THE SYNTHESES OF NO-CARRIER-ADDED AND CARRIER-ADDED ^{18}F-LABELLED HALOPERIDOL*

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ABSTRACT

Fluorine-18 labelled haloperidol (^{18}F-HP) was synthesized by a fluorine-fluorine exchange reaction on haloperidol, fluorine-chlorine exchange on a chloro-analog of haloperidol, and from ^{18}F-labelled p-fluorobenzonitrile prepared by two different exchange reactions. Nucleophilic fluorine was used in the form of tetra n-butylammonium fluoride. The overall radiochemical yield, expressed at the end of syntheses was 5% for exchange in haloperidol and about 2%-3% for exchange in chloroanalog in a 40 min synthesis (from the end of the irradiation). Specific activity up to 1 Ci/mmol for haloperidol and up to 5000 Ci/mmol for chloro-analog as substrates were obtained. The syntheses using p-substituted chloro-and nitro-benzonitriles as starting materials for the exchange reaction gave a product with an average specific activity of about 2000 Ci/mmol and in general an overall radiochemical yield of 5%-10%. Purification of [^{18}F]haloperidol was done by HPLC on a C-18 column. The radiochemical purity as assessed by thin layer radiochromatography (TLRC) of the final product was at least 95%, with high chemical purity.

KEY WORDS: NCA [^{18}F] haloperidol, NCA [^{18}F] p-fluoro-benzonitrile,
Nucleophilic substitution
NCA tetra-n-butylammonium [^{18}F] fluoride

INTRODUCTION

Compounds labelled with short-lived radioisotopes, especially radiopharmaceuticals labelled with positron-emitting radionuclides, have been in great demand. The use of these compounds with positron emission tomography (PET) enables us to measure regional cerebral blood flow, oxygen and glucose utilization (1), tissue pH (2), drug pharmacokinetics (3), and lately, to gauge qualitative distribution of dopaminergic receptors (4) and to estimate the dopamine pool (5) in the human brain.

Postmortem studies done on human brain tissue have indicated a change in the concentration of dopaminergic receptor sites in several diseases. (Changes in Parkinson's disease (6) and schizophrenia (7) are of relevance to this paper.) However, since the tissue analyses were carried out after the death of the patient, changes in the concentration of

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receptor sites during the progress of disease or treatment are still unknown. An attempt to determine the concentration of dopaminergic receptor sites with PET using ^{11}C N-methyl-spiroperidol has been described (4).

Spiroperidol, haloperidol, brombenperidol, and benperidol are known as dopamine-antagonists (8). Because of their high binding affinity for the receptors mentioned (8) they have been suggested as tracers for in vivo mapping of dopaminergic receptors (9-14). Since spiroperidol also binds to the 5-HT serotonergic receptor sites (8,15) and haloperidol has been considered a purer dopamine antagonist than spiroperidol (8,15), we chose to synthesize no-carrier-added (NCA) ^{18}F haloperidol. The usefulness of [^{18}F]haloperidol as a tracer for PET studies remains controversial (8-11) and further discussion is not appropriate here.

Introduction of fluorine-18 into the aromatic ring has been extensively investigated (16-25). The use of a triazene (20-22), of diazonium salt decomposition (Balz-Schiemann reactions) (23), and of organometallics (24,25) as starting materials has been described as routes for introducing fluorine into the aromatic ring. The first two methods had a very low radiochemical yield (except for very recent report by Kilbourn et al. (22)) and the latter two cannot give an NCA product. When antagonists are used as in vivo tracers for the receptor studies they must have a very high specific activity. These requirements generally exclude the last two reactions as syntheses for producing haloperidol and spiroperidol for in vivo use. Considerable effort has also been put into the labelling of other dopamine antagonists with other positron emitting radionuclides as ^{11}C (12) and ^{75}Br (13,14,26).

