in a reaction vessel (1.0 ml mini-vial, Alltech, Deerfield, IL), containing FLB 604 (2-hydroxy precursor, 2.2 mg), DMSO (300 μl) and sodium hydroxide (5 *M*, 2 μl). The vessel was sealed and heated at 80°C for 3 min. Mobile phase (600 μl) was added before injection into the semipreparative HPLC column. Carbon-11-FLB 457 eluted after 11–13 min (Fig. 2) with a retention time identical to a standard reference sample. After evaporation of the mobile phase, the residue was dissolved in 8 ml of sterile phosphate buffer saline (pH = 7.4) and filtered through a Millipore filter (0.22 μm), yielding a solution which was sterile and free from pyrogens.

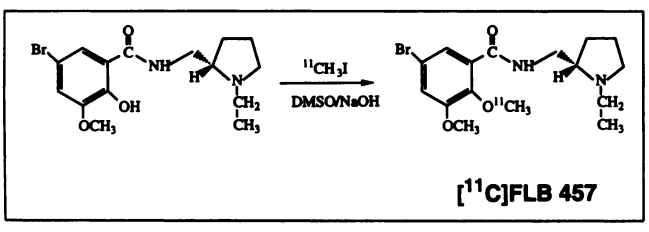

FIGURE 1. Incorporation of [^{11}C]methyl iodide to [^{11}C]FLB 457.

Biochemical Characterization

The affinities of FLB 457 to various receptors were determined in vitro using rat brain receptors and cloned human D3 dopamine receptors. Male Sprague-Dawley rats weighing 150–220 g were obtained from Alab Laboratorietjänst AB (Sollentuna, Sweden). The rats were decapitated and the striata, cortex and hippocampus were dissected on ice and the membranes were prepared essentially as described earlier (*17*). The CHO-cell line (Chinese hamster ovary) expressing human cloned D3 dopamine receptors was grown and the cell membranes prepared as described by Malmberg et al. (*18*).

The binding assays were performed as previously described (*19,20*). The incubations with radioligand and tissue homogenate were terminated and washed by rapid filtration through a Whatman GF/B glass fiber (Maidstone, U.K.) filter using a Brandell cell harvester (Beckman, Fullerton, CA). The bound radioactivity was determined in a Packard 2200CA liquid scintillation counter with about 50% efficiency (Meridien, CT). The K_i values (inhibition constants) of the test compounds were determined from inhibition curves using the iterative nonlinear curve-fitting program LIGAND (*21*).

PET Systems

Two PET systems were used. The first was Scanditronix PC2048-15B (Uppsala, Sweden) (*22*) which consists of an eight-ring system and measures radioactivity in 15 horizontal slices with a separation of 6.5 mm and a spatial resolution of about 4.5 mm FWHM. The second was the recently installed Siemens ECAT EXACT HR (Knoxville, TN) which measures radioactivity in 47 slices with a separation of 3.3 mm and a spatial resolution of about 3.8 mm FWHM (*23*).

PET Studies on Monkeys

Three male Cynomolgus monkeys weighing about 4 kg were supplied by the National Laboratory for Bacteriology. Anesthesia

was induced by repeated intramuscular injections of ketamine (Ketalar®, 5–10 mg $kg^{-1}hr^{-1}$). The first monkey was examined with the Scanditronix PC2048-15 PET camera and the two other monkeys with the Siemens ECAT EXACT HR. A head-fixation system was used to secure a fixed position of the monkey's head during the PET experiments (*24*). The positioning was parallel to the canto-meatal line. Body temperature was controlled by a heating pad with thermostat.

Two experiments were performed in the first monkey. In the first experiment, 37 MBq [^{11}C]FLB 457 was injected as a bolus during 2 sec into a sural vein. In the second experiment, which was performed 3 hr later, 5 mg of unlabeled raclopride was injected intravenously 23 min after the injection of [^{11}C]FLB 457. Two experiments were also performed with the second monkey: a control experiment similar to the one described above, and a second experiment performed 3 hr later in which 8 mg haloperidol were injected intravenously 23 min after the injection of [^{11}C]FLB 457. The third monkey received 40 MBq [^{11}C]FLB 457. Brain radioactivity was measured according to a preprogrammed sequence of frames during 60, 80 and 93 min, respectively.

