Iodine-122-Labeled Amphetamine Derivative with Potential for PET Brain Blood-Flow Studies

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The positron emitter ^{122}I ($t_{1/2}$ 3.6 min) was collected from a xenon-122/iodine-122 ($^{122}Xe/^{122}I$) generator and incorporated into an amphetamine analog, 2,4-dimethoxy-*N,N*-dimethyl-5-[^{122}I]iodophenylisopropylamine (5-[^{122}I]-2,4-DNNA). The remote synthesis was achieved in 3 min with a 50% radioincorporation yield and a product radiopurity of >98%. 5-[^{122}I]-2,4-DNNA was injected into a beagle dog and a brain section imaged with positron emission tomography (PET). The uptake and retention of 5-[^{122}I]-2,4-DNNA was compared to that of $^{82}Rb^+$ in the same animal. Dynamic PET activity data were obtained 0-20 min postinjection of 5-[^{122}I]-2,4-DNNA and showed rapid uptake by brain and good cerebral/extracerebral tissue distinction. A whole-body scan of a dog was also obtained with 5-^{123}I-2,4-DNNA showing uptake in brain, lung, and other body organs. The feasibility of incorporating ^{122}I into an extracted brain perfusion agent for use with PET is demonstrated.

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A blood-flow agent combining the properties of a highly extracted compound labeled with a generator-produced, short-lived positron emitter would permit convenient measurement of regional cerebral blood flow (rCBF) with positron emission tomography (PET). A radionuclide suited for such studies is ^{122}I ($t_{1/2}$ 3.6 min), the daughter of ^{122}Xe ($t_{1/2}$ 20.1 hr). A generator system for the production of iodine-122 (^{122}I) from xenon-122 (^{122}Xe) has been described (*1*). Iodine-122 has the advantage of availability of multiple doses for repeat studies at ~30 min intervals from the generator, which can be supplied from a distant cyclotron. An amphetamine analog was sought that had good brain uptake and provided sufficient speed and efficiency of radiolabeling to be useful with ^{122}I.

A group of amphetamine analogs which could be rapidly labeled with radioiodine has been described (*2*). Of those compounds, the highest brain uptake was found with 2,5-dimethoxy-*N,N*-dimethyl-4-[^{131}I]iodophenylisopropylamine (4-[^{131}I]-2,5-DNNA). The radiolabeling required iodine monochloride and high temperature which proved cumbersome in the synthesis cave used to produce 4-[^{122}I]-2,5-DNNA. The analog 2,4-dimethoxy-*N,N*-dimethyl-5-[^{122}I]iodophenylisopropylamine (5-[^{122}I]-2,4-DNNA) was investigated because the labeling with [^{122}I]-iodide is much simpler. It occurs with higher yield and greater speed due to the enhanced activation to electrophilic attack by the ^{122}I at the 5-position on the aromatic ring. The reaction occurs in physiologically compatible solutions, and the new compound also showed good brain uptake. The first PET images of ^{122}I are reported here.

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MATERIALS AND METHODS

$^{122}Xe/^{122}I$ generator

The ^{122}Xe gas was a byproduct of the Crocker Nuclear Laboratory (CNL) $^{127}I(p,5n)^{123}Xe$ production of high purity ^{123}I (*3*). The $^{127}I(p,6n)^{122}Xe$ nuclear reaction cross-section maximum extends from 60 MeV to >90 MeV (*4*), and protons entering the thin NaI target at 65 MeV and exiting at 43 MeV produced ~3 mCi of ^{122}Xe per μAh. The mixed radioxenons (^{122}Xe, ^{123}Xe and ^{125}Xe) were collected for shipment after the decay of sufficient