During preparation of this manuscript details of NCA synthesis of [^{18}F]spiroperidol and [^{18}F]benperidol were published (16). The synthesis of these two dopamine antagonists at a NCA level is based on a nucleophilic substitution reaction similar to those used in the work reported here and that reported by Berridge et al (17) and Attina et al (18) in activated benzene rings. After the first submission of this manuscript another paper describing the synthesis of ^{18}F haloperidol and spiroperidol using triazines as substrates and the exchange reaction in simple aromatic substrates was published (22).

Here we report the syntheses of NCA [^{18}F]haloperidol by three different synthetic routes and a synthesis for medium specific activity [^{18}F] haloperidol. No-carrier-added syntheses are based on the heterogenous exchange of the hetero atom/group with fluoride. The syntheses of [^{18}F]carrier-added haloperidol is based on a fluorine-fluorine exchange in

the haloperidol molecule. The exchange reactions were done on a chloro-analog of haloperidol [4- (4-(p-chlorophenyl)-4-hydroxypiperidino) -4'-chlorobutyrophenone (3)] , p-nitrobenzonitrile (6), p-chlorobenzonitrile (7), and haloperidol (4).

MATERIALS AND METHODS

Dimethyl sulfoxide (DMSO) was dried by distillation over calcium hydride and stored over 4A-molecular sieves. Organic extracts were dried over sodium sulfate. Solvents were removed on a rotary evaporator under reduced pressure (0.3 mmHg) and at a bath temperature of 80°C unless otherwise noted. The products were characterized by their melting points, mass spectra, proton nuclear magnetic resonance (^{1}H-NMR), ^{19}F-NMR, IR, and chromatographic properties. ^{1}H-NMR was done on a Varian XL-200 or a Varian-60A spectrometer at 200-MHz and 60 MHz respectively, using tetramethylsilane as an internal standard. ^{19}F-NMR spectra were obtained also in chloroform-d on a Bruker WP-80SY spectrometer at 75.386 MHz or on a Varian XL-200 at 300 MHz using trichlorotrifluorethane (with a chemical shift of -82.204 ppm) as an external standard. Mass spectra analyses were obtained on a HP 5980A mass spectrometer. Thin layer chromatographic analyses were done on hard-layer silica gel plates with a fluorescent indicator (λ =254 nm) in solvent systems specified in the synthesis of a particular compound. The products were detected by examining plates under ultraviolet light.

The final products were purified by HPLC using a RP-18 Spheri-Sorb-10 ODS column (Brownlee Labs) or a semi-preparative C-18 column (Whatman Inc). Silica gel (mesh 40-140) was used for flash chromatography of unlabelled compounds. The specific activity of the final product for all syntheses was determined by measuring the radioactivity in an isotope calibrator and determining an absolute amount of the final product by HPLC using a UV-detector. The latter was done by comparing the response of the UV-detector at λ = 255 nm to a standard with known concentration of HP and to an aliquote from the final solution of ^{18}F-labelled HP.

All radiochemical yields in this manuscript are expressed at the end of synthesis (EOS) and relative to the radioactivity of ^{18}F available in the first reaction step (exchange reaction step), not in the irradiated water. Only conditions giving the highest yields are

described, however, large number of experiments was done by changing reaction temperature, reaction solvents (DMSO, dimethylformamide and CH_3CN), mixture of these solvents, and reaction time.

Synthesis of 4,4'-dichloro-butyrophenone (2) (fig. 1).

A solution of 4-chlorobutyryl chloride (6g, 43 mmol) in carbondisulfide (CS_2) (5 ml) was added to a cooled suspension of aluminium chloride (16 g, 160 mmol) and chlorobenzene (4.5 g, 40 mmol) in CS_2 (15 ml). The reaction mixture was stirred for 3 hours at 0°C. The CS_2-layer was discarded and after the oily residue was poured into ice-water, the solid precipitate was filtered, washed with water, and distilled under vacuum (BP. 99°C, 0.5 mm Hg). The product (2), obtained as white crystals (yield 80%, m.p: 45-48° C) was used without further purification in the subsequent step.

^{1}H-NMR ($CDCl_3$) δ = 2.18 (m, 2H, - CH_2 -), 3.15 (t, 2H, -CH_2-Cl), 3.68 (t, 2H, -CH_2,-C-), 7.6 (AB-system, 4H, phenyl-). IR(CCl_4); 2960 (C-H), 1680 (C=O), 780 (C-Cl) cm^{-1}.

