RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Synthesis and Biodistribution of Neutral Lipid-Soluble Tc-99m Complexes that Cross the Blood-Brain Barrier

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Three Tc-99m-labeled neutral 1,2-dithia-5,8-diazacyclodecane (BAT) chelates that are capable of crossing the blood-brain barrier (BBB) were prepared and evaluated. Biodistribution (i.v.) in rats showed a significant brain uptake (1–3%/whole brain) at 2 min. At 15 min the uptake dropped to about a tenth of the original level, indicating free passage in both directions across the BBB. Gamma camera images of a monkey confirmed the high initial brain uptake. This group of Tc-99m BAT compounds clearly exhibited in vivo stability and the ability to cross the BBB after an i.v. injection. Derivatives containing tertiary amine groups should have prolonged brain retention and might be suitable for SPECT studies of brain perfusion.

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Brain-perfusion imaging with single-photon emission computerized tomography (SPECT) requires new radiopharmaceuticals that can cross the blood-brain barrier (BBB) and will maintain a fixed brain distribution pattern reflecting regional perfusion. Recently we reported a group of Se-75- and I-123-labeled tertiary diamines (*1–4*) that showed the desired properties. These diamines, which are neutral and lipid-soluble at blood pH (7.4), can diffuse freely across the BBB. In brain tissue, where the pH is lower (7.0), the diamines combine with hydrogen ions and become positively charged. In this form the molecules are no longer lipid-soluble and are temporarily "trapped" because they cannot diffuse out. One of the I-123-labeled diamines, HIPDM (N,N,N′-trimethyl-N′-[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine), is currently under clinical trial. A monoamine, IMP (N-isopropyl-*p*-[^{123}I]iodoamphetamine), developed earlier, also has high brain uptake (*5,6*), and several recent reports have validated qualitatively and quantitatively the clinical usefulness of this monoamine as an indicator of local cerebral blood flow (*7–9*).

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In the past few years, the need for Tc-99m-labeled, lipid-soluble, brain-imaging agents has been recognized (*10–13*). Loberg (*10,13*) and Oldendorf (*11,12*) proposed a new class of Tc-99m radiopharmaceuticals that would be sufficiently lipid-soluble to penetrate the intact BBB and have prolonged retention for brain-perfusion imaging. Our approach to this problem is to prepare a neutral stable complex of Tc-99m with suitable physical and biological properties (such as stability, lipid-solubility, etc). The ligand can then be modified by adding one or more extra amino groups to provide brain retention. This paper presents preliminary data on the stable lipid-soluble Tc-99m complexes. Amine derivatives of these compounds have not yet been prepared or evaluated.

Lipophilic Tc-99m compounds have been reported with ligands such as aminoethanethiol (*14*), long-chain alkyl derivatives of carbamoylmethyliminodiacetate, oxines (*13*), N,N′-diesters of EDTA and DTPA (*15*), tropolone (*16*), 2,4-pentanedione (*17*), and bis-aminoethanol (*18*). None of these Tc-99m-labeled chelates, however, was reported to show significant brain uptake after i.v. injection (*13,14*). This may be due to high protein binding (*13*) or poor in vivo stability.

Several tetradentate ligands based on bis-aminoethanethiol (BAT) chelating groups have been reported

(*19–23*). One of the tetramethyl-substituted ligands, 3,3,6,6-tetramethyl-1,2-dithia-5,8-diazacyclodecane (BAT-TM) has been synthesized (*20*) and the Tc-99m BAT complex was shown to be neutral and lipid-soluble (*19,23*), but its biodistribution has not been studied.

This ten-member ring heterocycle (1,2-dithia-5,8-diazacyclodecane, BAT) was chosen as the backbone of the ligand system for chelating reduced Tc. A series of BAT neutral chelates labeled with Tc-99m was synthesized. This paper reports studies on three of these complexes. The biodistribution was measured in rats with 4-[^{125}I]iodoantipyrine (*24*), a freely diffusible tracer, as the internal reference.

EXPERIMENTAL

Melting points were determined on a Nalge hot stage and are reported uncorrected. Elemental analyses were performed commercially and all values are within ±0.4% of theoretical numbers. NMR spectra were recorded, taken in either deuterated chloroform or dimethyl sulfoxide, with tetramethylsilane as the internal standard. Infrared spectra were determined as KBr pellets. Spectral properties were consistent with the proposed structures. Radioactivity was determined using a dual-channel automatic gamma counter. High-performance liquid chromatography (HPLC) was done on a Hamilton PRP-1 reverse-phase column* eluted with acetonitrile/water (85:15).