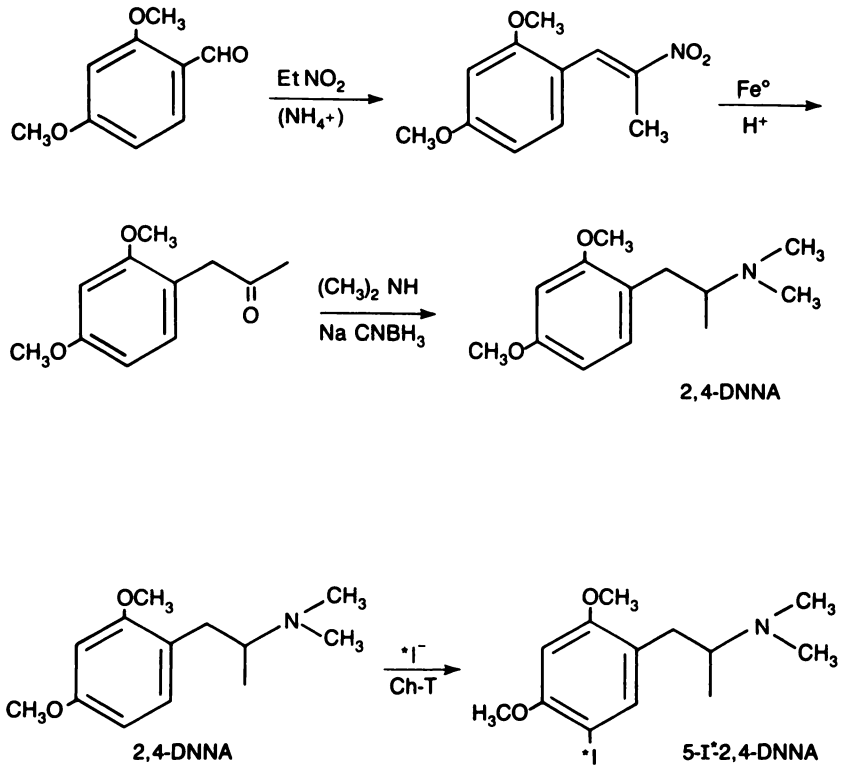

FIGURE 1
Synthesis of precursor amphetamine analog (2,4-DNNA) and radiosynthesis of 5-I*-2,4-DNNA using chloramine-T (Ch-T) and radioiodide (*I-)

^{123}Xe ($t_{½}$ 2.1 hr) to meet CNL ^{123}I production requirements. Upon receipt at Donner Laboratory, the radioxenons were transferred from the shipping container to a permanent storage reservoir contained in a shielded cave. The generator system was designed, with several modifications, after that described by Richards and Ku (*1*). The transfer of the radioxenons from the storage reservoir to the ^{122}I ingrowth/reaction vessel was performed at liquid nitrogen temperature under vacuum. The generator was utilized 24 hr after the end of cyclotron bombardment permitting ^{123}Xe to decay to less than 1% of the total radioxenon activity. The amount of ^{125}I impurity in the reaction vessel from ^{125}Xe decay was kept low by maintaining a short period of ingrowth for ^{122}I (*5*). A period of 10 min permitted 85% of the maximum ingrowth of ^{122}I and limited ^{125}I contamination to ~15 μCi. After ingrowth of the ^{122}I, the radioxenons were returned to the storage reservoir by cryogenic transfer.

2,4-Dimethoxy-N,N-dimethylphenylisopropylamine (2,4-DNNA)

The synthesis of the precursor amphetamine (2,4-DNNA) was analogous to that reported for 2,5-dimethoxy-*N,N*-dimethylphenylisopropylamine (*2*). 2,4-Dimethoxybenzaldehyde* was condensed with nitroethane (in excess nitroethane as solvent) employing ammonium acetate as a catalyst. The resulting beta-nitrostyrene was reduced in acetic acid employing elemental iron, and the intermediate ketone (2,4-dimethoxyphenylacetone) reductively aminated with dimethylamine and sodium cyanoborohydride to yield the precursor (overall synthesis yield 37%). 2,4-DNNA contains an optically active center at the alpha carbon atom and was synthesized as a racemic (R,S) mixture. This compound appeared to have an indefinite shelf life (stable for over a year at room temperature) and was prepared well in advance of the radioiodination with ^{122}I. The synthesis scheme is outlined in Fig. 1.

Synthesis of 2,4-dimethoxy-N,N-dimethyl-5-iodophenylisopropylamine (5-I-2,4-DNNA).

A solution containing 5 mg of 2,4-DNNA in 2 ml of 0.20*M* phosphoric acid and 100 μg of chloramine-T was added to the ^{122}I generator reaction vessel on whose interior surface 60 mCi of [^{122}I] iodide had been deposited by the gas containing 70 mCi of ^{122}Xe prior to removal of the gas by cryogenic transfer. The reaction vessel was heated to 60°C and the reaction allowed to proceed for 90 sec. The contents of the reaction vessel were then loaded onto an anion exchange column and the 5-[^{122}I]-2,4-DNNA product eluted with 10 ml of a 0.12*M* phosphate buffer solution (pH 7.4) through a 0.22 μm Millipore filter into a syringe.

The synthesis of 5-[^{123}I]-2,4-DNNA proceeded as above except that it was necessary to begin the ingrowth of ^{123}I from ^{123}Xe within 8 hr after the end of cyclotron bombardment because of the 2.1 hr half-life of the parent. An ingrowth period of 30 min provided several mCi of [^{123}I]iodide from a generator containing about 50 mCi of ^{123}Xe.

Macroscopic quantities of iodinated (cold) 5-I-2,4-DNNA were synthesized for NMR analysis by adding 229 mg (1.0 mmol) of chloramine-T to a 0.20*M* phosphoric acid solution containing 150 mg (0.67 mmol) of 2,4-DNNA and 120 mg (0.80 mmol) of potassium iodide at 60°C. The reaction was allowed to proceed for 5 min with vigorous stirring and was quenched by adding 285 mg (1.5 mmol) of sodium metabisulfite. The amines were extracted into dichloromethane against a basic aqueous solution and the solvent removed. The iodinated product (65% yield) was separated from the starting material by semipreparative high performance liquid chromatography (HPLC).