Synthesis of 4- (4-(p-chlorophenyl)-4-hydroxypiperidino) -4'- chlorobutyrophenone (3) (chloro-analog of HP) (fig. 1)

Compound (3) was prepared by reacting 4,4'-dichlorobutyrophenone (2) (2.6 mg, 1 mmol) with 4-chlorophenylpiperidine-4-ol (423 mg, 2 mmol) in toluene (2 ml). A few crystals of potassium iodide (27) were added to the reaction mixture, which was heated in a closed reaction vessel at a bath temperature of 120°C for 6 hours. The product (3) appeared as a solid precipitate, which was filtered from the cooled reaction mixture and washed with water and cold ether. Recrystallization of the crude product from isopropanol gave pale yellow crystals (yield 70%, m.p.: 154°C).

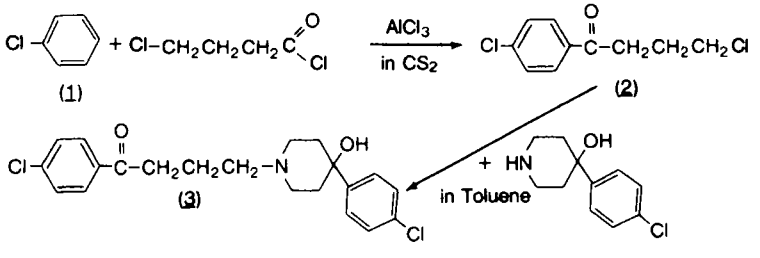

Figure 1: Reaction scheme used in the syntheses of chloro-analog of haloperidol (3)

Elemental analysis for $C_{21}H_{23}Cl_2NO_2$: C, 64.12; H, 5.85; N, 3.56; Cl, 18.32 found: C, 63.94; H, 5.87; N, 3.84; Cl, 18.55. ^{1}H-NMR ($CDCl_3$): δ = 2.18 (m, 9H, piperidyl and —OH), 2.24 (m, 2H, $-CH_2-$), 2.47 (t, 2H, $-CH_2-N$), 2.97 (t, 2H, $-CH_2-C$), 7.33 (m, 4H, p-chlorophenyl- bound to 4-hydroxypiperidino $^3J_{HH}$ = 9.2 Hz), 7.7 (semi AB-system, 4H, p-chlorobenzoyl-), $^3J_{HH}$ = 8.75 Hz) with protons ortho position to chlorine centered at δ = 7.45 ppm and those at meta to chlorine centered at δ = 7.92 ppm. MS: m/e (relative intensity): 392 (0.81, M^+), 226 (34.46), 224 (100), 206 (34.39).

Synthesis of ^{18}F-labelled haloperidol (4) (Fig. 2 and 3).

Fluorine-18 was produced by irradiating ^{18}O-enriched water with a 9 MeV (on target material) proton beam in a stainless steel target box. We have been able to produce several hundred mCi (800 mCi) of ^{18}F-fluoride in an irradiation (30 min) with protons of about 9 MeV and intensities of about 30 μ A. A dry no-carrier-added tetra-n-butylammonium ^{18}F

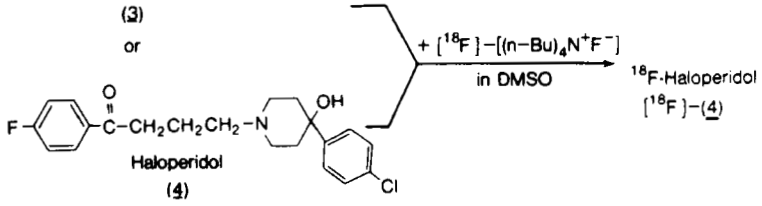

Figure 2: Scheme outlining one step synthesis of NCA[^{18}F]haloperidol and HSA ^{18}F haloperidol.