Preparation of 2,2-dithio-bis(2-methylpropanal). This compound was prepared according to a reported method (*20,21*) with slight modification. Isobutyraldehyde (72 g, 1 mole) in 250 ml of carbon tetrachloride was heated at 55°C under nitrogen, and S_2Cl_2 was added dropwise at a speed that kept the development of hydrogen chloride under control. Upon the completion of addition, the residual hydrogen chloride was eliminated by bubbling nitrogen through the solution. The reaction mixture was condensed and distilled under vacuum to give the product (60–70 g, bp 96–100°C/0.4 Torr, lit. [*21*] bp 92–93°C/0.3 Torr) with yield 45–52%.

Preparation of 2,2′-dithio-bis(2-ethylbutanal). This compound was prepared by a similar procedure. The product precipitated from the crude mixture was crystallized from carbon tetrachloride and methylene chloride (yield 20–30%). Recrystallization from benzene-hexane gave a pure product, mp 58–59°C. IR —CHO, 1720 cm^{-1}; NMR($CDCl_3$) δ 0.9 (t, 12H, J=8Hz), 1.67 (m, 8H), 8.70 (s, 2H). Elemental analysis $C_{12}H_{22}S_2O_2$; theory C: 54.92, H: 8.45; found C: 54.98, H: 8.54.

Preparation of 3,3,6,6-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene. This compound was prepared according to a reported method (*20,21*) with slight modification. Ethylene diamine (12 ml, 160 mmol) was added to an abs. ethanol solution (50 ml) of 2,2′-dithio-bis-(2-methylpropanal) (10.3 g, 50 mmol). The mixture was heated gently on a hot plate at the boiling point for 0.5 hr. A precipitate appeared and the mixture was kept at room temperature overnight (18 hr). The product was filtered (10 g) and an additional 0.6 g of product was recovered from the mother liquor (yield 92%). The product was recrystallized from ethyl acetate (mp 164–166°C, lit. [20] mp 162–164°C).

Preparation of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene. A mixture of 2,2′-dithio-bis(2-methylpropanal) (6.6 g, 32 mmol) and 2-methyl-1,2-propanediamine (2.9 g, 33 mmol) in 10 ml of ethanol was heated on a hot plate for 0.5 hr. Upon standing overnight at 0°C, heavy crystals were formed (6.1 g, yield 72%). The analytical sample was recrystallized from ethyl acetate (mp 85–86°C). IR —C=N—, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (m, 18H), 3.41 (q, 2H, J_1 = 31.5 Hz, J_2 = 9Hz), 7.49, (m, 2H). Elemental analysis $C_{12}H_{22}N_2S_2$; theory C: 55.77, H: 8.58, N: 10.84; found C: 55.89, H: 8.80, N: 10.88.

Preparation of 3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene. A mixture of 2,2′dithio-bis(2-ethylbutanal) (3 g, 12 mmol) and ethylenediamine (0.8 g, 16 mmol) in 10 ml of ethanol was heated at the boiling point for 0.5 hr. The product precipitated on standing (1.7 g, yield 55%). The sample for analysis was recrystallized from ethyl acetate (mp 85–86°C). IR—C=N—, 1640 cm^{-1}; NMR ($CDCl_3$), δ 0.87 (t, 12 H, J = 8 Hz), 2.80 (m, 8 H), 3.79 (q, 4 H, J_1 = 32 Hz, J_2 = 6 Hz), 6.83 (s, 2 H). Elemental Analysis $C_{14}H_{26}N_2S_2$; theory C: 58.69 H: 9.15 N: 9.78; found C: 58.67, H: 9.47, N: 9.76.

Preparation of 3,3,6,6-tetramethyl-1,2-dithia-5,8-diazacyclodecane hydrochloride (TM). Sodium borohydride (4 g, 105 mmol) was added to a suspension of 3,3,6,6-tetramethyl-1,2-dithio-5,8-diazacylcodeca-4,8-diene (4 g, 17 mmol) in 50 ml of ethanol. The solution was stirred at room temperature for 18 hr, then heated on a hot plate at the boiling point for 0.5 hr. The solution was treated with an equal volume of water, extracted with methylene chloride (3 × 50 ml). The organic extracts were combined and condensed. The residue was redissolved in ethanol and treated with dry HCl gas. The precipitate was collected to give 4 g of product (yield 76%). The salt was recrystallized from methanol; mp >220°C, lit. (20) mp 255–256°C.

