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^{18}F-Labelled N,N-Dimethylamphetamine Analogues for Brain Imaging Studies

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The radiochemical yields of nine N,N-dimethyl-2-(substituted phenyl)-isopropylamines (amphetamine analogues) were determined following reaction with [^{18}F]acetyl hypofluorite in a 0.1 M HCl solution at room temperature. The *meta*-dimethoxy substituted amphetamines gave the highest radiofluorination yields (24–32%, at EOB). Purification of the ^{18}F-labelled amphetamines was achieved in 10–20 min. 5-^{18}F-2,4-Dimethoxy-N,N-dimethylamphetamine (5-^{18}F-2,4-DNNA) was utilized to determine brain and lung uptake in rats. Positron emission tomography studies were conducted in a dog to determine the dynamic brain uptake and retention of this agent. The 5-^{18}F-2,4-DNNA exhibited decreased initial uptake and more rapid loss of radioactivity in cerebral tissue compared to the iodinated homologue.

Introduction

The measurement of regional cerebral blood flow (rCBF) utilizing single photon emission computed tomography (SPECT) and radiohalogen-labelled amphetamine and diamine derivatives has been shown to be of considerable clinical value.(1–3) Sargent and colleagues reported the first radiohalogen-labelled amphetamine analogue [2-(4-[^{82}Br]bromo-2,5-dimethoxyphenyl)isopropylamine] that showed good cerebral uptake and long retention in human brain.(4) Subsequent synthetic and brain imaging studies by these investigators(5–7) included the use of other radiolabels such as ^{77}Br, ^{131}I and ^{123}I at the 4-position of 2,5-dimethoxyphenylisopropylamine (2,5-dimethoxyamphetamine). An ^{123}I-labelled amphetamine (N-isopropyl-4-iodophenylisopropylamine, termed IMP) and a diamine (N,N,N′-trimethyl-N′-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine, termed HIPDM) have also been developed for SPECT studies.(8,9) However, the SPECT systems have decreased spatial resolution and sensitivity compared to positron emission tomography (PET).

The most common method for measuring rCBF by PET utilizes the diffusible tracer ^{15}0-water, but the quantitative accuracy and precision of this technique are limited.(10–12) Some halo-amphetamines are extracted from the blood with high efficiency and are retained by the brain for long times; this simplifies quantitation of rCBF.(13) We have sought to label amphetamine analogues with positron-emitters and apply them to PET studies of rCBF. Several amphetamine derivatives(14,15) have been labelled with the generator-produced positron emitter ^{122}I ($t_{1/2}$ 3.6-min), but the availability of the ^{122}Xe parent is presently limited.(16) The longer lived ^{18}F-radionuclide ($t_{1/2} = 109.8$ min) is more widely available at cyclotron facilities, and its longer half-life allows more time for radiopharmaceutical synthesis and PET data collection. The relatively long half-life of ^{18}F also offers the possibility of shipment of the radiopharmaceutical to PET centers without on-site cyclotrons from a regional production facility. The low kinetic energy of the ^{18}F-positron may be of advantage for PET studies utilizing the high resolution (2–3 mm) tomographs presently under construction.(17)

Previous syntheses using direct halogenation on 2,5-dimethoxyamphetamine utilized protective groups, which were later removed, to hinder the oxidative attack of the electrophile upon the primary amine.(6) The N,N-dimethyl substitution pattern was utilized in subsequent studies with this compound and protected the amine against oxidation by electrophilic iodine.(15,18) It also permitted rapid purification of the products after reaction without the requirement of deblocking. In addition, the 4-iodo-2,5-dimethoxy-N,N-dimethylamphetamine had good brain uptake and retention in rats and dogs. Studies were undertaken to determine the usefulness of this pattern for labelling with [^{18}F]acetyl hypofluorite. We sought to produce an ^{18}F-labelled amphetamine derivative in high radiochemical yield and to evaluate its potential for use in PET brain perfusion studies.