Product analysis

The radiochemical purity of the ^{122}I-labeled amphetamine derivative was determined by HPLC. The radiochemical purity of the ^{123}I-labeled product was determined by HPLC and thin layer chromatography (TLC). The chemical purity of the iodinated (cold) compound was also determined by HPLC. For HPLC the uv adsorbance and radioactivity of the eluent stream were measured with a Waters Model 450 uv detector (254 nm) and a NaI(Tl) detector in series; for TLC, the plastic backed sheets were visualized by quenching of 254 nm fluorescence and the radioactivity quantitated by counting sheet fractions in a gamma well counter.

Analytical HPLC was performed on a 4.6 mm × 25 cm 10 μm particle size Hamilton PRP-1 column which was eluted with methanol/2 *M* NH_4OH/1 *M* NH_4NO_3 (650/50/25) at a flow rate of 2 ml/min. The retention volumes for iodide, 2,4-DNNA and 5-I-2,4-DNNA were 4 ml, 16 ml, and 27 ml, respectively. Semipreparative HPLC separation of the 2,4-DNNA precursor from the iodinated product was performed on a 9 mm × 50 cm 10 μm silica column† using a dichloromethane/methanol/n-propylamine (250/4/1) eluent. The retention volumes of 5-I-2,4-DNNA and 2,4-DNNA were 80 and 130 ml, respectively.

TLC sheets‡ were developed with ethyl acetate/ethanol/ammonium hydroxide (34:4:1). Rf's were $^{123}I^-$ = 0.0 and 5-[^{123}I]-2,4-DNNA = 0.9.

Nuclear magnetic resonance (NMR) spectra were obtained on the UC Berkeley 200 MHz FT-NMR. NMR of the cold product showed a spectrum consistent with a 5-iodo-2,4-dimethoxy pattern on the phenyl ring [NMR of the free base ($CDCl_3$) δ:0.91 (d, 3H, CH_3CH), 2.34 (6H, $(CH_3)_2N$), 2.76 (m, 2H, CH_2), 2.85 (m, 1H, $CHCH_3$), 3.83 (3H, OCH_3), 3.88 (3H, OCH_3), 6.40 (s, 1H, Ar-H), 7.43 (s, 1H, Ar-H)].

Imaging

The dynamic uptake and retention of 5-[^{122}I]-2,4-DNNA were determined in a 1-cm-thick section of the brain of a beagle dog under Metofane anesthesia with the Donner 280 crystal PET scanner (*6*). Whole-body scans of a mongrel dog given 5-[^{123}I]-2,4-DNNA were performed with the Anger Mark II 64 crystal whole-body scanner (*7*); the blood clearance was measured by serial venous samples counted in a gamma well counter.

RESULTS

Chemistry

Approximately 50% of the [^{122}I]iodide collected in the reaction vessel was incorporated into the 5-[^{122}I]-2,4-DNNA product (Fig. 1). Ten percent of the activity ([^{122}I]iodide) was retained by the anion exchange column, and the remainder (40%) was left on the reaction vessel wall. The radiochemical purity of the product was >98%. When the generator contained 70 mCi of ^{122}Xe, 35 mCi of 5-[^{122}I]-2,4-DNNA were produced (decay corrected to the time of ^{122}Xe removal); the radiosynthesis, including purification, required 3 min. The product typically contained 20 mCi of 5-[^{122}I]-2,4-DNNA and 8 μCi of 5-[^{125}I]-2,4-DNNA at the end of synthesis.

Blood clearance and whole-body scanning

The blood clearance of ^{123}I activity after injection of 5-[^{123}I]-2,4-DNNA in a dog is shown in Fig. 2. The amount of radioactivity in the blood decreased rapidly and maintained a constant level from 15-60 min following i.v. injection. A whole-body scan at 13 min is also shown in Fig. 2, indicating uptake in brain, lung, and liver. Subsequent serial scans showed almost complete clearance from lung by 30 min and a high bladder concentration at 54 min.

PET imaging

The PET images of the uptake of 5-[^{122}I]-2,4-DNNA and $^{82}Rb^+$ in a coronal section of the head of a beagle dog are shown in Fig. 3. The images are not corrected for the decay of the radionuclide and represent data collection summed over 100–300 sec and 0–300 sec postinjection of 18 mCi of ^{82}RbCl and 5 mCi of 5-[^{122}I]-2,4-DNNA, respectively. The ^{82}Rb ($t_{½}$ 76 sec) image, in the same plane, was obtained just prior to the ^{122}I injection and is shown in Fig. 3 (lower left) as a reference for extracerebral soft-tissue localization. $^{82}Rb^+$ is excluded from normal brain parenchyma by an intact blood-brain barrier (*8*); the dog brain appears as a dark area surrounded by $^{82}Rb^+$ activity in the extracerebral soft tissue of the head. The 5-[^{122}I]-2,4-DNNA image is shown in Fig. 3 (lower right); the brain is the bright area with no visible activity in the surrounding extracerebral tissue. It was estimated from ^{122}I calibration standards that 2.5% of the injected dose was taken up by the dog brain, assuming a 70-g brain in 12 kg dog.

