No-Carrier-Added *N*-(3-[^{18}F]Fluoropropyl)spiroperidol: Biodistribution in Mice and Tomographic Studies in a Baboon

Chyng-Yann Shiue, Lan-Qin Bai,* Ren-Rui Teng†, Carroll D. Arnett, and Alfred P. Wolf

Department of Chemistry, Brookhaven National Laboratory, Upton, New York

Two potential radioligands, no-carrier-added (NCA) *N*-(2-[^{18}F]fluoroethyl)spiroperidol (**3**) and *N*-(3-[^{18}F]fluoropropyl)spiroperidol (**4**) have been synthesized for PET imaging of dopamine receptors in humans. Compounds **3** and **4** were synthesized by *N*-alkylation of spiroperidol with NCA 1-bromo-2-[^{18}F]-fluoroethane (**2b**), 1-[^{18}F]fluoro-3-iodopropane (**2c**) and 1-bromo-3-[^{18}F]fluoropropane (**2d**) respectively. The biodistribution of **4** in mice showed that the mouse brain uptake of radioactivity was similar to that of [^{18}F]-*N*-methylspiroperidol (1.1% of the administered dose), but the activity in bone (femur) increased with time. The kinetic distribution of compound **4** in baboon brain was similar to that of [^{18}F]-*N*-methylspiroperidol, and the striatal accumulation of radioactivity was also blocked stereoselectively by butaclamol. The ratio of striatum to cerebellum radioactivities at 3 hr after injection was 5.9. Analysis of the metabolic stability of **4** in mouse brains for 1 hr indicated that, like [^{18}F]-*N*-methylspiroperidol, it is relatively stable to metabolic transformation in the central nervous system. These results suggest that compound **4** may be a useful radioligand for PET studies of the dopamine receptor in humans.

J Nucl Med 28:1164–1170, 1987

There is great interest in the application of positron labeled radioligands to map the neuroreceptors in the living brain (*1*). For example, carbon-11- (^{11}C) labeled *N*-methylspiroperidol has been used in positron emission tomography (PET) studies of the dopamine receptor in human brain (*2*). We recently reported a general synthetic method for the preparation of no-carrier-added (NCA) fluorine-18- (^{18}F) labeled butyrophenones (*3,4*) using the nucleophilic aromatic substitution reaction (*5*). Using this method, NCA [^{18}F]haloperidol (*3,6*), [^{18}F]benperidol (*3*), [^{18}F]spiroperidol (*3,6*), [^{18}F] pipamperone (*3*) and [^{18}F]-*N*-methylspiroperidol ([^{18}F] NMS) (*4*) were synthesized. Based on studies in mice and baboons, we found that [^{18}F]NMS is an ideal radioligand for studying the dopamine receptor in humans (*7,8*). Subsequent human studies (*9*) have confirmed this conclusion.

Although we are able to prepare [^{18}F]NMS in large quantities (15–30 mCi) and high specific activity (~5–10 Ci/μmol at EOB), the synthesis of this tracer is multi-step, and the starting materials (cyclopropyl *p*-nitrophenyl ketone and 3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one) are not commercially available. For this reason, we have searched for radioligands which will have similar kinetic behavior but are perhaps more lipophilic than [^{18}F]NMS and can be prepared more quickly in higher yield. Recently, a series of *N*-alkylated and *p*-brominated analogs of spiroperidol (*10, 11*), 3-*N*-fluoroethyl, 3-*N*-chloroethyl- and 3-*N*-bromoethylspiroperidol, were synthesized, evaluated, and found to display high affinity for the dopamine receptor both in vitro (*12*) and in vivo (*13*).

Since nitrogen basicity probably contributes significantly to the biologic properties of the compounds, it is

Received July 2, 1986; revision accepted Feb. 4, 1987.

For reprints contact: C.-Y. Shiue, PhD, Dept. of Chemistry, Brookhaven National Laboratory, Upton, NY 11973.

* Permanent address: Visiting Scholar from Institute of Atomic Energy, Beijing, People's Republic of China.

† Permanent address: Visiting Scholar from Institute of Modern Physics, Academia Sinica, Lanzhou, People's Republic of China.

important to minimize the impact of the electronegativity of the fluorine atom by having it in a position as far away from nitrogen as possible. The substitution of a fluorine for a hydrogen in an ethyl derivative of normetazocine causes a significant reduction in basicity (pKa's of the nitrogen atom in *N*-(2-fluoroethyl)-normetazocine and *N*-ethylnormetazocine are 8.35 and 9.42, respectively) (*14*). Recently, theoretical studies predicted that the influence of a fluorine atom three carbons removed from nitrogen is small (*15,16*). In addition, the *N*-propyl group is known to increase the potency of a number of neurotransmitter amines (*17*). Thus, a ligand labeled with the *N*-3-[^{18}F]fluoropropyl group might be a suitable radioligand for studying receptor binding.