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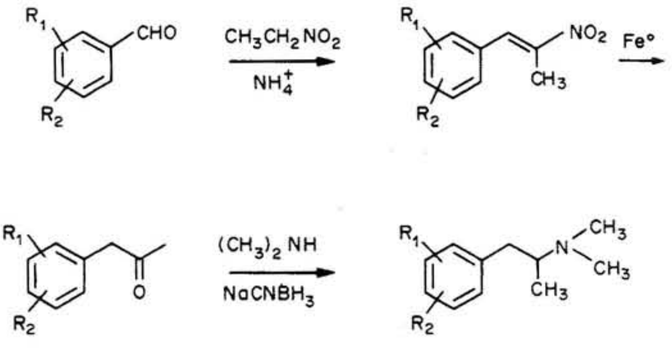
Methods and Results

All starting reagents were 98% or higher purity and were used without further purification. Melting points are uncorrected. Distillations were carried out using a Kugelrohr apparatus at the temperatures and vacuum pressures indicated. High performance liquid chromatography (HPLC) was conducted with a Waters 6000A pump and U6K injector with a Waters Model 450 u.v. detector (254 nm) and NaI(Tl) detector in series for absorbance and radioactivity detection. The HPLC separations were performed on a Hamilton PRP-1 reverse phase column (4.6×250 mm 10 μm) eluted with methanol/2M NH_4OH/1M NH_4NO_3 (650/50/25) and an Altex silica column (4.6×250 mm 10 μm) eluted with methylene chloride/methanol/n-propylamine (250/4/1). Semi-preparative HPLC separation of the fluorinated amphetamine analogue for NMR analysis was conducted on a Whatman M9 Partisil column (9×500 mm 10 μm) using CH_2Cl_2/MeOH/n-propylamine (100/1/0.5) eluent. Measurements of ^{18}F-activity were made in a calibrated ionization chamber (Capintec CRC-30) and are not decay corrected (except were noted). ^{19}F-NMR was conducted on the UC Berkeley Chemistry Department 250 MHz FT-NMR and ^1H-NMR was performed on the 180 MHz FT-NMR.

Precursor syntheses

A schematic outlining the general synthetic approach for the preparation of the various phenyl-substituted N,N-dimethylamphetamines is shown in Scheme 1. The 2,5-dimethoxy-N,N-dimethylamphetamine (2,5-DNNA), and the *meta*-dimethoxy-N,N-dimethylamphetamines (2,4-DNNA, 3,5-DNNA, and 2,6-DNNA) were prepared as previously described.[18,19]

2,5-Dimethyl-N,N-dimethylphenylisopropylamine (2,5-DMNNA). A solution of 24.0 g of 2,5-dimethylbenzaldehyde (Aldrich Chemical Co.) and 1.0 g of ammonium acetate in 200 mL of nitroethane was held on a steam bath for 18 h. The nitroethane was removed *in vacuo* giving a yellow-orange oil. The oil was vacuum distilled (110–120°C/0.4 mmHg) and the distillate added to 50 mL of hot methanol which upon cooling yield yellow crystals, 26.0 g of the 2,5-dimethyl-β-methyl-β-nitrostyrene (76% yield), m.p. 24.5–25.5°C. A solution of 25.2 g of the nitrostyrene in 250 mL of warm acetic acid was added to a suspension of 70 g of electrolytic iron dust in 100 mL of acetic acid. The mixture was heated on a steam bath for ~5 min (until the generation of copious fumes) and removed to allow the reaction to proceed without further heating. The thick grey paste was diluted with 100 mL of acetic acid and heated on the steam bath for 30 min. The reaction mixture was poured into 2 L of water and filtered to remove unreacted iron. The filtrate was extracted 3 times with 100 mL of methylene chloride, and the pooled extracts washed with 50 mL 5% NaOH. The solvent was removed *in vacuo* to yield 15.5 g (72% yield) of the 2,5-dimethylphenylacetone (140–150°C/0.4 mmHg). A solution of 14.0 g of the phenylacetone in 100 mL methanol was added to a warm solution of 30 g dimethylamine hydrochloride in 100 ml methanol. With stirring 4.0 g of sodium cyanoborohydride were added. The solution was kept at pH $\simeq 6$ by the addition of conc. HCl over 6 days. The methanol was removed *in vacuo* and 500 mL of 1M H_2SO_4 added to the residue. The mixture was extracted two times with