The decay corrected dynamic data following injection of 5-[^{122}I]-2,4-DNNA are plotted for three regions of in-

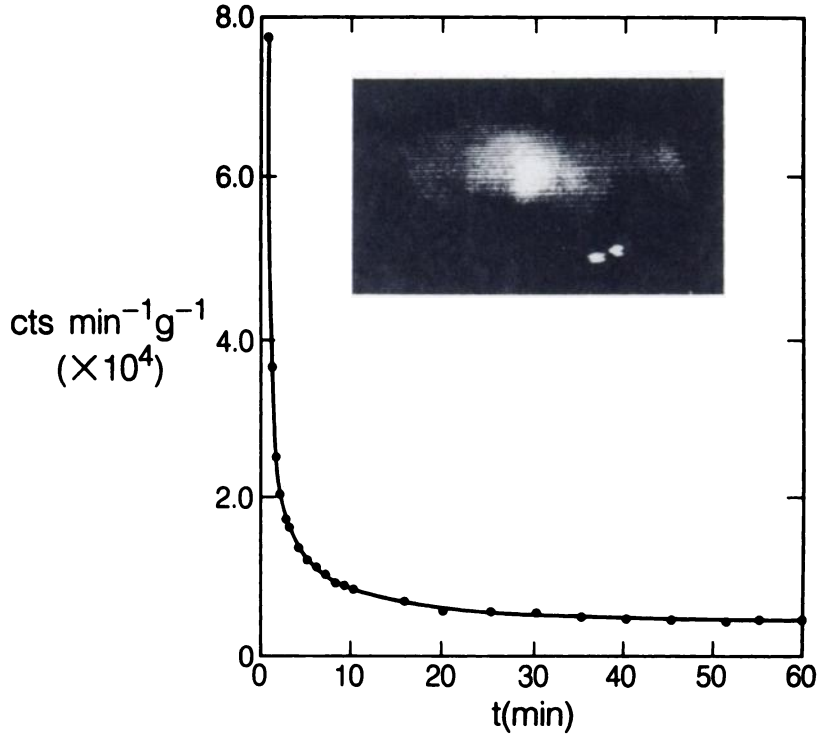

FIGURE 2
Blood activity clearance curve following i.v. injection of 300 μCi of 5-[^{123}I]-2,4-DNNA in a mongrel dog. Whole-body scan (inset) was taken 13 min after injection and shows activity in brain, lung, liver, kidneys and in a syringe at the injection site (lower right)

terest (ROIs) in Fig. 4. The radioactivity reached a maximum in the brain 5 min after injection and decreased to 80% of the maximum value at 20 min, with a plateau from 2–10 min. By 2 min, the brain activity was 90% of its maximum value indicating rapid uptake by the brain. A ROI drawn around extracerebral tissue including the snout and scalp areas but excluding the brain contained much less activity than the brain and is plotted in Fig. 4 for comparison. The ratio of the activity concentration in brain/extracerebral tissues was ~6 during the plateau