We recently reported the syntheses of a series of NCA [^{18}F]fluoroalkyl halides (**2a–d**) by nucleophilic aliphatic substitution of alkyl halides (**1a–d**) with NCA [^{18}F]fluoride in 30–40% yield (EOB) (*18*) and the application of these [^{18}F]alkyl halides for the syntheses of NCA *N*-(2-[^{18}F]fluoroethyl)spiroperidol (**3**) and *N*-(3-[^{18}F]fluoropropyl)spiroperidol (**4**) (Fig. 1). We here report the tissue distribution of **4** in mice, the metabolism of this compound in mouse brain and baboon plasma, and tomographic studies of this compound in a baboon. Preliminary reports of this study have appeared previously(*19,20*).

MATERIALS AND METHODS

Synthesis of NCA *N*-(3-[^{18}F]Fluoropropyl)spiroperidol (4)

NCA *N*-(3-[^{18}F]fluoropropyl)spiroperidol was synthesized from two different substrates **2c** and **2d** as described previously (*18*). Typically, from 100 mCi of [^{18}F]fluoride and substrate **2c**, 9.5 mCi of **4** was produced with a mass of ~2–5 nmol in a synthesis time of 70 min from EOB. The use of substrate **2d** gave **4** in poor yield (~1% EOB). This is probably due to the low boiling point of 1-bromo-3-fluoropropane (b.p. = 101.4°C) compared with 1-fluoro-3-iodopropane (b.p. = 128°C/742 mm).

Tissue Distribution of NCA *N*-(3-[^{18}F]Fluoropropyl)spiroperidol (4) in Mice

Female albino mice (BNL strain), 22–27 g, were injected in a lateral tail vein with 24–85 μCi of *N*-(3-[^{18}F]fluoropropyl)spiroperidol in 100 μl of isotonic saline solution. To demonstrate specific localization each mouse was pretreated with 2 mg/kg, i.v. of either (−)-butaclamol (control) or (+)-butaclamol (to block stereospecific binding sites) 45–55 min before injection of the radioligand. The mice were killed at 5, 60, and 120 min after injection. The dissected tissues were blotted to remove adhering blood and placed in tared counting vials. A sample of blood was obtained from the trunk immediately after killing. The radioactivity in the entire tail was measured to verify the patency of the tail vein injection. The radioactivity of each sample was measured, the sample weighed, and the activity expressed as percent of injected dose per organ or percent of injected dose per gram of tissue.

Metabolic Stability of *N*-(3-[^{18}F]Fluoropropyl)spiroperidol in Mouse Brains

Three female albino mice (BNL strain), 27–30 g, were injected in a lateral tail vein with 100–200 μCi of *N*-(3-[^{18}F]fluoropropyl)spiroperidol in 100 μl of isotonic saline solution. At 1 hr after injection, the mice were killed. Each brain was rapidly removed and put in a test tube which contained a mixture of 2 ml of CH_3OH and 4 ml of 0.4*M* $HClO_4$. The brain was exposed for 2 min to an ultrasonic probe designed for cell disruption,* and centrifuged. The radioactivity in the supernatant and precipitate was measured. The recovery of radioactivity (supernatant and precipitate) using this procedure was 100–104%. The entire supernatant was applied to a C-18 SEP-PAK cartridge† and eluted sequentially with H_2O, NaOH, and CH_3OH as was done for the separation of metabolites of [^{18}F]spiroperidol (*7*) and [^{18}F]NMS (*8*). The MeOH eluate was analyzed by HPLC (C-18 column, 4.5 × 250 mm, CH_3OH:0.2 *N* NH_4CO_2H (90:10), 1.5 ml/min). The recovery of radioactivity applied to the SEP-PAK was 98%. The percent of unchanged *N*-(3-[^{18}F]fluoropropyl)spiroperidol in each brain sample was taken as a product of the percent of the total applied ^{18}F recovered in the CH_3OH eluate and the fraction of this radioactivity which coeluted with the carrier *N*-(3-fluoropropyl)spiroperidol in the HPLC.

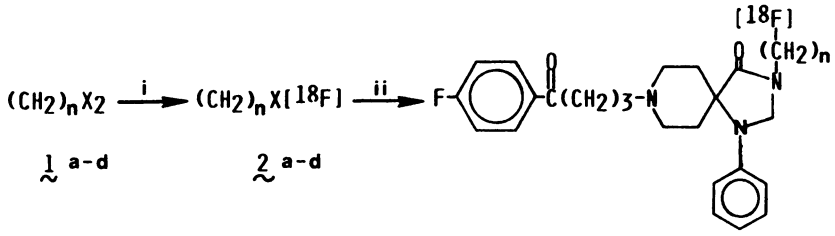

FIGURE 1
Synthesis of NCA *N*-[^{18}F]fluoroalkyl-spiroperidols.