R_1	R_2	Compound
2-OCH_3	5-OCH_3	2,5-DNNA
2-CH_3	5-CH_3	2,5-DMNNA
2-OCH_3	-H	2-MNNA
4-OCH_3	-H	4-MNNA
2-OCH_3	4-OCH_3	2,4-DNNA
3-OCH_3	5-OCH_3	3,5-DNNA
2-OCH_3	6-OCH_3	2,6-DNNA

Scheme 1

100 mL methylene chloride (discarded) and, after making the aqueous solution basic with 25% NaOH, reextracted with methylene chloride (3 × 100 mL). The solvent was removed from the pooled extracts giving 3.2 g of an amber oil which was distilled (115–125°C/0.35 mmHg), yielding 1.88 g (11% yield) of an opalescent oil (2,5-DMNNA).

2 - Methoxy - N,N - dimethylphenylisopropylamine (2-MNNA). A solution of 15.0 g of 2-methoxyphenylacetone (Aldrich Chemical Co.) in 100 mL methanol was added to a warm solution of 40 g of dimethylamine hydrochloride in 100 mL methanol. With vigorous stirring 6.4 g of $NaCNBH_3$ and conc. HCl was added as needed to maintain a pH of ~6. The solution was stirred at room temperature for 2 days and worked up as described above. Distillation produced 9.4 g (53% yield) of the 2-MNNA as a clear, colourless oil (75–85°C/0.3 mmHg).

4 - Methoxy - N,N - dimethylphenylisopropylamine (4-MNNA). In the same manner, 10.0 g of 4-methoxyphenylacetone (Aldrich Chemical Co.) yielded 4.0 g (34% yield) of the 4-MNNA as a colourless oil (70–85°C/0.3 mmHg).

3 - Iodo - 2,6 - dimethoxy - N,N - dimethylphenylisopropylamine (3-I-2,6-DNNA). To 1.2 g of 2,6-DNNA in 5 mL glacial acetic acid there was added 1.0 g ICl, and the mixture was heated on a steam bath for 10 min. The solution was made basic with 25% NaOH and extracted with 3 × 50 mL methylene chloride. The solvent was stripped and the residue distilled (140–155°C/0.3 mmHg) to yield 1.4 g of an amber oil. HPLC analysis identified 3-I-2,6-DNNA ($k' = 6.6$ on PRP-1 and 2.7 on silica) in 95% yield and 2,6-DNNA ($k' = 2.8$ on PRP-1 and 6.2 on silica) in 2% recovery. The ring substitution pattern of 3-I-2,6-DNNA was confirmed with ^{1}H-NMR.(18) An additional HPLC peak ($k' = 9.2$ on PRP-1) was assumed to be the 3,5-diiodo-2,6-dimethoxy-N,N-dimethylamphetamine (~3% yield).

3- Bromo - 2,6 - dimethoxy - N,N - dimethylphenylisopropylamine (3-Br-2,6-DNNA). In the same manner, to 1.0 g of 2,6-DNNA there was added 0.8 g of Br_2 in 5 mL acetic acid. The mixture was extracted into methylene chloride against a basic aqueous solution and the solvent stripped. The residue was distilled (130–140°C/0.4 mmHg) to yield 1.1 g of a clear oil. HPLC of the distillate indicated 94% purity of 3-Br-2,6-DNNA ($k' = 4.4$ on PRP-1 and 3.8 on silica) and the remainder was starting material (2,6-DNNA).