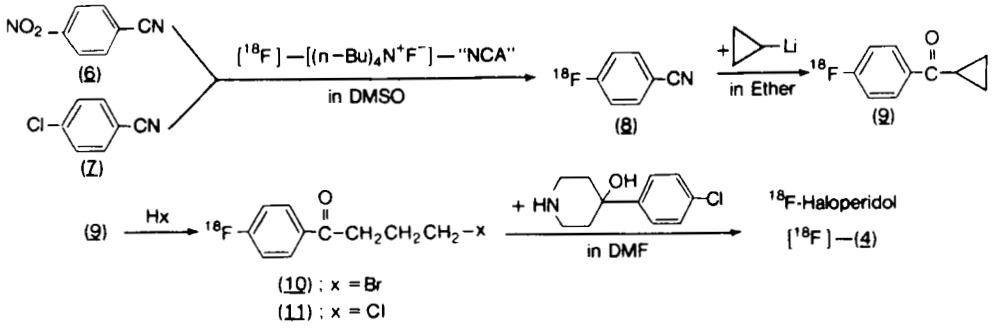

Figure 3: Reaction scheme outlining the synthesis of NCA[^{18}F] p-fluoro-benzonitrile and steps used in the synthesis of NCA[^{18}F] haloperidol (4)

fluoride has been prepared with a good yield. An aliquot of irradiated water (250 µl, 20 mCi) was added to the tetra-n-butylammonium hydroxide (10 mg, 35µ mol) in water in a platinum crucible or pyrex flask and the water was evaporated to dryness in a sand or oil bath at 120°C with a stream of dry nitrogen passing through. The residue was dried by adding benzene and acetronitrile, and by further evaporation. After drying cycles we were able to get into 0.3-0.5 ml of DMSO about 40%-70% (the best was 80%) of the tetra-n-butyl ammonium [^{18}F]fluoride. DMSO solution (300-500µl) of fluoride was added to the reaction vial containing a chloro-analog of haloperidol (3) (1-5 mg, 2.6-12.8 µmol), haloperidol (4) (1 mg, 2.7µ mol), p-chloro-benzonitrile (6) (40-80 mg, 0.27-0.54 mmol) or p-nitro-benzontrile (7) (20-68.5 mg, 0.12-0.4 mmol) depending on the synthesis used. The vial was closed and the reaction mixture kept in an oil bath at 150-155°C for 15 minutes to induce an exchange reaction.

When the exchange was done on compounds (3) and (4), [^{18}F]haloperidol was isolated from the reaction mixture by diluting the solvent with (~1 ml) water and extracting the product with chloroform (~3 ml). The chloroform layer was washed with water and a 0.1 M solution of KF before it was injected on the HPLC column. In the case of a fluorine-fluorine exchange in haloperidol, after reducing the volume the purification of the organic layer through a Sep-Pack reverse phase column (Waters Scient. RP-18) was sufficient to obtain 95% pure ^{18}F-HP. Recovery of haloperidol was about 50% in experiments where the exchange was done in haloperidol. Separation of ^{18}F-HP from a precursor (3) was accomplished by HPLC using a mixture of MeOH-H_2O (92 + 8 ml) HOAC (glacial, 0.16 ml), and NH_4OAC (0.1 mg/ml) mixture having pH=4.8 as an elution solvent on a reverse phase column. The capacity factor (elution volume) for ^{18}F-HP and its Cl-analog was 3.2 (V_R = 8 ml) and 5.3 (V_R = 12 ml), respectively. To decrease the amount of Cl-analog in the NCA ^{18}F-HP fraction the purification was repeated twice. The synthesis time was 30 minutes after the end of the fluorine uptake into DMSO. The radiochemical yield was 2%-3% for the exchange on a chloro-analog with specific activity up to 5000 Ci/mmol and about 5% for the exchange on haloperidol with specific activity of about 1 Ci/mmol, with a radiochemical purity exceeding 95%.