PET Baboon Studies

A young adult (11 kg) female baboon (*Papio anubis*) was anesthetized initially with ketamine and subsequently maintained under halothane/nitrous oxide anesthesia for two PET studies as described previously (*7,8*). In the first study, the animal was pretreated with 0.5 mg/kg of (−)-butaclamol, i.v., 36 min before an i.v. bolus injection of 7.4 mCi of *N*-(3-[^{18}F]-fluoropropyl)spiroperidol in 2.5 ml of saline solution. In the second study (1 wk later), the same baboon was pretreated with 0.5 mg/kg of (+)-butaclamol, i.v., 25 min before a bolus i.v. injection of 7.9 mCi of *N*-(3-[^{18}F]fluoropropyl)spiroperidol in 2.2 ml of saline solution. PET scans were made continually for 4 hr from the time of radioisotope injection. The PET used for these studies is a PETT VI, which was operated in the high resolution mode, with a reconstructed resolution of ~0.9 cm in the transaxial plane and ~1.3 to 1.4 cm in the axial direction. Regions of interest corresponding to the striata and cerebellum were selected as described previously (*7,8*). The PET data are not corrected for differences in recovery due to geometric limitations of the size of the region of interest. Such corrections must allow for the dynamic changes in "background" levels of radioactivity and for nonhomogeneity in radioactivity distributions.

Baboon Plasma Analyses

Blood was sampled from the femoral artery at initial intervals of 5 sec. The radioactivity in aliquots of plasma was measured to determine the total plasma radioactivity clearance curve. Representative samples were also analyzed for unchanged *N*-(3-[^{18}F]fluoropropyl)spiroperidol by a procedure as described for the metabolic stability of compound **4** in mouse brains. The total recovery of ^{18}F applied to C-18 SEP-PAK ranged from 90 to 103%.

RESULTS

Tissue Distribution

Table 1 shows the distribution of radioactivity in various mouse tissues at 5, 60, and 120 min after injecting *N*-(3-[^{18}F]fluoropropyl)spiroperidol (**4**). The mouse brain uptake of radioactivity was similar to that of [^{18}F]NMS (1.1% of the administered dose). A comparison of the mouse tissue distribution of radioactivity following injection of **4** (Table 1) with the radioactivity tissue distribution reported for [^{18}F]NMS (*4*) shows that the uptake of **4** in each tissue is higher than that of [^{18}F]NMS. The activity in the femur increases with time for compound **4** indicating that in vivo defluorination may occur.

Brain Metabolism of *N*-(3-[^{18}F]Fluoropropyl)spiroperidol (4) in Mice

Table 2 shows the metabolic stability of *N*-(3-[^{18}F] fluoropropyl)spiroperidol (**4**) in mouse brains 1 hr after injection. The extraction efficiency of ^{18}F radioactivity from the brain was 77–82% with one extraction, but increased to 95% when the precipitate was extracted with CH_3OH-$HClO_4$ a second time. The retention of radioactive metabolites of **4** by mouse brain was not a major factor at early times after injection. At 1 hr at least 76% of brain radioactivity was due to unchanged *N*-(3-[^{18}F]fluoropropyl)spiroperidol. If there are no dif-

TABLE 1
Tissue Distribution of *N*-(3-[^{18}F]Fluoropropyl)spiroperidol in Mice (n = 1 − 4)