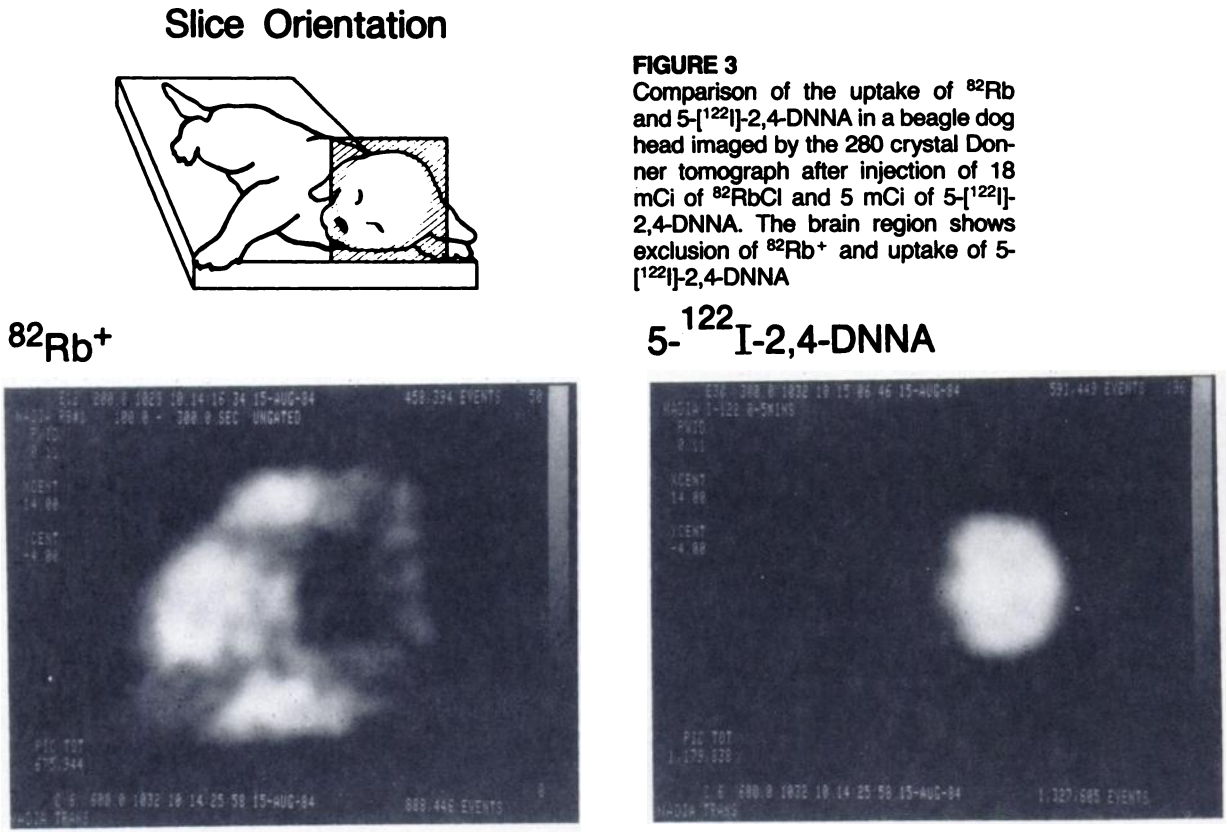

FIGURE 3
Comparison of the uptake of ^{82}Rb and 5-[^{122}I]-2,4-DNNA in a beagle dog head imaged by the 280 crystal Donner tomograph after injection of 18 mCi of ^{82}RbCl and 5 mCi of 5-[^{122}I]-2,4-DNNA. The brain region shows exclusion of $^{82}Rb^+$ and uptake of 5-[^{122}I]-2,4-DNNA

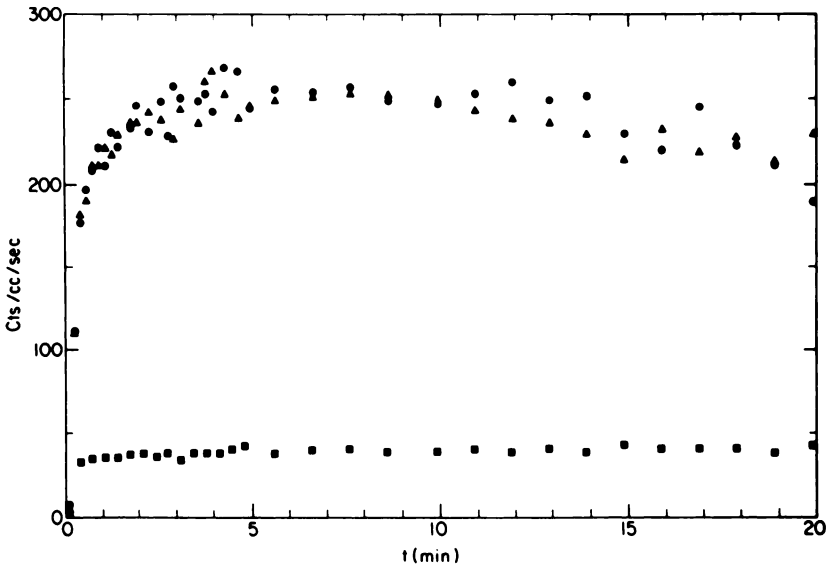

FIGURE 4
Dynamic decay corrected PET activity data shown in Fig. 3. ROIs were drawn over the left (▲) and right (●) cerebral hemispheres and over the snout/scalp (extracerebral) (■) areas

period. Although the dog brain in the coronal section is ~6 cm across and the 280 crystal Donner tomograph has a 8 mm full width at half maximum (FWHM) resolution (*6*), the ^{122}I image in Fig. 3 exhibits a sharp brain/extracerebral tissue contrast and some distinction between gray and white matter. There was significantly less ^{122}I activity in the surrounding extracerebral tissue than in the brain, indicating that the 5-[^{122}I]-2,4-DNNA compound is selectively taken up and retained by the cerebral tissue.

DISCUSSION

Radiopharmaceuticals for rCBF measurements are composed of two categories: freely diffusible and highly extracted/retained tracers. Most compounds used so far in PET studies have been the freely diffusible type and include ^{15}O water, [^{11}C]butanol, [^{11}C]iodoantipyrine, $C^{15}O_2$, $CH_3{}^{18}F$, $^{13}N_2O$, krypton-77, neon-19 and ^{18}F-4-fluoroantipyrine (*9-19*). They diffuse into brain as reflected by their brain to blood partition coefficient and are removed from brain relatively rapidly by the same diffusion mechanism when the compound clears the blood. The rapid washout of diffusible tracers presents some problems for accurate quantitation (*9, 10, 20-22*).