Regions of interest (ROIs) were drawn on the summation images which were reconstructed from 9 to 60, 80 or 93 min, respectively, after injection of [^{11}C]FLB 457. The cerebellum, thalamus, neocortex, striatum and the whole brain contour were defined on each slice according to an atlas of a cryosectioned Cynomolgus monkey head. For each anatomical region, the ROIs were pooled for the two hemispheres. Radioactivity was calculated for the sequence of time frames, corrected for the radioactivity decay and plotted versus time.

The percent of injected [^{11}C]FLB 457 present in the brain at time of the maximal radioactivity level, i.e., 3–6 min after the injection of [^{11}C]FLB 457, was used as an index of drug uptake in the brain. This percentage was calculated by multiplying the brain volume with the radioactivity concentration in the ROI for the whole brain divided by the injected dose of radioactivity. Brain volume was obtained by multiplying the sum of the brain areas of all PET slices with the plane separation.

Plasma Metabolite Studies

The fraction of the radioactivity in monkey plasma that corresponds to unchanged [^{11}C]FLB 457 and that which is represented by metabolites was determined. The method was a modification of the HPLC method which was developed for several other PET ligands (*25–27*). Blood samples (2 ml) were obtained from the third monkey at 5, 16, 22, 37, 50, 69 and 86 min after injection of 40 MBq of [^{11}C]FLB 457. The supernatant (0.5 ml) obtained after centrifugation at 2000g for 1 min was mixed with acetonitrile (0.7 ml) containing a standard of FLB 457. The radioactivity in the supernatant (1.1 ml) obtained after centrifugation at 2000g for 1 min was measured in the well counter and 1 ml was subsequently injected into the HPLC column. The mixture was chromatographed through the column and the UV absorption and radioactivity peaks were integrated and the data were stored in a PC.

The reverse-phase HPLC Kontron system consists of 2 Kontron 420 pumps, a Rheodyne injector (7125 with a 1.0-ml loop) equipped with a Waters μ-Bondapak-C18 column (300 × 7.8 mm, 10 μm) and a Kontron 432 UV-spectrophotometer (254 nm) in series with a Packard Radiochromatography detector Series A-100 (1-ml cell). Phosphoric acid (0.01 *M*) (A) and acetonitrile (B) were used as the mobile phases with a flow rate of 6.0 ml/min. Gradient elution was employed in all metabolite analyses. The gradient profile was the following: HPLC time 0–5 min, (A/B) 80/20-60/40; 5–7.5 min, (A/B) 60/40–30/70; 7.5–8.5 min, (A/B) 30/70–80/20; 8.5–9.5 min (A/B) 80/20 isocratic; and 9.5 min until the end of the profile. The Kontron 450 Multitasking system was used as an efficient controller and PC integration system. Fractions that correlated with standards of FLB 457 and the corresponding radioactive peaks were also taken and counted in a well counter. The radioactivity in a certain fraction was divided by the total radioactivity and expressed as a percentage of the total.

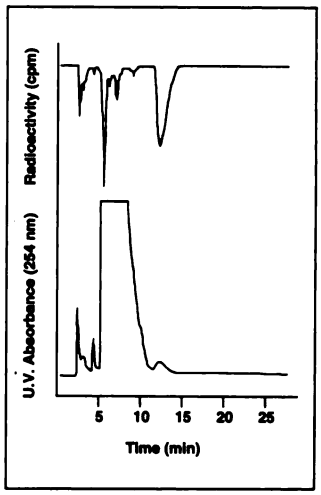

FIGURE 2. Semipreparative HPLC chromatogram (u.v. and radioactivity versus time) using a Waters μ-Bondapak C-18 column. .