Organ	Pre-treatment*	5 min		Time after injection 60 min		120 min	
		%/g	%/Organ	%/g	%/Organ	%/g	%/Organ
Striatum	−	3.4 (3.2–3.7)	0.084 (0.068–0.099)	4.1 (3.2–4.7)	0.089 (0.064–0.142)	4.3 (4.0–4.7)	0.14 (0.11–0.17)
	+	1.6 (1.2–2.1)	0.051 (0.037–0.065)	0.51 (0.39–0.60)	0.013 (0.009–0.018)	0.36	0.010
Cerebellum	−	3.4 (2.0–7.1)	0.24 (0.13–0.45)	0.55 (0.48–0.64)	0.040 (0.032–0.048)	0.42 (0.33–0.52)	0.028 (0.023–0.032)
	+	1.6 (1.2–2.0)	0.11 (0.08–0.14)	0.27 (0.20–0.35)	0.019 (0.013–0.25)	0.15	0.012
Whole brain	−	2.7 (2.3–3.2)	1.1 (0.9–1.4)	1.6 (1.4–1.8)	0.67 (0.59–0.77)	1.2 (1.0–1.5)	0.56 (0.44–0.63)
	+	1.8 (1.3–2.2)	0.79 (0.57–1.00)	0.37 (0.26–0.50)	0.16 (0.11–0.23)	0.21	0.097
Blood	−	1.8 (1.4–2.0)	—	0.80 (0.62–1.01)	—	0.33 (0.26–0.43)	—
	+	1.7 (1.4–2.1)	—	0.85 (0.66–1.17)	—	0.33	—
Heart	−	5.5 (4.9–6.2)	0.58 (0.48–0.72)	1.1 (0.9–1.3)	0.12 (0.09–0.14)	0.44 (0.34–0.52)	0.045 (0.036–0.051)
	+	5.3 (3.8–6.7)	0.58 (0.44–0.71)	1.2 (0.8–1.6)	0.14 (0.10–0.20)	0.46	0.045
Lungs	−	35 (28–41)	4.5 (3.8–5.0)	4.4 (3.8–5.0)	0.56 (0.48–0.61)	1.8 (1.5–2.0)	0.24 (0.22–0.26)
	+	28 (24–32)	4.1 (2.8–5.4)	4.2 (3.5–5.4)	0.69 (0.56–0.88)	—	—
Liver	−	16 (9–19)	19 (13–22)	6.0 (4.7–7.2)	7.4 (5.7–10.2)	3.1 (2.7–3.4)	3.6 (3.2–4.0)
	+	16 (13–20)	23 (19–27)	6.0 (4.4–8.5)	8.7 (6.5–12.6)	3.3	4.4
Spleen	−	10 (6–12)	1.3 (0.8–1.8)	2.9 (2.5–3.2)	0.38 (0.28–0.48)	1.1 (0.9–1.2)	0.12 (0.09–0.16)
	+	14 (10–17)	1.9 (1.6–2.3)	2.8 (1.8–3.5)	0.43 (0.27–0.53)	1.1	0.16
Kidneys	−	19 (15–22)	5.9 (4.6–7.1)	4.1 (3.4–5.2)	1.3 (1.0–1.7)	1.9 (1.5–2.1)	0.61 (0.47–0.72)
	+	20 (15–25)	7.8 (6.5–9.1)	4.7 (3.8–6.6)	1.6 (1.3–2.4)	2.4	0.79
Small intestines	−	8.8 (6.7–9.6)	9.6 (7.2–11.3)	5.6 (4.9–6.0)	6.2 (4.8–7.6)	2.5 (1.8–3.5)	2.6 (1.8–3.8)
	+	8.8 (7.1–10.5)	9.3 (8.5–10.1)	8.3 (4.5–14.9)	11 (4.2–23.7)	4.8	4.4
Femur	−	3.3 (2.2–3.8)	—	9.1 (8.5–10.0)	—	9.0 (8.1–9.9)	—
	+	3.8 (3.0–4.7)	—	6.5 (4.7–10.6)	—	8.4	—
Muscle	−	3.1 (2.6–3.5)	—	1.0 (0.8–1.2)	—	0.64 (0.32–1.03)	—
	+	3.7 (2.6–4.7)	—	1.3 (0.8–1.9)	—	0.53	—

* Mice were pretreated with 2 mg/kg, i.v., of either (−)-butaclamol (−), or (+)-butaclamol (+).

TABLE 2

Metabolic Stability of *N*-(3-[^{18}F]Fluoropropyl)spiroperidol in Mouse Brains 1 hr After Injection. Averages and (Ranges) of Three or Four Determinations

Treatment	Percent recovery of total ^{18}F applied to C-18 SEP-PAK			Percent of ^{18}F in MeOH as *N*-(3-[^{18}F]-fluoropropyl)spiroperidol	Percent of unchanged *N*-(3-[^{18}F]-fluoropropyl)spiroperidol*
	H_2O eluate	NaOH eluate	MeOH eluate		
MeOH-HClO4†	4.2	1.3	73	94	69
	(4.0–4.4)	(1.2–1.3)	(73–74)	(91–97)	(66–72)
2X MeOH-HClO4‡	11	3.1	81	94	76
	(11–11)	(3.0–3.1)	(81–81)	(94–94)	(76–76)

* The product of percent in the MeOH eluate and column 3.

† The precipitates were separated without further washings.

‡ The precipitates were separated and washed with MeOH-$HClO_4$ again.

ferences in the metabolism of this radioligand between mouse and primate brain, then we may assume minor contribution from radioactive metabolites during PET brain studies with *N*-(3-[^{18}F]fluoropropyl)spiroperidol.