In contrast, highly extracted/retained tracers remain in the brain after first-pass extraction and wash out relatively slowly, behaving like "molecular microspheres." The high extraction and long residence time provide higher total integrated counts with better statistics per amount of injected radiopharmaceutical and eliminate the washout corrections required for diffusible tracers (*9, 10, 20-22*). Quantitation is simplified when concentration is proportional to flow (*23*). At present, no radiopharmaceutical in the extracted/retained category successfully meets the criteria required of a PET rCBF agent for human applications. Microspheres labeled with positron emitters (*24*) are not appropriate for human studies because of the need for carotid injection and the danger of cerebral capillary occlusion. Although $^{13}NH_3$ is extracted from blood into brain and retained by virtue of incorporation into glutamate and glutamine (*25*), the extraction varies with flow and hence is not useful for quantitative rCBF measurements (*26*).

One of the most promising classes of highly extracted/retained tracers appears to be derivatives of amphetamine. The first of these were 4-[^{82}Br]-2,5-dimethoxyphenylisopropylamine, which showed brain uptake in humans (*27*) and the ^{131}I-labeled 2,5-dimethoxyphenylisopropylamine analog which showed first-pass extraction in monkey brain (*28*). Winchell et al. (*29*), after studying a variety of other analogs, chose the *N*-isopropyl-4-[^{123}I]iodophenylisopropylamine (IMP), and subsequent clinical trials with single photon emission computed tomography (SPECT) systems have demonstrated its usefulness in rCBF studies (*23, 30, 31*). A diamine compound, *N,N,N'*-trimethyl-*N'*-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine (HIPDM), has been labeled with ^{123}I (*32*) and has also been used in SPECT studies (*33*). The mechanism of the uptake and retention of this class of agents has not been fully elucidated, yet their application to rCBF measurements appears promising. 5-[^{122}I]-2,4-DNNA was chosen here based upon the success of the amphetamine analogs in SPECT studies and the ease and speed of incorporation of [^{122}I]-iodide into 2,4-DNNA. It may also prove to be useful when labeled with ^{123}I for single photon imaging.

The 5-[^{122}I]-2,4-DNNA as prepared here was from a no-carrier-added synthesis. The specific activity of 5-[^{122}I]-2,4-DNNA was greater than 30,000 Ci/mmol; this specific activity value is a lower limit determined by the detection sensitivity of the uv detector. The 5 mg of unreacted precursor was not separated before injection. Since the precursor and labeled product may have similar

biological properties, the effective specific activity of the product may be as low as 0.1 Ci/mmol. The animals have shown no adverse effects from the injection of 5 mg of 2,4-DNNA, and necessary studies are presently underway to determine the toxicology of the precursor prior to human use. The minimum amount of precursor necessary to achieve labeling is also under study, and it can be reduced to 0.5 mg without significantly reducing the 5-[^{122}I]-2,4-DNNA radiochemical yield.

The whole-body dose per mCi of 5-[^{122}I]-2,4-DNNA is approximately three times that of $H_2{}^{15}O$ (*34*); the maximum positron energy of ^{122}I (3.1 compared with 1.7 MeV) and the longer half-life of ^{122}I (3.6 compared with 2 min) contribute to this difference. It is anticipated that three to four times less 5-[^{122}I]-2,4-DNNA will be required to obtain the same number of counts as $H_2{}^{15}O$ for rCBF measurements because of the long retention of 5-[^{122}I]-2,4-DNNA by brain tissue. A comparison of doses to the target organs must necessarily await animal distribution studies with 5-[^{131}I]-2,4-DNNA, and the per mCi doses to lung, liver, and kidney will probably be higher than for $H_2{}^{15}O$.

The inevitable presence of ^{125}I in the product represents a potential thyroid dose to human subjects. The extent of this risk may be considered in terms of the steps that can be taken to limit the amount present and whether it contributes a significant radiation exposure. There are several strategies by which the ^{125}I can be reduced.

1. Increasing the beam energy from the present 65-43 MeV to 80-60 MeV would span the maximum of the ^{122}Xe production cross-section and decrease ^{125}Xe production by a factor of about 10 (*4*). Few accelerators presently can produce proton beams in this energy range at the requisite high-beam current for isotope production.
2. The ingrowth time for the ^{122}I can be held to a minimum, which limits ingrowth of ^{125}I from ^{125}Xe (*5*).
3. Installing a new storage vessel for each ^{122}Xe delivery can reduce the carry-over of ^{125}I deposited in the storage vessel from previous generators (*35*).

If 5-[^{125}I]-2,4-DNNA is not significantly deiodinated, as was the case for its primary amine analog 4-[^{131}I]-2,5-dimethoxyphenylisopropylamine (4-[^{131}I]-2,5-DPIA) (*36*), the ^{125}I will be excreted organically bound to the metabolites of 5-[^{125}I]-2,4-DNNA. The metabolism of 5-[^{125}I]-2,4-DNNA is under investigation, and if it is found to be similar to 4-[^{131}I]-2,5-DPIA the radiation dose to the thyroid because of ^{125}I would be <400 mR per 10 μCi of 5-[^{125}I]-2,4-DNNA in the product (*37*). Blocking the thyroid uptake of [^{125}I]iodide with sodium perchlorate or Lugol's solution would reduce this dose even further.