[^{18}F]Acetyl hypofluorite

Fluoride-18 labelled fluorine gas was produced via the ^{20}Ne(d,α)^{18}F nuclear reaction(20,21) utilizing the 193-cm cyclotron at Crocker Nuclear Laboratory, University of California, Davis. Typical production parameters were 21 MeV deuterons on target at 20 μA. The target consisted of 24 atm neon and 70 μmol of carrier fluorine in a 100 mL passivated nickel target. After irradiation the contents of the target were passed through a potassium acetate/acetic acid (1:1.5) column(22) and [^{18}F]acetyl hypofluorite ([^{18}F]AcOF) was produced in 45% yield, relative to the amount of ^{18}F-activity removed from the target. [^{18}F]AcOF in Ne was bubbled (50 mL/min) through solutions containing the amphetamine precursors in a glass vessel and the reaction allowed to proceed for 5 min after bubbling had ceased. A soda lime column and activated charcoal (at −196°C) downstream from the reaction vessel trapped unreacted activity; these traps contained <5% of the total assayed activity.

Table 1. Effect of reaction conditions upon the yield of ^{18}F-2,4-DNNA

Solvent	Temperature (°C)	Yield* (%)
$CFCl_3$	−78	<1
$CFCl_3$	0	<1
$CFCl_3/CH_2Cl_2$† (70/30)	−78	10
HOAc	25	<1
$HOAc/H_2O$ (19/1)	25	5
CF_3COOH	25	<1
HCl (0.1 M)	2	28
HCl (0.1 M)	25	32
H_3PO_4 (0.1 M)	25	30

*Based upon the amount of ^{18}F-activity removed from the target (decay corrected to end of bombardment).

†The perchlorate salt of 2,4-DNNA was dissolved in the $CFCl_3/CH_2Cl_2$ solution.

^{18}F-Labelled amphetamines

Typical reactant concentrations were 10–30 mg of the amphetamine in 2–3 mL acid solution or 8 mL of Freon-11. The molar ratio of amphetamine to AcOF bubbled through the solution was always >2. The products of a single 1 h bombardment could be utilized for as many as six different experiments. A variety of reaction conditions and solvents were employed (Table 1). Analytical samples of the crude reaction mixtures were separated by HPLC and radiochemical yields determined using the flow through radioactivity detector. The [^{18}F]fluoro-

Table 2. ^{18}F-radiochemical yields of N,N-dimethylamphetamine analogues*

Precursor†	Yield‡ (%)
2,5-DNNA	2
2,5-DMNNA	5
2-MNNA	6
4-MNNA	3
2,4-DNNA	32
3,5-DNNA	28
2,6-DNNA	24
3-I-2,6-DNNA	<1
3-Br-2,6-DNNA	<1

*Reaction conditions: ~20 mg of precursor in 2–3 mL of 0.1 M HCl at 25°C.

†Key to compound lettering given in Scheme 1.

‡Yields based upon the amount of ^{18}F-activity removed from the target (decay corrected to end of bombardment).

amphetamines eluted prior to the precursor amphetamines on both PRP-1 and silica; typical k' differences were 1–2. The ^{18}F-labelled amphetamines were purified by making the solution basic with 25% NaOH followed by: (1) passage through a Waters C_{18} Sep-Pak cartridge and removal of the product from the Sep-Pak with 100% ethanol (>94% radiopure product) or (2) extracting with methylene chloride followed by solvent evaporation resulting in radiopurities of >97%. Use of alumina columns removed some of the ^{18}F-impurities, but resulted in product purities of less than 80% indicating labelled products other than fluoride. Product purification required 10–20 min.

The reaction conditions and yields resulting in the fluorination of 2,4-DNNA with [^{18}F]AcOF (Scheme 2) are shown in Table 1. Reaction in dilute HCl at room temperature provided the optimum labelling conditions with this compound. Fluorination of 2,5-DNNA resulted in low isolated yields (~2%); varying solvents and reaction conditions did not improve the yields. A summary of the radiofluorination yields relative to the amount of activity removed from the target is given in Table 2; the reaction conditions were identical and utilized a 0.1M HCl solution at room temperature. Passage of the entire target contents through a dilute HCl solution containing 30 mg of 2,4-DNNA following a 20 μAh bombardment produced 50–70 mCi of 97% radiopure 5-^{18}F-2,4-DNNA at the end of synthesis.