Baboon Blood Kinetics and Metabolism

The baboon blood total plasma radioactivity clearance curve following injection of compound **4** is depicted in Figure 2. As with other ^{18}F-labeled butyrophenones in the series (*7,8*), the blood clearance was very rapid. The appearance of metabolites in the blood was also rapid (Table 3). At 10 min after injection 68% of plasma radioactivity was due to unchanged *N*-(3-[^{18}F]fluoropropyl)spiroperidol. The most striking difference in metabolism between compound **4** and [^{18}F]NMS is the difference in the profile of labeled metabolites. Compound **4**, like [^{11}C]NMS (*21*), gave a significantly greater in vivo production of radioactive basic metabolites ($HClO_4$ soluble radioactivity) in plasma than [^{18}F]NMS, in agreement with what one would predict based on the position of labeling (*21,22*).

Baboon Brain Kinetics

The distribution of radioactivity in the baboon brain following injection of *N*-(3-[^{18}F]fluoropropyl)spiroperidol is depicted in Figure 3. The top row of this figure is of PET scans taken at the level of the striatum at various times after radioligand injection in the control condition (after pretreatment with (−)-butaclamol). This shows decay-corrected radioactivity increasing in the striatum region and declining in the cortical regions at this slice level. The bottom row of Figure 3 shows the corresponding scans, normalized for the difference in dose administered, after pretreating the animal with (+)-butaclamol. These scans show the nonspecific distribution of the radioligand.

Figure 4 shows the kinetic curves of radioactivity distribution to striatum and cerebellum of the baboon in the control study and following pretreatment with (+)-butaclamol. The absolute striatal uptake for this compound in the control study (0.030% dose per cm^3) was intermediate between that of [^{18}F]spiroperidol (0.024% dose per cm^3) (*7*) and [^{18}F]NMS (0.055% dose

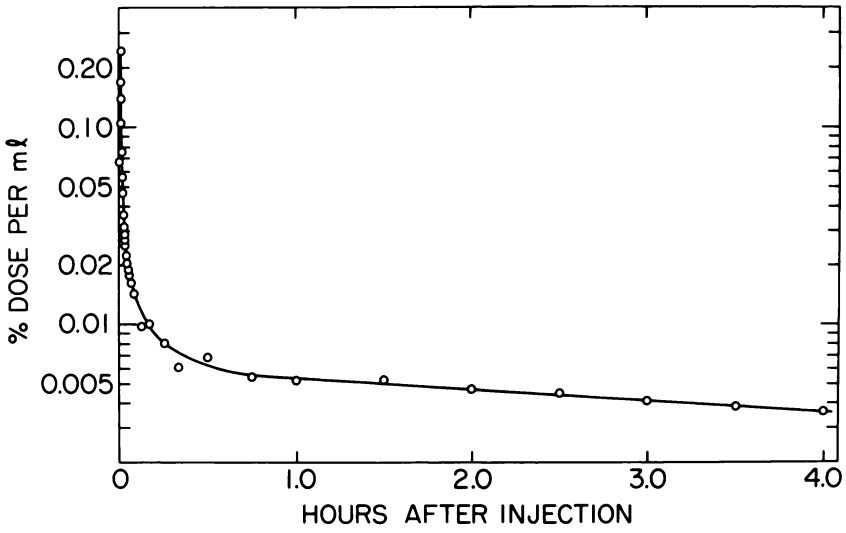

FIGURE 2
Blood plasma total radioactivity clearance curve for *N*-(3-[^{18}F]fluoropropyl)spiroperidol in the baboon.

TABLE 3
Analysis of ^{18}F Radioactivity in Baboon Plasma Samples*

Min after injection	% Recovery of total ^{18}F applied to C18 SEP-PAK			% of ^{18}F in MeOH as *N*-(3-[^{18}F]Fluoropropyl)spiroperidol as determined by HPLC	% of Unchanged *N*-(3-[^{18}F]fluoropropyl)spiroperidol
	H_2O eluate	NaOH eluate	MeOH eluate		
0.67	8	2	93	98	98
4.0	10	4	83	99	82
10	17	6	71	96	68
30	31	14	45	90	41
120	49	18	30	74	22

* Plasma samples were extracted with MeOH-0.4*M* $HClO_4$ as described in the Materials and Methods section.

per cm^3) (*8*). As were found for [^{18}F]spiroperidol and [^{18}F]NMS, influx of compound **4** into both brain regions was nearly equal for the first few minutes, but radioactivity then declined rapidly in the cerebellum, while increasing for up to 4 hr in the striatum. Pretreatment of the baboon with the same dose of the pharmacologically active (+)-butaclamol demonstrated stereoselective inhibition of the striatal retention of radioactivity.