Xenon-122 is at present produced in useable quantities as a byproduct of ^{123}I production at two accelerators in the U.S., the Crocker Nuclear Laboratory cyclotron at the University of California, Davis and the BLIP accelerator at Brookhaven National Laboratory. It is quite possible that ^{122}Xe will be more readily available in the future if the demand for high purity ^{123}I continues to increase.

This study demonstrates the feasibility of using generator produced ^{122}I for PET brain imaging studies with an extracted/retained tracer. Despite the short physical half-life of ^{122}I, it can be incorporated into a radiopharmaceutical from a portable generator with a high radiochemical yield. The image quality of the ^{122}I in the PET camera was quite good despite the potential adverse effect of accidental coincidences from the 18% abundance of 564 keV photons and a maximum positron energy of 3.1 MeV.

Validation of 5-[^{122}I]-2,4-DNNA as a quantitative rCBF agent for PET applications will require additional experimental work to determine first-pass extraction and the linearity of extraction with flow (*23, 26, 38*). Images of the extraction and retention patterns in the brain will provide relative flow information, which should be of clinical value. If absolute rCBF values are required, it may be necessary to perform arterial blood sampling as described by Kuhl and co-workers (*23*). In addition, quantitative rCBF measurements with extracted/retained tracers must account for metabolites in the blood (*23, 39*). Studies to evaluate this radiopharmaceutical as a quantitative rCBF agent are currently underway.

FOOTNOTES

*Aldrich Chemical Company, Milwaukee, WI.

†Whatman, Chemical Separation Inc., Clifton, NJ.

‡Eastman Chromogram No. 6060 Silica Gel Sheets, Rochester, NY.

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REFERENCES

1. Richards P, Ku TH: The ^{122}Xe-^{122}I system: A generator for the 3.62-min positron emitter, ^{122}I. *Int J Appl Radiat Isot* 30:250–254, 1979
2. Sargent III, T, Shulgin AT, Mathis CA: Radiohalogen-labeled imaging agents. 3. Compounds for measurement of brain blood flow by emission tomography. *J Med Chem* 27:1071–1077, 1984
3. Jungerman JA, Lagunas-Solar MC: Cyclotron production of high-purity iodine-123 for medical applications. *J Radioanal Chem* 65:31–45, 1981
4. Lundqvist H, Malmborg B, Langstrom B, et al: Simple production of ^{77}Br and ^{123}I and their use in the labelling of [^{77}Br]BrUdR and [^{123}I]IUdR. *Int J Appl Radiat Isot* 30:39–43, 1979
5. Mausner LF, Prach T, Richards P: Production of radionu-