RESULTS

Chemistry

The incorporation of [^{11}C]methyl iodide to [^{11}C]FLB 457 was 40%–50% (using 2.2 mg of FLB 604 (2-hydroxy precursor), Figs. 1 and 2). The total radiochemical yield of [^{11}C]FLB 457, calculated from the end of bombardment (EOB) and decay correction, was 25%–35% with a total synthesis time of 30 min. Purification was performed by semipreparative reversed-phase HPLC yielding [^{11}C]FLB 457 with a radiochemical purity better than 99%. The retention times of [^{11}C]FLB 457 and FLB 604 were 11.5–13.5 and 5–10, min, respectively (Fig. 2). The retention time of [^{11}C]FLB 457 on the analytical reversed-phase HPLC system was 5.6 min. The specific radioactivity obtained at the end of [^{11}C]FLB 457 synthesis was about 1300 Ci/mmole (48 GBq/μmole), and about 1000 Ci/mmole (37 GBq/μmole) at time of injection corresponding to an injected dose of about 0.50 μg in the monkey experiments.

Biochemical Characterization

The affinity of FLB 457 for D2 and D3 dopamine receptors was high (Table 2). FLB 457 inhibited binding to other putative central receptors at high concentrations only.

PET Studies on Monkeys

After intravenous injection of [^{11}C]FLB 457 in the first Cynomolgus monkey, there was a rapid accumulation of radioactivity in the brain. Four minutes after injection, 3.5% of the total radioactivity injected was present in the monkey brain (Fig. 3). The highest uptake of radioactivity was observed in the striatum, whereas radioactivity was lower in the cerebellum, a reference region with a low

TABLE 2
Affinities of FLB 457 for Various Brain Receptors as Studied in In Vitro Receptor Binding Assays Using Radioligand and Tissue Shown (K_i, nM)

Receptor	Radioligand	Tissue	Ki (nM)	s.e.m	n
D_2	[^{125}I]NCQ 298	Rat striatum	0.022	0.001	4
D_3	[^{125}I]NCQ 298	Cell membranes	0.017	0.001	2
D_1	[^{3}H]SCH 23390*	Rat striatum	>1000	—	2
α_1	[^{3}H]prazosin	Rat cortex	≈1000	—	2
α_2	[^{3}H]RX821002	Rat cortex	1200	—	1
β	[^{3}H]DHA	Rat cortex	>1000	—	2
M	[^{3}H]QNB	Rat cortex	>1000	—	2
5-HT_{1A}	[^{3}H]8-OH-DPAT	Rat hippocampus	180	29	3
5-HT_2	[^{3}H]ketanserin	Rat cortex	>1000	—	2

*Forty nanomoles of ketanserin were added to prevent binding to 5-HT_2 receptors.

density of D2 dopamine receptors (Fig. 4A). In the striatum there was a continuous accumulation of radioactivity. The striatum-to-cerebellum ratio was about 15 after 60 min. Uptake in extrastriatal brain regions such as the thalamus and the neocortex was 4 and 2.5 times higher than in the cerebellum (Fig. 4C).

In the displacement experiments, radioactivity in the striatum, thalamus and neocortex was markedly reduced after intravenous injection of 5 mg of unlabeled raclopride (Fig. 4B) or 8 mg of haloperidol (Fig. 4D).

The third monkey was examined for 93 min with the Siemens ECAT EXACT HR PET system with high resolution of 3.8 mm (FWHM) giving a striatum-to-cerebellum ratio of 25 at 93 min (Fig. 5).

Plasma Metabolite Studies

Blood samples were processed, and plasma was isolated and extracted. The recovery was higher than 95%. The peaks of UV and radioactivity were integrated simultaneously by the PC and the chemical identity was determined by a simultaneous addition of a standard of FLB 457. The integrated values agreed well with the collected fractions measured in the well-counter. Experiments showed that >98% of the injected radioactivity was recovered from the column.

The percentages of total radioactivity in plasma representing unchanged compound obtained after injection of 40 MBq [^{11}C]FLB 457 are shown in Figure 6. The fraction of the total radioactivity representing [^{11}C]FLB 457 in plasma was 80% at 5 min and 34% at 86 min after injection. A three-dimensional plot of HPLC chromatograms obtained from the seven time-points showing radioactivity versus time is shown in Figure 7.