Characterization of 5-fluoro-2,4-dimethoxy-N,N-dimethylamphetamine

For the purpose of chemical identification, the fluorinated 2,4-DNNA compound was prepared as described above, except for the addition of 300 μmol of carrier fluorine gas to the target and 500 μmol of 2,4-DNNA to the reaction vessel; a stoichiometric excess of starting material was required to decrease side-reactions.[23] The products were separated on a Whatman M9 HPLC column and the solvent stripped. ^{19}F-NMR and ^{1}H-NMR were performed on the collected isolated fractions. The ^{19}F-NMR spectrum showed an unresolved broad singlet at -146.5 ppm relative to $CFCl_3$ as internal standard in $CHCl_3$ indicating that fluorination had occurred on the aromatic ring. ^{1}H-NMR was conducted in $CDCl_3$ using tetramethylsilane as internal standard. NMR of the 2,4-DNNA precursor: δ 0.89 (d, 3H, $\underline{CH_3}CH$), 2.33 [s, 6H, $(CH_3)_2N$], 2.8–2.95 (m, 3H, $\underline{CH_2}$ and $\underline{CH}CH_3$), 3.79 (s, 6H, $2(CH_3O)$, 6.38–6.43 (m, 2H, H3 and H-5, $J^{o}_{HH} = 8.1$ Hz, $J^{m}_{HH} = 2.4$ Hz), 6.99 (d, 1H, H-6, $J^{o}_{HH} = 8.1$ Hz). NMR of the fluorinated 2,4-DNNA product: δ 1.01 (d, 3H, $\underline{CH_3}CH$), 2.45 [s, 6H, $(CH_3)_2N$], 2.9–3.0 (m, 3H, $\underline{CH_2}$ and $\underline{CH}CH_3$), 3.82 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 6.50 (d, 1H, H-3, $J^{m}_{HF} = 7.5$ Hz), 6.86 (d, 1H, H-6, $J^{o}_{HF} = 11.7$ Hz).

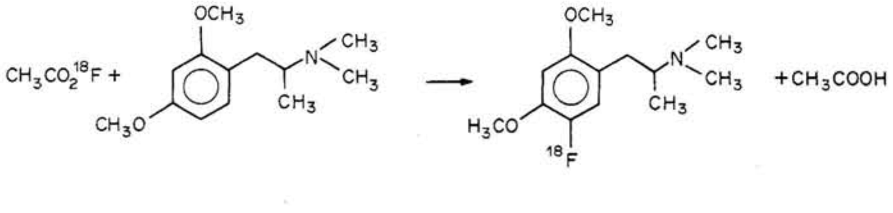
Table 3. Rat organ distribution studies

Compound	Time (min)	Brain % Inj. dose	Lungs (2) % Inj. dose
^{18}F-2,4-DNNA*	2	1.7	4.2
	10	1.0	2.1
	30	0.4	0.5
^{131}I-2,4-DNNA*	2	1.9	14.0
	10	2.0	5.5
	30	1.2	4.0
^{131}I-2,5-DNNA(19)	5	3.4	4.5
	30	1.1	2.4
[^{125}I]IMP(9)	2	2.6	30.0
	15	2.8	12.5
	30	2.4	14.4
[^{125}I]HIPDM(9)	2	2.7	36.5
	15	2.9	22.7
	30	2.4	23.7

*Average distribution value for three rats.