clides for generator systems. In *Radionuclide Generators*, Knapp FF, Butler TA, eds. Washington DC, American Chemical Society, ACS Symposium Series 241, 1984, pp 77-95
6. Derenzo SE, Budinger TF, Huesman RH, et al: Imaging properties of a positron tomograph with 280 BGO crystals. *IEEE Trans Nucl Sci* 28:81-89, 1981
7. Budinger TF: Quantitative nuclear medicine imaging: Application of computers to the gamma camera and whole-body scanner. In *Recent Advances in Nuclear Medicine* Vol. IV, Lawrence JH, ed. New York, Grune and Stratton, 1974, pp 41-130
8. Yen CK, Budinger TF: Evaluation of blood-brain barrier permeability changes in rhesus monkeys and man using ^{82}Rb and positron emission tomography. *J Comput Assist Tomogr* 5:792-799, 1981
9. Raichle ME, Martin WRW, Herscovitch P, et al: Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 24:790-798, 1983
10. Huang SC, Carson RE, Hoffman EJ, et al: Quantitative measurement of local cerebral blood flow in humans by positron computed tomography and ^{15}O-water. *J Cerebr Blood Flow Metab* 3:141-153, 1983
11. Raichle ME, Martin WRW, Herscovitch P, et al: Measurement of cerebral blood flow with C-11 butanol and positron emission tomography. *J Nucl Med* 24:P63, 1983 (abstr)
12. Ginsberg MD, Lockwood AH, Busto R, et al: ^{11}C-Iodoantipyrine for the measurement of regional cerebral blood flow by positron emission tomography. *Stroke* 12:745-750, 1981
13. Jones SC, Greenberg JH, Reivich M: Error analysis for the determination of cerebral blood flow with the continuous inhalation of ^{15}O-labeled carbon dioxide and positron emission tomography. *J Comput Assist Tomogr* 6:116-124, 1982
14. Frackowiak RSJ, Lenzi G, Jones T, et al: Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: Theory, procedure and normal values. *J Comput Assist Tomogr* 4:727-736, 1980
15. Holden JE, Gatley SJ, Hichwa RD, et al: Cerebral blood flow using PET measurements of fluoromethane kinetics. *J Nucl Med* 22:1084-1088, 1981
16. Madsen MT, Hichwa RD, Nickles RJ: An investigation of ^{11}C-methane, ^{13}N-nitrous oxide and ^{11}C-acetylene as regional cerebral blood flow agents. *Phys Med Biol* 26:875-882, 1981
17. Yamamoto YL, Thompson CJ, Meyer E, et al: Dynamic positron emission tomography for study of cerebral hemodynamics in a cross-section of the head using positron emitting ^{68}Ga-EDTA and ^{77}Kr. *J Comput Assist Tomogr* 1:43-56, 1977
18. Tilbury RS, Rottenberg DA, MacDonald JM, et al: Cyclotron production of neon-19 and its use in positron emission tomography. *J Label Cmpds Radiopharm* 18:183-185, 1981
19. Lambrecht RM, Duncan CC, Shiue C-Y: Design and evaluation of radiotracers for determination of regional cerebral blood flow with PET. In *Nuclear Medicine and Biology*, Raynaud C, ed. Proceedings of the Third World Congress, Paris, Pergamon Press, 1982, pp 654-657
20. Herscovitch P, Markham J, Raichle ME: Brain blood flow measured with intravenous $H_2{}^{15}O$. I. Theory and error analysis. *J Nucl Med* 24:782-789, 1983
21. Lambrecht RM, Rescigno A: Re: Brain blood-flow measurement with bolus intravenous $H_2{}^{15}O$. *J Nucl Med* 25:729-730, 1984
22. Herscovitch P, Mintun MA, Raichle ME: Reply. *J Nucl Med* 25:730-732, 1984
23. Kuhl DE, Barrio JR, Huang SC, et al: Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]Iodoamphetamine (IMP) tomography. *J Nucl Med* 23:196-203, 1982
24. Turton DR, Brady F, Pike VW, et al: Preparation of human serum [methyl-^{11}C]methylalbumin microspheres and human serum [methyl-^{11}C]methylalbumin for clinical use. *Int J Appl Radiat Isot* 35:337-344, 1984
25. Cooper AJL, McDonald JM, Gelbard AS, et al: The metabolic fate of ^{13}N-labeled ammonia in rat brain. *J Biol Chem* 254:4982-4992, 1979
26. Phelps ME, Huang SC, Hoffman EJ, et al: Cerebral extraction blood flow and capillary permeability-surface area product. *Stroke* 12:607-619, 1981
27. Sargent T, Kalbhen DA, Shulgin AT, et al: In vivo human pharmacodynamics of the psychodysleptic 4-Br-2,5-dimethoxyphenylisopropylamine labeled with ^{82}Br or ^{77}Br. *Neuropharmacology* 14:165-174, 1975
28. Braun U, Shulgin AT, Braun G, et al: Synthesis and body distribution of several iodine-131 labeled centrally acting drugs. *J Med Chem* 20:1543-1546, 1977
29. Winchell HS, Baldwin RM, Lin TH: Development of I-123-labeled amines for brain studies: localization of I-123 iodophenyl alkylamines in rat brain. *J Nucl Med* 21:940-946, 1980
30. Hill TC, Holman BL, Lovett R, et al: Initial experience with SPECT (single-photon computerized tomography) of the brain using N-isopropyl I-123 p-iodoamphetamine: Concise communication. *J Nucl Med* 23:191-195, 1982
31. Lee RGL, Hill TC, Holman BL, et al: Predictive value of perfusion defect size using N-isopropyl-(I-123)-p-iodoamphetamine emission tomography in acute stroke. *J Neurosurg* 61:449-452, 1984
32. Kung HF, Tramposch KM, Blau M: A new brain perfusion agent: [I-123] HIPDM: N,N,N′-trimethyl-N′[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine. *J Nucl Med* 24:66-72, 1983
33. Fazio F, Lenzi GL, Gerundini P, et al: Tomographic assessment of regional cerebral perfusion using intravenous I-123 HIPDM and a rotating gamma camera. *J Computer Assist Tomogr* 8:911-921, 1984
34. Kearfott KJ: Absorbed dose estimates for positron emission tomography (PET): $C^{15}O$, ^{11}CO, and $CO^{15}O$. *J Nucl Med* 23:1031-1037, 1982
35. Mathis CA, Lagunas-Solar MC, Sargent III T, Yano Y, Vuletich A, Harris LJ: A ^{122}Xe-^{122}I generator for remote radio-iodinations. *Int J Appl Radiat Isotopes:* in press
36. Sargent III T, Budinger TF, Braun G, et al: An iodinated catecholamine congener for brain imaging and metabolic studies. *J Nucl Med* 19:71-76, 1978
37. MIRD Dose-Estimate Report No 5: Summary of current radiation dose estimates to humans from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I and ^{132}I as sodium iodide. *J Nucl Med* 16:857-860, 1975
38. Raichle ME, Eichling JO, Straatman MG, et al: Blood-brain barrier permeability of ^{11}C-labeled alcohols and ^{15}O-labeled water. *Am J Physiol* 230:543-552, 1976
39. Lucignani G, Nehlig A, Blasberg R, et al: Metabolic and kinetic considerations in the use of (I-125) HIPDM as a tracer for quantitative measurement of regional cerebral blood flow. *J Cerebr Blood Flow Metab* 5:86-96, 1985