Preparation of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane hydrochloride (BAT-HM). Sodium borohydride (2 g, 53 mmol) was added to a solution of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecadiene (3 g, 12.3 mmol) in 50 ml of ethanol. The mixture was stirred at room temperature for 18 hr. After extracting the product with methylene chloride and condensing the organic extracts, the desired product was precipitated from an ethanolic solution by bubbling HCl gas through the solution. Recrystallization from abs. methanol gave 2.1 g of pure product (yield 51%); mp

232-233°C, NMR (DMSO-d_6) δ 1.30 (m, 18H), 2.97 (m, 4H), 4.33 (broad, 6H). Elemental analysis $C_{12}H_{28}N_2S_2Cl_2$; theory C: 42.97, H: 8.42, N: 8.35, S: 19.12; found C: 43.10, H: 8.40, N: 8.26, S: 19.28.

Preparation of 3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodecane hydrochloride (BAT-TE). 3,3,6,6-Tetraethyl-1,2-dithio-5,8-diazacylcodeca-4,8-diene was reduced by sodium borohydride as above (yield 96%). The product was recrystallized from methanol; mp 225-230°C, NMR (DMSO-d_6) δ 0.87 (m, 12H), 1.53 (m, 8H), 3.17 (m, 8H). Elemental analysis $C_{14}H_{32}N_2S_2Cl_2$; theory C: 46.27, H: 8.88, N: 7.71; found C: 46.07, H: 9.16, N: 7.70.

Radiolabeling. Sodium[^{99m}Tc]pertechnetate (1-10 mCi, 0.3-0.5 ml) was added to a test tube containing the BAT ligand (2-4 mg) and sodium borohydride (15 mg). The mixture was vortexed and kept at room temperature for 0.5 hr. To this solution, 1 ml each of saline and hexane (or hexane-ethyl acetate 50:50) were added. The solution was vortexed and the hexane layer was separated. This extraction process was repeated three times and the combined hexane extracts were dried over anhydrous sodium sulfate. The filtered solution was then condensed to dryness with a stream of nitrogen. The residue was redissolved in abs. ethanol (yields 30-50%).

To label the ligands using Sn(II) as the reducing agent, a stock solution of Sn(II)/PPi was prepared by mixing 25 mg of sodium pyrophosphate and 0.25 ml of stannous chloride solution ($SnCl_2 \cdot 2H_2O$, 10 mg/ml of 0.1*N* HCl) in 25 ml of water. A mixture of BAT ligand (2-4 mg) and sodium [Tc-99m]pertechnetate and 0.1-1.0 ml of the stock solution was heated in a water bath at 80°C for 15 min. The rest of the procedure was the same as described above. The yields were similar: 30-50%.

Animal distribution study. Sprague-Dawley male rats (220-300 g) under halothane anesthesia were injected intravenously with 0.2 ml of a saline/ethanol (1:1) solution containing 0.5-20 μCi of the Tc-99m BAT compound and 0.5-5 μCi of I-125 IAP. At different periods after the i.v. injection, rats were killed by cardiectomy. The organs of interest were excised, weighed, and counted in a dual-channel automatic gamma counter.

The % dose/organ was determined by comparison of tissue radioactivity levels with suitably diluted aliquots of the injected dose. The spillover counts into each window were corrected by a computer program. The approximate % dose/g of wet tissue can be calculated by dividing the % dose/organ by the mean organ weight (mean weights: heart 0.85 g, brain 1.65 g, blood 18 g, liver 9 g, kidneys 1.9 g, lungs 1.6 g). The brain-to-blood concentration ratio was calculated from the % dose/gram of wet tissue.

A monkey was sedated with ketamine (10 mg) and then anesthesized with pentobarbital. For the imaging studies, a dose of 5 mCi of Tc-99m BAT-HM was injected intravenously. Immediately after the injection, images (1 min per frame) were collected and stored in a computer. The brain area was flagged and the total net count in this area was plotted against time. Static imaging was obtained by adding the frames from 1 min to 5 min.