Animal distribution and uptake studies

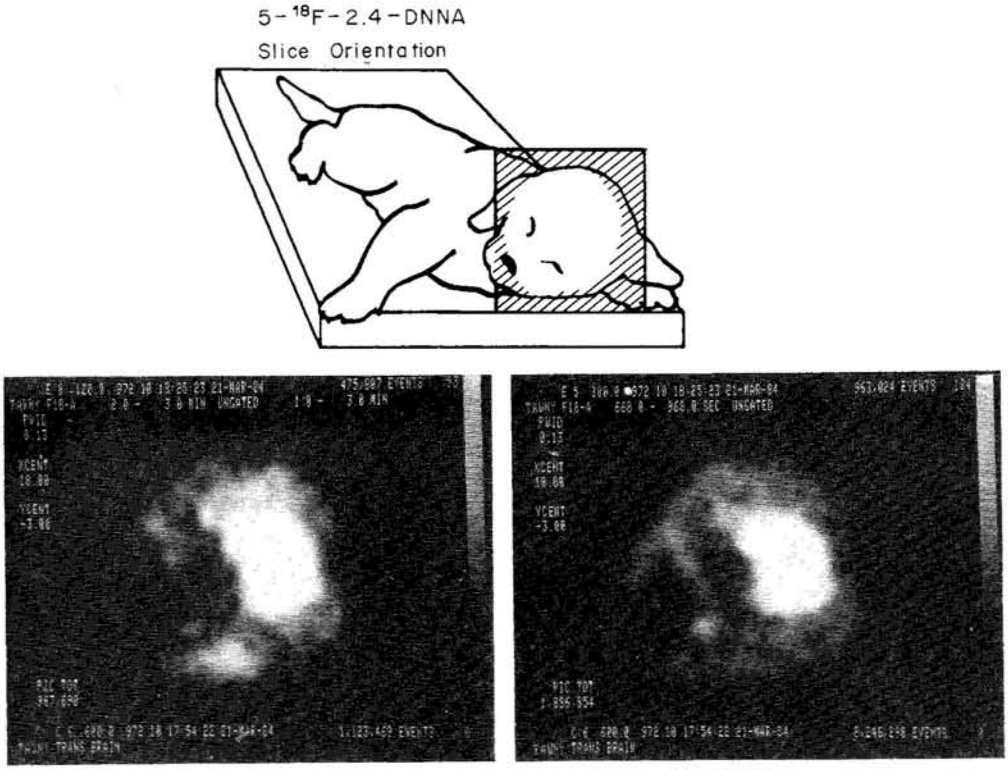
5-^{18}F-2,4-DNNA was purified by extraction into methylene chloride, the solvent evaporated and the residue taken up in isotonic, phosphate buffered saline (pH 7.4). Injections were made in the tail veins of male Sprague–Dawley rats weighing 150–200 g and restrained in plastic holders. Bolus injections of 200 μL of solution containing 30–60 μCi of the ^{18}F-labelled compound were made. The specific activity at the time of injection was ~1 Ci/mmol resulting in the injection of ~20 μg of fluoroamphetamine per rat. Because the unlabelled precursor (2,4-DNNA) may have biological properties similar to the fluorinated amphetamine, the *effective* specific activity of the product was ~500 mCi/mmol. The rats were sacrificed by decapitation at different times after injection and the organs of interest excised immediately after sacrifice and counted in a γ-well counter. A calibrated standard was prepared by serial dilution