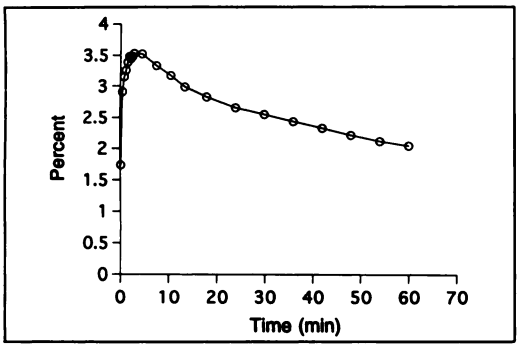

FIGURE 3. Brain radioactivity in percent of injected [^{11}C]FLB 457 in Cynomolgus monkey brain.

DISCUSSION

Chemistry

The selective dopamine D2 receptor antagonist raclopride has been previously labeled with ^{11}C by O-methylation of the corresponding desmethyl compound with [^{11}C]methyl iodide (*4*). Because the ^{11}C methylation is taking place at the 2-hydroxyl position of both compounds, the preparation of [^{11}C]FLB 457 was expected to be similar

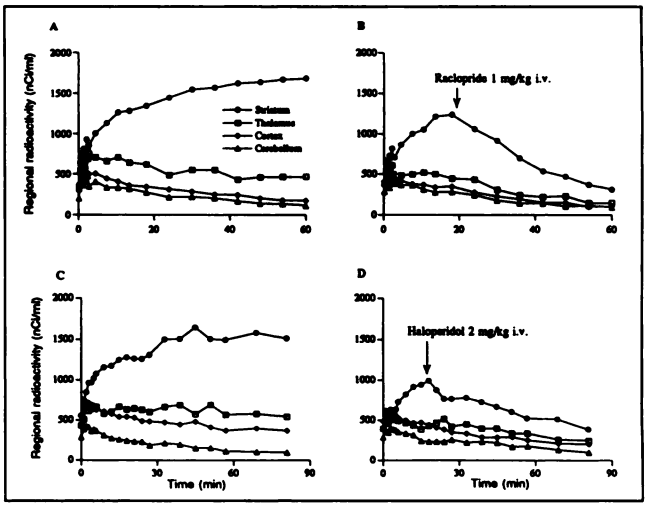

FIGURE 4. Time course for regional radioactivity (nCi/ml) in the brains of two Cynomolgus monkeys after intravenous administration of [^{11}C]FLB 457 (A and C). Displacement experiment with 5 mg raclopride at 23 min after intravenous injection of [^{11}C]FLB 457 (B). Displacement experiment with 8 mg haloperidol at 23 min after intravenous injection of [^{11}C]FLB 457 (D). Experiments A and B were performed with the PET-camera system Scanditronix PC2048-15B and C and D were performed with Siemens ECAT EXACT HR.