Partition coefficients. The partition coefficient was measured by mixing the Tc-99m BAT compound with 3 g each of 1-octanol and buffer (pH 7.0 or 7.4, 0.1*M* phosphate) in a test tube. The tube was vortexed 3 min at room temperature and then centrifuged for 5 min. Two weighed samples (0.5 g each) from the 1-octanol and buffer layers were counted in a well counter. The partition coefficient was determined by calculating the ratio of cpm/g of octanol to that of buffer. Samples from the octanol layer were repartitioned until consistent partition coefficient values were obtained. Usually the measurement was repeated three times.

Protein binding. The binding of the Tc-99m BAT compounds to human serum proteins was determined by equilibrium dialysis. Human serum (0.4 ml, pooled) and 0.4 ml of phosphate buffer (0.15 *M*, pH 7.4) containing the test compound (0.025 μCi) were separated by a dialysis membrane†. The dialysis cells were rotated in a water bath at 37°C for 18 hr. At the end of the incubation, aliquots from both sides were weighed and counted. The percentage free of protein binding was determined by calculating the radioactivity concentration ratio of buffer to serum, multiplied by 100. To determine possible membrane binding, the membrane was counted at the end of the experiment. Usually less than 5% of the original activity was found on the membrane.

Autoradiography. Under halothane anesthesia, male Sprague-Dawley rats (200-300 g) were injected intravenously with 0.2 ml of a solution containing 50 mCi of Tc-99m HM. At 1 or 15 min after injection, the rats were killed under halothane anesthesia. The brain was removed and the radioactivity measured. After freezing at −25°C in embedding medium, 20-μ sections were cut with a cryostat microtome maintained at −15°C to −20°C. Each section was mounted on a glass slide and air-dried. Autoradiograms were made with Kodak film (NMB). After overnight exposure, the films were developed.

Electrophoresis. Cellulose electrophoresis strips were soaked in 0.005 *M* phosphate buffer (pH 7.0) for at least 30 min before spotting the sample. The strips were placed in a electrophoresis chamber containing 200 ml of 0.005 *M* phosphate buffer (pH 7.0) and the sample was spotted. The strips were run at 350 V for 5 min. After drying, the strips were cut and counted.

RESULTS

Chemistry. The BAT ligands were prepared by condensing substituted aldehydes with diamines to give di-

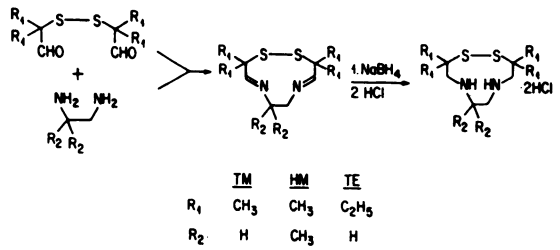

FIG. 1. Preparation of BAT ligands.

imines. These were readily reduced by sodium borohydride in ethanol (Fig. 1). The reaction scheme is the same as that reported by Kramer et al. (*18*).

Labeling of the BATs was achieved by reducing pertechnetate with either sodium borohydride or Sn(II)-PPi in ethanol. The lipid-soluble Tc-99m BAT complexes were separated by extraction with hexane (yield 30–50%) after condensing the hexane solution, the compounds were dissolved in ethanol. The purity was checked by HPLC using a Hamilton PRP-1 reverse-phase column (acetonitrile/water, 85:15) and usually was over 95% pure.

The electrophoresis of the Tc-99m BAT complexes and pertechnetate showed that the neutral complexes stayed at the origin while the charged pertechnetate moved toward the anode, as expected (Fig. 2). Since very lipid-soluble materials may be bound at the origin, the lack of mobility does not definitively prove neutrality, but it is a strong indication that the complex is uncharged.

These BAT complexes are very lipid-soluble, with partition coefficients (P.C.) of 80 to 541. As expected, the partition coefficients at pH 7.0 and at pH 7.4 are essentially the same (Table 3).

Based on the data presented by Epps, et al. (18), the most likely structure of the Tc(V)-BAT complexes is shown in Fig. 3.