DISCUSSION

A series of NCA [^{18}F]fluoroalkyl halides (**2**) have been synthesized by nucleophilic aliphatic substitution of alkyl halides (**1**) with NCA [^{18}F]fluoride in 30–40% yield (EOB). These [^{18}F]fluoroalkyl halides have been used to synthesize NCA *N*-(2-[^{18}F]fluoroethyl)-spiroperidol (**3**) and *N*-(3-[^{18}F]fluoropropyl)spiroperidol (**4**) by *N*-alkylation of spiroperidol. The synthe-

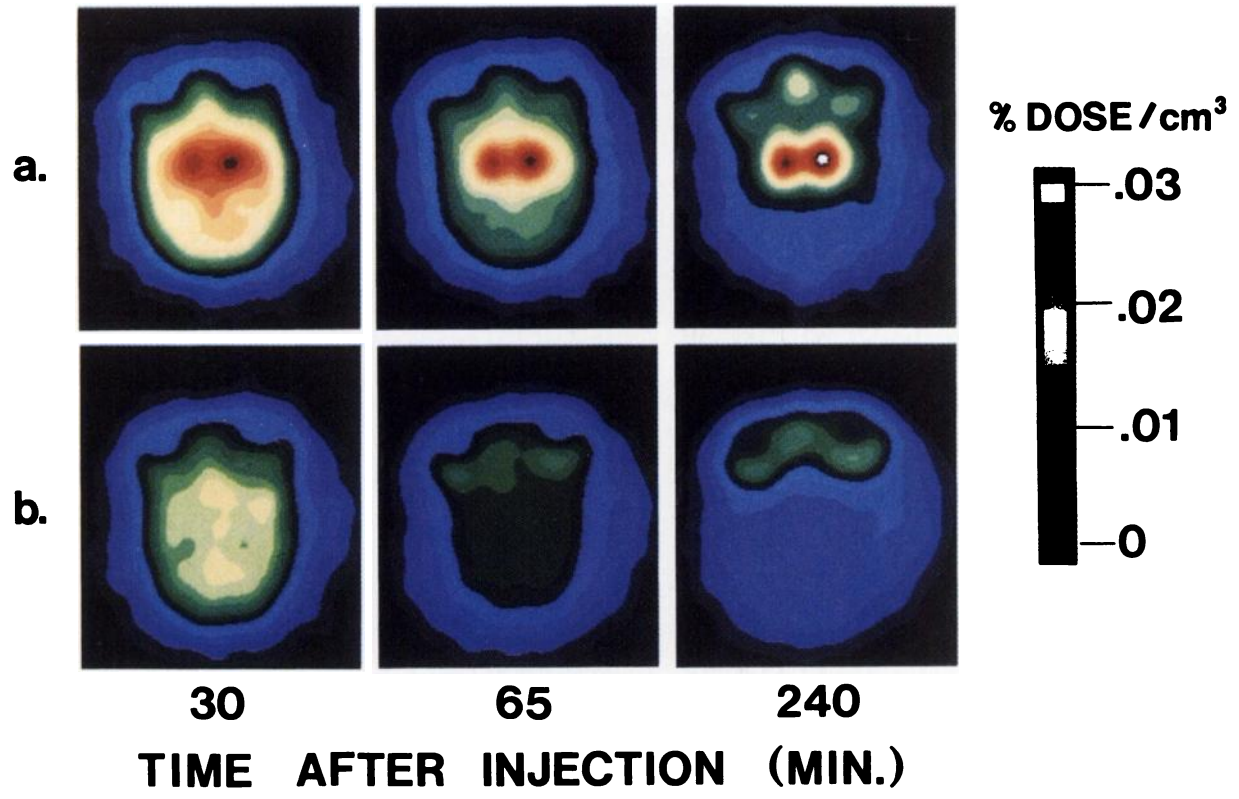

FIGURE 3
Baboon brain PET scans at the level of the striatum showing the regional distribution of radioactivity (in % dose per cm^3) at 30, 65, and 240 min after injection of *N*-(3-[^{18}F]fluoropropyl)spiroperidol. The animal was pretreated with 0.5 mg/kg of either (−)-butaclamol (A: top row) or (+)-butaclamol (B: bottom row).