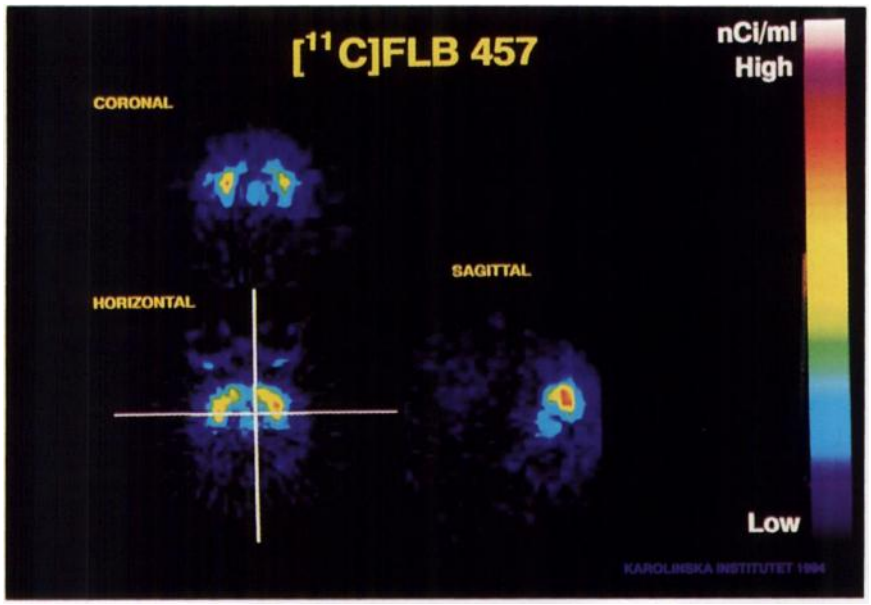

FIGURE 5. Color-coded PET image shows the distribution of radioactivity in the horizontal, coronal and sagittal sections through the Cynomolgus monkey brain after intravenous administration of 40 MBq of [^{11}C]FLB 457 (measured between 9–93 min). The PET system was a Siemens ECAT EXACT HR.

to that of [^{11}C]raclopride. Furthermore, the 2-hydroxy precursor (FLB 604) has been alkylated with 1-bromo-2-fluoroethane in DMSO to furnish NCQ 616 (Table 1) (*14*). Fluorine-18-NCQ 616 has also been labeled in a similar way starting from [^{18}F]1-bromo-2-fluroethane (*15*). In this article, [^{11}C]FLB 457 was labeled by O-methylation of FLB 604 with [^{11}C]methyl iodide in DMSO with sodium hydroxide as base (80°C for 3 min). Based on optimization results, we found that the amount of precursor and base could be reduced significantly compared to the amounts used in the preparation of [^{11}C]raclopride (*4*).

The procedure developed permitted the use of reversed-phase semipreparative HPLC which was found to be sufficient for the purification of [^{11}C]FLB 457 from precursor, reaction solvent and labeled byproducts. Carbon-11-FLB 457 eluted with the same retention time as a standard reference sample. After evaporation of the mobile phase, the residue was dissolved in sterile phosphate buffer saline (pH = 7.4) and filtered yielding a solution which was sterile and free from pyrogens. To avoid mass effects on ligand binding to receptors, the specific radioactivity of the radioligand has to be high. The specific radioactivity obtained at end of synthesis (about 1300 Ci/mmole (48 GBq/μmole) is sufficiently high for studying the dopamine D2 receptor system in the primate brain in vivo with PET.

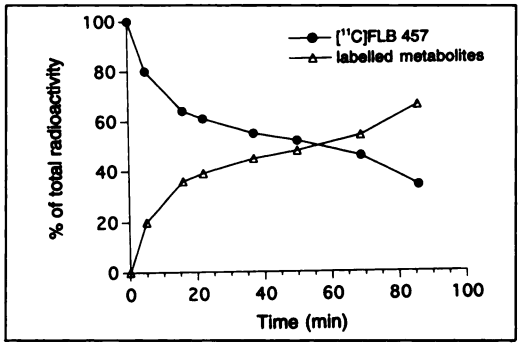

FIGURE 6. Determination of unchanged ligand and labeled metabolites in monkey plasma (% of total radioactivity versus time) of [^{11}C]FLB 457.

Biochemical Characterization

It was demonstrated that FLB 457 has high affinity and selectivity both for D2 and D3 dopamine receptors in vitro (Table 3). The D3 dopamine receptor has been found in low density (about 1 pmole/g) in the shell of the nucleus accumbens and the Islands of Calleja of the human brain, but not in significant density in any other brain region (*28,29*). It can thus be assumed that [^{11}C]FLB 457 binding in the striatum and in most extrastriatal regions represents selective binding to D2 dopamine receptors.