2,4-DNNA

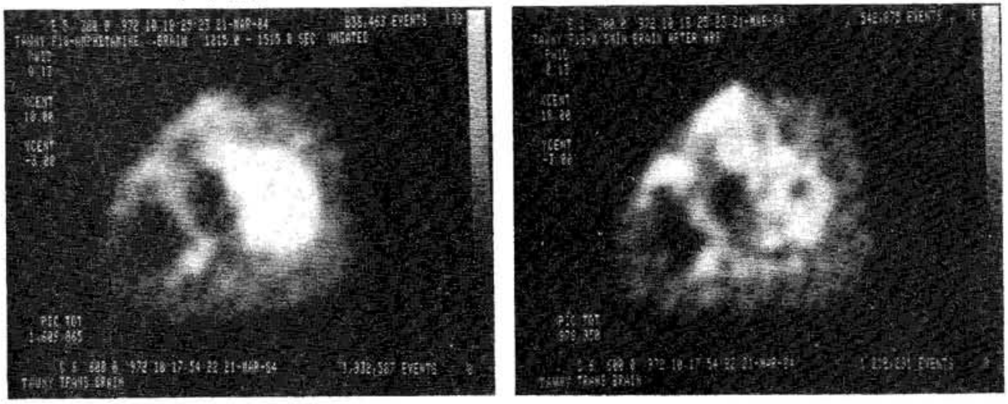
5-^{18}F-2,4-DNNA

Scheme 2



1-3 min

11-16 min



20-25 min

60-65 min

Fig. 1. Comparison of the activity in a beagle dog head at different times after injection of 3.6 mCi of 5-^{18}F-2,4-dimethoxy-N,N-dimethylamphetamine imaged by the 280-crystal Donner tomograph. The pictures are sum file collections (not decay corrected) over the times noted. The 60–65 min file shows loss of distinction between cerebral and extracerebral tissue.

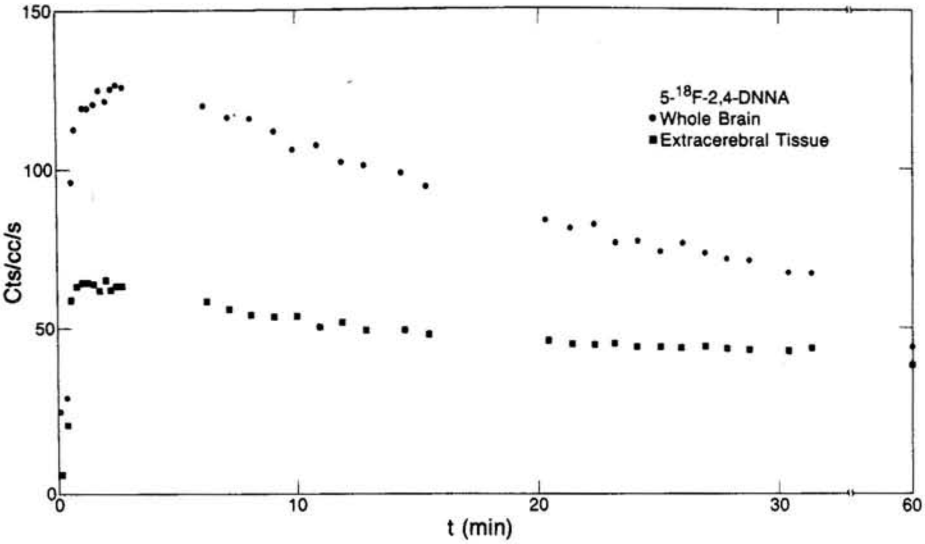


Fig. 2. Dynamic decay corrected PET activity data of the dog shown in Fig. 1. Regions of interest were drawn over the entire brain and portions of extracerebral tissue containing significant activity. Missing data points from 3–6 min and 17–20 min resulted from performing whole body scans (not shown). Cerebral and extracerebral activity concentrations were approximately equivalent at 60 min.

of the injected compound, and percent dose per organ of the injected amount was determined. The brain and lung activity following injection of 5-^{18}F-2,4-DNNA are shown in Table 3, and literature results of several iodoamphetamines and HIPDM are included for comparison.

The dynamic uptake and retention of 5-^{18}F-2,4-DNNA in a 12 kg beagle under Metofane anaesthesia were determined using the Donner 280-crystal positron tomograph$^{(15)}$ following the i.v. injection of 3.6 mCi ($\sim$2 mg) of the amphetamine mixture. PET images of 5-^{18}F-2,4-DNNA in a 1 cm thick coronal section of the dog head at different times post injection are shown in Fig. 1. The brain is clearly distinct from surrounding extracerebral tissue at early times, but distinction disappears at 60 min. Dynamic decay corrected data for several regions of interest in the dog brain are plotted in Fig. 2. Activity in the brain reached a maximum 2–3 min after injection and decreased to levels comparable to surrounding tissue at 60 min. The ratio of cerebral/extracerebral activity was at most 2/1. It was estimated from ^{18}F-calibration standards that the maximum brain uptake was 1.6% of the injected dose, assuming a 70 g brain in the dog. The biological half-life of activity in the brain was $\sim$40 min and monophasic.