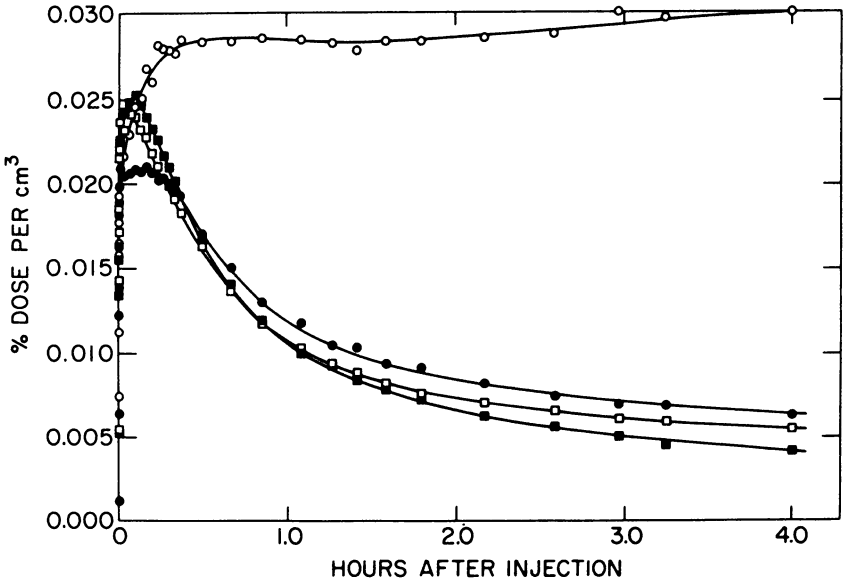

FIGURE 4
Baboon brain kinetic curves for *N*-(3-[^{18}F]fluoropropyl)spiroperidol distribution to striatum (circles) and cerebellum (squares) following pretreatment with (−)-butaclamol (open symbols) or (+)-butaclamol (filled symbols).

sis of **4** from 1-[^{18}F]fluoro-3-iodopropane (**2c**) maximizes the product activity and experimental simplicity and provides **4** in ~15–20% radiochemical yield (EOB) with a mass of 2–5 nmol. Since the *N*-fluoropropyl group seems to have some advantages over *N*-fluoromethyl and *N*-fluoroethyl groups, and the overall radiochemical yield of *N*-(3-[^{18}F]fluoropropyl)spiroperidol (**4**) was higher than that of *N*-(2-[^{18}F]fluoroethyl)spiroperidol (**3**), the biologic behavior of **4** in mice and baboon was also investigated. The biodistribution of **4** in mice showed that the brain uptake of radioactivity was similar to that of [^{18}F]NMS (1.1% of the administered dose), but the activity in the femur increased with time for compound **4** indicating that in vivo defluorination may occur. The kinetic distribution of compound **4** in baboon brain was similar to that of [^{18}F]NMS, and the striatal accumulation of radioactivity was also blocked stereoselectively by butaclamol, although the absolute striatal uptake (in % dose per cm^3) was lower than that of [^{18}F]NMS (0.030% versus 0.055%). The baboon blood total plasma radioactivity clearance was very rapid. Analysis of baboon blood at 10 min after injection indicated that 68% of the radioactivity in the plasma was due to unchanged *N*-(3-[^{18}F] fluoropropyl)spiroperidol. The ratio of striatum to cerebellum radioactivities at 3 hr after injection was 5.9, which is close to the corresponding ratio of 6.1 found for [^{18}F]NMS. These results indicate that compound **4** may be a useful radioligand for PET studies of the dopamine receptor in human brain.

NOTES

* Heat Systems-Ultrasonics, Inc., Model No. H-1.

† Waters Chromatography Division, Millipore, Milford, MA.

Note Added in Proof

After the submission of this paper, a series of papers on a similar topic have appeared.

1. Chi DY, Kilbourn MR, Katzenellenbogen JA, et al. Synthesis of no-carrier-added *N*-([^{18}F]fluoroalky)spiperone derivatives. *Appl Radiat Isot* 1986; 12:1173–1180.

2. Kiesewetter DO, Eckelman WC, Cohen RW, et al. Syntheses and D_2 receptor affinities of derivatives of spiperone containing aliphatic halogens. *Appl Radiat Isot* 1986; 12:1181–1188.

3. Welch MJ, Chi Dy, Mathias CJ, et al. Biodistribution of *N*-alkyl and *N*-fluoralkyl derivatives of spiroperidol; radiopharmaceuticals for PET studies of dopamine receptors. *Nucl Med Biol* 1986; 13:523–526.

4. Satyamurthy N, Bida GT, Barrio JR, et al. No-carrier-added 3-(2′-[^{18}F]-fluoroethyl)spiperone, a new dopamine receptor-binding tracer for positron emission tomography. *Nucl Med Biol* 1986, 13:617–624.

ACKNOWLEDGMENTS

This research was carried out at Brookhaven National Laboratory under contract DE-AC02-76CH00016 with the U.S. Department of Energy and supported by its Office of Health and Environmental Research and also supported by the National Institutes of Health, Grant NS-15380. The authors thank D. R. Christman, J. S. Fowler, P. King, W. Mancuso, E. F. Norton, and A. A. F. Tesoro for advice and assistance; A. L. Feliu for a sample of 1-bromo-3-fluoropropane; and Janssen Pharmaceutica, Inc. for the sample of spiroperidol.