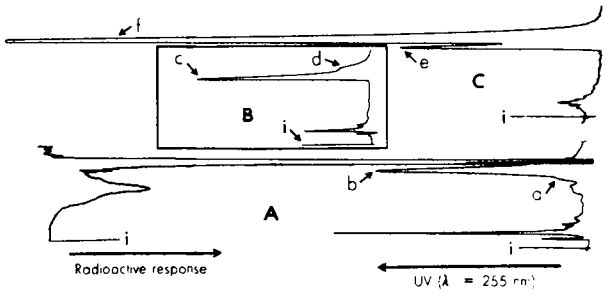

Figure 4: A composite HPLC chromatogram of $CHCl_3$ layer. Injection is identified with letter i. (see text for more details).

An HPLC chromatogram of the chloroform layer of the crude product of ^{18}F haloperidol and total fraction of haloperidol synthesized by exchange in chloro-analog (3) of haloperidol (Fig. 2) is shown in Fig. 4. In the part A radioactive and UV traces are given. Haloperidol and chloro-analog peaks are identified by letters a and b, respectively. Radioactive trace indicates presence of two [^{18}F] compounds. A larger peak corresponds to NCA [^{18}F] haloperidol with the same elution volume as authentic sample. The part B shows UV-trace of the reaction mixture to which "cold" haloperidol was added. Peaks e and f correspond to haloperidol and chloro-analog, respectively. The insert C shows a chromatogram of entire fracation of purified [^{18}F] haloperidol after decay of ^{18}F. The presence of a small amount of chloro-analog is seen in the chromatogram, identified by letter d. Haloperidol is identified by letter c.

In experiments where the exchange was done on p-nitrobenzonitrile (6) or p-chlorobenzonitrile (7), the product (8) ([^{18}F] p-fluorobenzonitrile) was extracted from the reaction mixture with ether. (R_f for NCA [^{18}F] p-fluorobenzonitrile was 0.56 in hexane-ethyl acetate (9:1) and it was identical to an authentic sample). After drying over sodium sulfate the ether solution of (8) was added to an ether solution of cyclopropyl lithium (28) and refluxed for 10 minutes. After evaporation of ether with a stream of nitrogen, either hydrobromic acid (2 ml, 48%) or hydrochloric acid (2 ml, 36%) was added at 0°C to open the compound's cyclopropyl (9) ring. The reaction vessel was then closed and heated at 100°C for 10 minutes to complete the ring opening. The products (10) and (11) were extracted with chloroform, and the chloroform layer washed with a solution of sodium bicarbonate (2%) and water. The organic solvent was evaporated, the residue dissolved in dimethylformamide

(DMF) (100-500 µl), and added to a vial containing 4-(p-chlorophenyl)-4-hydroxypiperidine (63-105 mg, 0.3-0.5 mmol), sodium iodide (1-5 mg), and/or anhydrous sodium carbonate (5-31.8 mg, 0.05-0.3 mmol) (15). The vial was closed and kept in a 150°C bath for 20 min. The reaction mixture was diluted with water (1 ml) and [^{18}F] haloperidol extracted with chloroform and purified by HPLC using the column and solvent described above. The elution volume of ^{18}F-HP was identical to that of an authentic sample extracted from the drug haloperidol. The synthesis time was about 85 minutes after the end of irradiation and the overall radiochemical yield of these syntheses was generally 5%-10%. Unlabelled haloperidol synthesized by procedures identical to those described above for ^{18}F-labelled haloperidol was identified by ^{1}H-NMR, ^{19}F-NMR, IR and MS-spectroscopy. The unlabelled HP had a melting point of 147°C (lit: 148-149°C (27)) and the following spectroscopy data:
^{1}H-NMR ($CDCl_3$): δ = 2.18 (m, 9H, piperidyl and -OH), 2.24 (m, 2H, $-CH_2-$), 2.47 (t, 2H, $-CH_2-N$), 2.97 (t, 2H, $CH_2-C=O$), 7.13 (t, 2H, ring protons adjacent to fluorine $^{3}J_{HF}$ = 8.44 Hz), 7.34 (m, 4H, p-chlorphenyl), 8.02 (m, 2H, ring protons adjacent to carbonyl groups) J_{HF} = 5.48, J_{HH} = 9 Hz); ^{19}F-NMR ($CDCl_3$): ϕ = -106.94 ppm (m, 4H $J_{HF(ortho)}$ = 8.44 Hz, $J_{HF(para)}$ = 5.48 Hz). MS: m/e (relative intensity), 375 (0.37, M^+), 237 (58.07), 206 (21.59).