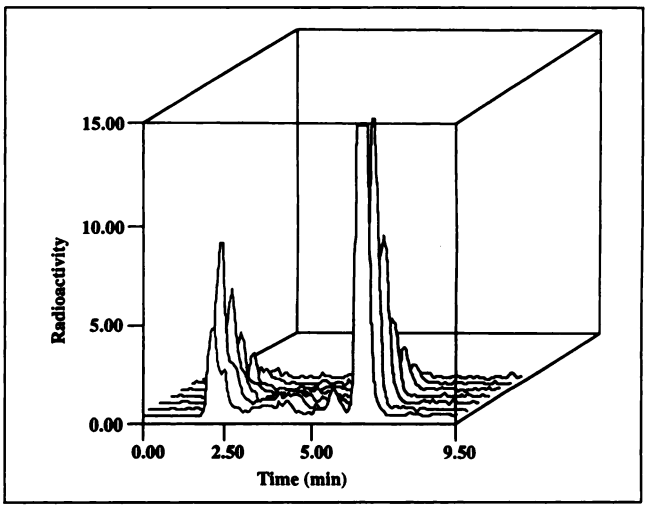

FIGURE 7. HPLC chromatograms of blood samples from a Cynomolgus monkey after intravenous injection of [^{11}C]FLB 457. From front to rear, the curves represent the consecutive samples, obtained after 5, 16, 22, 37, 50, 69 and 86 min after administration of the radioligand. The peak at 6.6 min represents [^{11}C]FLB 457.

PET Studies on Monkeys

Four minutes after injection of [^{11}C]FLB 457, 3.5% of the total radioactivity injected was present in the monkey brain (Fig. 3). This uptake is higher than the total uptake of 1%–2% previously demonstrated for useful PET ligands such as [^{11}C]SCH 23390 or [^{11}C]raclopride (*6,30*).

The regional distribution of radioactivity was in accordance with the known distribution of D2 dopamine receptors, with the highest density in the basal ganglia, lower density in extrastriatal regions such as the thalamus and neocortex and negligible density in the cerebellum (Figs. 4A, 4C and 5) (*9*). There was a continuous accumulation of radioactivity in the striatum. The striatum-to-cerebellum ratio was about 15 after 60 min (Fig. 4A). This ratio for [^{11}C]FLB 457 is the highest so far obtained in any PET study of the D2 dopamine receptor. The higher ratio obtained in the third monkey, 25 after 93 min, could be explained by the use of the higher resolution PET camera (Siemens ECAT EXACT HR) (*23*). The higher resolution gives a less partial volume effect and a higher recovery coefficient (*22*).

In contrast to previously developed radioligands such as [^{11}C]raclopride, [^{11}C]FLB 457 showed a considerable accumulation of radioactivity in extrastriatal brain regions such as the thalamus (Figs. 4A, 4C and 5). The ratio of thalamus- and neocortex-to-cerebellum was 4 and 2.5, respectively.

In the displacement experiments, radioactivities in the striatum, thalamus and neocortex were almost completely displaced after injection of raclopride or haloperidol (Figs. 4B and 4D), thus demonstrating that [^{11}C]FLB 457 binding to D2 dopamine receptors in vivo is selective and reversible.

Plasma Metabolite Studies

The integrated values obtained at the HPLC system, after injection of radioactivity, were in good agreement with the collected fractions measured in the well counter. The resolution between radioligand and labeled metabolites is sufficient (Fig. 7). Compared to the experimentally simple but time-consuming TLC procedure that allows only a few samples to be processed (*31*), the HPLC method is both rapid, efficient and reliable.

Carbon-11-FLB 457 was rather rapidly metabolized in the monkey (Fig. 6). A rapid metabolism is seen for many radioligands and does not preclude that [^{11}C]FLB 457 may be useful in PET studies. A problem occurs if the metabolites cross the blood-brain barrier and bind to dopamine receptors. It is known, however, that the regioisomer remoxipride (5-bromo-2,6-dimethoxybenzamide) is extensively metabolized in the pyrrolidine moiety in humans (*32*). Thus, it is likely that FLB 457 is metabolized in an analogous way in primates. This would lead to N-dealkylated and/or pyrrolidone and hydroxypyrrolidone derivatives devoid of affinity for dopamine receptors (*32*). In future human studies, the radiolabeled metabolites will be identified to support this assumption.

CONCLUSION

Carbon-11-FLB 457 bound with high affinity to central D2 and D3 dopamine receptors as demonstrated in vitro and by displacement experiments in the monkey brain in vivo. It accumulated not only in the striatum but also in several extrastriatal brain regions known to have D2 dopamine receptors. Carbon-11-FLB 457 should be a useful PET radioligand for reliable examination of extrastriatal D2 dopamine receptors in humans. This potential is particularly useful for research on schizophrenia and antipsychotic drugs.

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