Discussion

The low radiofluorination yields obtained with 2,5-DNNA (Table 2) were less than anticipated based upon the previously reported fluorination yields of anisole (75%) utilizing nonradioactive AcOF in Freon-11.$^{(23,24)}$ The low yield obtained in the reaction of 2,5-DNNA with [^{18}F]AcOF could be attributed to competitive side-reactions of [^{18}F]AcOF with: (1) the nitrogen of the amine group, (2) the HCl solution, or (3) other ring positions leading to polymer formation.$^{(23)}$ Yields obtained with the monomethoxy amphetamine analogues were low (3–6%), indicating that competitive side-reactions also predominated with these derivatives. In contrast, reaction of the *meta*-dimethoxy-N,N-dimethylamphetamine analogues with [^{18}F]AcOF produced good radiofluorination yields (24–32%). The *meta*-substitution pattern works in concert to activate the 3- and 5-positions of 2,4-DNNA, the 2-, 4- and 6-positions of 3,5-DNNA and the 3- and 5-positions of 2,6-DNNA. No fluorination at the 3-position was observed with 2,4-DNNA, probably due to steric effects as described for 1,3-dimethoxybenzene.$^{(23)}$ Similar steric effects would be expected to prevent fluorination at the 4-position of 3,5-DNNA.

Attempts to fluorinate the 3-I-2,6-DNNA and 3-Br-2,6-DNNA resulted in low yields. Oxidative attack by AcOF upon iodine and bromine cannot be ruled out, but an alternative explanation based upon results by Lerman *et al.* is likely.$^{(23)}$ They observed that acetyl hypofluorite attacks the electron-dense region between the ring carbons bearing the substitutes on *o*-bromoacetanilide. This leads to the formation of the substituted cyclohexadiene and to polymer and tar formation; reaction of *m*-bromoacetanilide with AcOF produced the *o*-fluoro isomers as expected. A similar mechanism could explain the low yields obtained with 3-I-2,6-DNNA and 3-Br-2,6-DNNA due to the expected high electron density on the phenyl ring between the 3-halo and 2-methoxy groups.

The low yields observed with the free base of

2,4-DNNA in Freon-11 (Table 1) were expected, since reaction of AcOF with the lone-pair electrons of N,N-dimethylaniline has been observed.(23) Formation of the perchlorate salt helped to protect 2,4-DNNA sufficiently to provide a 10% yield of 5-^{18}F-2,4-DNNA in Freon-11/CH_2Cl_2 mixture. Reaction of 2,4-DNNA in acetic acid and trifluoroacetic acid gave considerably reduced yields relative to dilute HCl solutions.

The rat distribution studies showed low lung uptake of 5-^{18}F-2,4-DNNA relative to the iodinated amphetamine and HIPDM (Table 3). Initial brain uptake of 5-^{18}F-2,4-DNNA was lower than that of the iodinated compounds and retention at 30 min was also reduced. The maximum uptake of 5-^{18}F-2,4-DNNA in dog brain was less than the 5-^{122}I-2,4-DNNA analogue (1.6% vs 2.5%), and the fluorinated agent showed faster washout of activity compared to the ^{122}I compound.(15) The cerebral/extracerebral activity ratio maximum in the dog was also lower with 5-^{18}F-2,4-DNNA than was observed with 5-^{122}I-2,4-DNNA (~ 2 vs 6).

Attempts to fluorinate iodo- or bromo-substituted amphetamine derivatives, which might have resulted in higher brain uptake and longer cerebral retention, resulted in low radiochemial yields as described above. Syntheses of other *meta*-dimethoxy derivatives is being explored in an attempt to provide ^{18}F-labelled lipophilic amphetamine derivatives in high radiochemical yield with the essential properties of retained rCBF agents.

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