Proof that chlorine in the benzene ring next to the carbonyl group exchanged with fluorine (there are two p-chloro-benzene rings) was obtained from ^{1}H-NMR spectra (for a compound prepared at micro-molar scale) where an upfield shift in the resonances corresponding to protons in the position ortho to chlorine at δ =7.45 ppm was moved to 7.13 ppm after introduction of fluorine, and a downfield shift from δ =7.92 ppm to 8.02 ppm corresponding to protons in meta position to chlorine/fluorine. Additional splitting at both resonances was observed after introduction of fluorine. Only one multiplet at ϕ = -106.94 in ^{19}F-NMR spectra which collapsed to singlet was also proof of the introduction of fluorine into the benzene ring connected to the carbonyl group. From the comparison of ^{1}H-NMR spectra of the chloro-analog and haloperidol resonance at 7.34 ppm was identified as that of the protons in p-chlorobenzene connected to the 4-hydroxypiperidone. This resonance did not change the splitting pattern or the chemical shift, thereby supporting the conclusion outlined above.

RESULTS AND DISCUSSION

The use of no-carrier-added ^{18}F-fluoride as a nucleophile for heterogenous exchange is becoming increasingly important in the synthesis of high specific activity radiopharmaceuticals needed for in vivo receptor studies in the human brain with PET. ^{18}F-haloperidol has been synthesized before by using triazine (20-22) and the Balz-Schiemann (23) fluorination reaction. Radiochemical yields of about 1% (20,21) obtained and 6-13% (22) were obtained for by a triazine reaction. The Balz-Schiemann reaction yields ^{18}F haloperidol with a relatively low specific activity, which is unsuitable for receptor studies. Nevertheless, radiochemical yields of about 15% were achieved (23).

Radiochemical yields of about 35% and 67% were obtained when the exchange was done on p-chloro- and p-nitro-benzonitrile, respectively. A significant difference in the radiochemical yields in the synthesis of NCA ^{18}F-labelled p-fluoro-benzonitriles found for these two substrates is similar to that recently reported by Shiue et al (16). Our yields are somewhat higher than theirs, but in their experiments fluoride was in the form of Rb^{18}F. Another source of discrepancy might be the calculation of the radiochemical yield because it is not clearly stated which activity was taken as 100% - activity in irradiated water or that taken up into solvent in the form of Rb^{18}F. Our yield for the exchange in p-nitro-benzonitrile agrees closely with that reported by Kilbourn et al (22).

The overall radiochemcial yield for NCA [^{18}F] haloperidol was 5%-10% when exchange on p-substituted benzonitrile was used in the syntheses outlined in Fig. 3. The use of p-nitro-benzonitrile is especially advantageous because after the exchange reaction is completed only p-fluoro-benzonitrile reacts in the subsequent step with cyclopropyl lithium, leaving p-nitro-benzonitrile nonreacted. The exchange yield is also higher for p-nitro-benzonitrile than that for p-chloro-benzonitrile. (See Experimental for details and Fig. 3 for reaction sequences.) Since p-nitro-benzonitrile does not react with cyclopropyl lithium the synthesis allows easier purification of the final product. The use of HCl and HBr for the opening of the cyclopropyl ring was also evaluated (Fig. 3). It has been observed that in the 10 min reaction time both acids yield high levels of compound (11) and (10). R_f of adduct (11) in ethyl acetate-hexane (1:9) was 0.44, identical to that of an authentic sample of adduct (11). However, the organic extract after reaction with HBr showed two spots corresponding to

compound (10) and starting material, adduct (9). Since the reactivity in the subsequent step of compound (11) was better than that of (10), we concluded that HCl is better than HBr for opening the cyclopropyl ring. The use of carbonate in the last step of the synthesis was reported by Wolf et al (19). However, our experiments indicate that the presence of carbonate might induce re-cyclization and formation of adduct (9), which has also been observed by others (29,30). A similar observation was reported by Shiue et al (16), who noted re-cyclization of γ-chloro-p-nitrobutyrophenone in the presence of NaOH.