REFERENCES

1. Wagner HN, Jr. Quantitative imaging of neuroreceptors in the living human brain. *Semin Nucl Med* 1986; 16:51–62.

2. Wagner HN, Jr., Burns HD, Dannals RF, et al. Imaging dopamine receptors in the human brain by positron tomography. *Science* 1983; 221:1264–1266.
3. Shiue C-Y, Fowler JS, Wolf AP, et al. Synthesis and specific activity determinations of no-carrier-added (NCA) ^{18}F-labeled butyrophenone neuroleptics-benperidol, haloperidol, spiroperidol and pipamperone. *J Nucl Med* 1985; 26:181–186.
4. Shiue C-Y, Fowler JS, Wolf AP, et al. No-carrier-added fluorine-18-labeled N-methylspiroperidol: Synthesis and biodistribution in mice. *J Nucl Med* 1986; 27:226–234.
5. Attina M, Cacace F, Wolf AP. Displacement of a nitro group by [^{18}F]fluoride ion. A new route to aryl fluorides of high specific activity. *J Chem Soc Chem Comm* 1983; 108–109.
6. Kilbourn MR, Welch MJ, Dence CS, et al. Carrier-added and no-carrier-added syntheses of [^{18}F]spiroperidol and [^{18}F]haloperidol. *Intl J Appl Radiat Isot* 1984; 35:591–598.
7. Arnett CD, Shiue C-Y, Wolf AP, et al. Comparison of three ^{18}F-labeled butyrophenone neuroleptic drugs in the baboon using positron emission tomography. *J Neurochem* 1985; 44:835–844.
8. Arnett CD, Fowler JS, Wolf AP, et al. [^{18}F]-*N*-Methylspiroperidol: the radioligand of choice for PETT studies of the dopamine receptor in human brain. *Life Sci* 1985; 36:1359–1366.
9. Arnett CD, Wolf AP, Shiue C-Y, et al. Improved delineation of human dopamine receptors using [^{18}F]-*N*-methylspiroperidol and PET. *J Nucl Med* 1986; 27:1878–1882.
10. Moerlein SM, Laufer P, Stöcklin G. Synthesis of no-carrier-added radiobrominated N-alkylated anologues of spiperone. *J Label Comp Radiopharm* 1985; 22:1007–1022.
11. Moerlein SM, Laufer P, Stöcklin G. Effect of lipophilicity on the *in vivo* localization of radiolabeled spiperone analogues. *Intl J Nucl Med Biol* 1985; 12:353–356.
12. Kiesewetter DO, Eckelman WC, Cohen RM, et al. Dopamine receptor ligands: Chemical syntheses and dopamine receptor affinities of halogenated derivatives of spiperone. 190th Am. Chem. Soc. National Meeting, Chicago, IL, September 8–13, 1985. Medi No. 40 [Abstract].
13. Coenen HH, Laufer P, Stöcklin G, et al. 3-*N*-(2-[^{18}F]-Fluoroethyl)spiperone: a novel ligand for cerebral dopamine receptor studies with PET. *Life Sci* 1987; 40:81–88.
14. Reifenrath WG, Roche EB, Al-Turk WA, et al. Synthesis and biological activity of fluoroalkylamine derivatives of narcotic analgesics. *J Med Chem* 1980; 23:985–990.
15. Topsom RD. The isolated molecule approach. Theoretical studies of the inductive effect. *J Am Chem Soc* 1981; 103:39–44.
16. Topsom RD. Theoretical studies of the inductive effect. *Tetra Lett* 1980; 21:403–406.
17. Seeman P, Watanabe M, Grigoriadis D, et al. Dopamine D_2 receptor binding sites for agonists. A tetrahedral model. *Mol Pharmacol* 1985; 28:391–399.
18. Shiue C-Y, Bai L-Q, Teng R-R, et al. Syntheses of no-carrier-added (NCA) [^{18}F]fluoroalkyl halides and their applications in the syntheses of [^{18}F]fluoroalkyl derivatives of neurotransmitter receptor active compounds. *J Label Comp Radiopharm* 1987; 24:55–64.
19. Shiue C-Y, Bai L-Q, Teng R-R, et al. No-carrier-added (NCA) *N*-[^{18}F]fluoroalkylspiroperidols—Syntheses and Biodistribution [Abstract]. *J Nucl Med* 1986; 27:906.
20. Arnett C, Shiue C-Y, Wolf AP, et al. Specific binding of *N*-(3-[^{18}F]fluoropropyl)spiroperidol to baboon brain dopamine receptors [Abstract]. *J Nucl Med* 1986; 27:1047.
21. Fowler JS, Arnett CD, Wolf AP, et al. A direct comparison of the brain uptake and plasma clearance of *N*-[^{11}C]methylspiroperidol and [^{18}F]*N*-methylspiroperidol in baboon using PET. *Intl J Nucl Med Biol* 1986; 13:281–284.
22. Soudijn W, Van Wijngaarden I, Allewijn F. Distribution, excretion and metabolism of neuroleptics of the butyrophenone type. Part I. Excretion and metabolism of haloperidol and nine related butyrophenone-derivatives in the Wistar rat. *Eur J Pharmacol* 1967; 1:47–57.