When p-chloro-benzonitrile was used, a chloro-analog of haloperidol (3) was also synthesized (by the reaction sequences shown in Fig. 3). [^{18}F]Haloperidol was purifed by reverse phase preparative HPLC column as described in the experimental section. Since haloperidol elutes first, reasonable separation is possible when a radioactive trace is used as a guide; however part of the labelled compound is lost due to incomplete separation (Fig. 4). In a typical experiment, from 10 mCi of tetra-n-butylammonium[^{18}F]fluoride 1 mCi of NCA [^{18}F]halperidol was obtained when the p-nitro-benzonitrile exchange was used, and 0.5 mCi when p-chloro-benzonitrile was used as the starting material. The synthesis, including the purification, required about 85 min from the end of irradiation. An average specific activity of NCA ^{18}F-HP was about 2000 Ci/mmol with a range between 500-5000 Ci/mmol.

The synthesis done by heterogenous exchange on the chloro-analog of haloperidol after separation by HPLC gave NCA[^{18}F]haloperidol in a radiochemical yield of 2%-3% (after the first submission the yields were doubled mainly by reducing losses during HPLC purification). The yield was somewhat reduced because a part of the product was lost in order to achieve complete separation of the final compound from the chloro-analog. A reduction in radiochemical yield was chosen rather than possible contamination resulting from the chloro-analog because pharmacological data on the binding of chloro-analog are not available. Specific activity of[^{18}F]haloperidol up to 5000 Ci/mmol was obtained.

The yield of[^{18}F]haloperidol reported here is higher than the 1%-2% yield (EOB yield) reported by Shiue et al (16) in the syntheses of[^{18}F]spiroperidol by exchange reaction on the chloro-analog of spiroperidol. As mentioned above, the environment of the nucleophile was different in their work and their yield might be relative to the ^{18}F present in irradiated water. Kilbourn et al (22) lately reported as a preliminary result that they obtained yields of

5-10% in an exchange of NO_2^- with $^{18}F^-$ in p-nitro analogs of haloperidol and spiroperidol but no experimental details were given.

The fluorine-fluorine exchange reaction yielded ^{18}F haloperidol of medium high specific activity (∿1 Ci/mmol). The radiochemical yield was a function of the amount of haloperidol used in the exchange reaction. (Use of 20 μmol increased the radiochemical yield in the exchange reaction to 15% but reduced the specific activity by a factor of about 15).

All three reactions reported here for the synthesis of NCA ^{18}F-HP could yield 5-10 mCi of NCA[^{18}F]haloperidol, the level we achieved. A one-step reaction using chloro-analog has certain advantages even though it has a rather low radiochemical yield. Of the other two, p-nitro-benzonitrile is the compound of choice because it does not follow the synthesis, making purification of the final product much simpler.

CONCLUSION

In this paper we describe the synthesis of [^{18}F] haloperidol at no-carrier-added and high specific activity levels. A 60-minute irradiation of $H_2{}^{18}O$ with a small medical cyclotron can yield about 10 mCi of NCA[^{18}F]haloperidol with specific activity sufficiently high to allow its use for in vitro visualization of dopaminergic receptors in the human brain with PET. The specific activity was in the range of 500-5000 Ci/mmol (average 2000 Ci/mmol) and about 1 Ci/mmol when the exchange was done on haloperidol. The syntheses described here were done by manual manipulation, a mode not recommended for everyday synthesis of these radiopharmaceuticals. However, the synthesis using a chloro-analog of haloperidol could easily be done by remote operation as it is a one-step synthesis with HPLC purification which can easily be carried out inside a hot-cell.

At present we are concentrating our efforts on increasing the radiochemical yield and devising a synthesis that can be done with minimum manual manipulation to reduce exposure to ionized radiation.

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