Biodistribution. *Rats.* To avoid individual animal differences due to weight, perfusion, anesthesia, etc.,

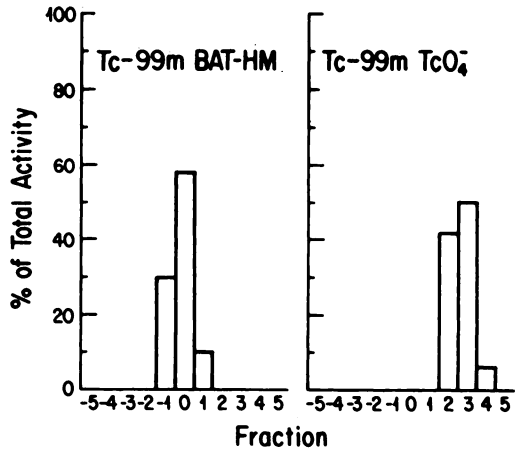

FIG. 2. Electrophoresis of Tc-99m BAT-HM and pertechnetate.

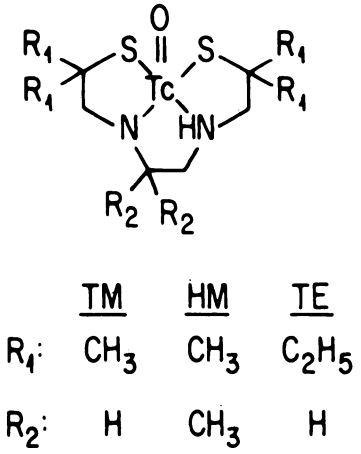

FIG. 3. Chemical structures for Tc-99m BAT complexes.

biodistribution of the lipid-soluble Tc-99m BAT complexes was evaluated in rats with 4-[^{125}I]iodoantipyrine (IAP) as the internal reference.

Two minutes after an i.v. injection, both I-125 IAP and the Tc-99m BAT complexes distributed throughout the body with a pattern similar to that of the cardiac output (*24*). A typical biodistribution study is shown in Table 1; the other BAT complexes gave similar results.

Total brain uptakes for the Tc-99m BAT complexes with TM, HM, and TE were 1.96, 2.77, and 2.92 % dose, respectively (Table 2). The brain uptake value was very close to that of I-123-labeled brain imaging agents, such as IMP and HIPDM. The brain uptakes for IMP and HIPDM at 2 min are 2.64 and 2.74 % dose, respectively (*4*).

The brain-to-blood ratio at 2 min for all BAT complexes was >1, demonstrating that the Tc-99m BAT compounds diffuse rapidly across the BBB. At 2 min the brain ratios for Tc-99m BAT complex to I-125 IAP were 1.58, 1.54, and 1.92 for TM, HM, and TE, respectively.

As expected, the Tc-99m BAT compounds showed little brain retention. At 15 min, the brain activity drops to about 1/10 of the original level: 0.26, 0.26, and 0.34 % dose for TM, HM, and TE, respectively. This indicates that the diffusion across the BBB is a reversible process; the Tc-99m BAT compounds move freely in and out of the brain.

The brain uptake of these Tc-99m BAT compounds is not affected by protein binding as measured by equilibrium dialysis. Compound TE, with the highest brain uptake, showed the highest protein binding: only 17% free (Table 3). The uptake in brain is more related to dynamic aspects of protein binding rather than equilibrium measurements.

Monkey. External imaging of a monkey showed that activity in brain increased sharply immediately after the intravenous injection of 5mCi of BAT-HM. Within 3

TABLE 1. BIODISTRIBUTION OF Tc-99m BAT-HM AND I-125 IAP IN RATS

Organ	%, Dose/Organ (Average of rats, and range) Tc-99m BAT-HM 2-min	Tc-99m BAT-HM 15-min	I-125 IAP 2-min	I-125 IAP 15-min
Blood	16.3 (13.3–21.0)	6.78 (6.22–7.51)	20.6 (16.9–24.3)	11.8 (10.7–12.3)
Muscle	6.14 (3.95–8.67)	15.16 (13.2–16.4)	9.35 (5.82–12.4)	26.8 (24.0–30.3)
Heart	2.90 (2.11–3.55)	0.32 (0.30–0.35)	1.60 (1.50–2.04)	0.41 (0.35–0.48)
Lungs (2)	4.05 (2.04–7.47)	0.86 (0.63–1.01)	2.45 (1.56–3.91)	0.90 (0.81–1.01)
Spleen	0.52 (0.33–0.62)	0.17 (0.14–0.20)	0.53 (0.36–0.66)	0.22 (0.22–0.23)
Kidneys (2)	4.78 (4.08–5.50)	1.95 (1.74–2.17)	2.95 (2.58–3.29)	1.64 (1.35–2.12)
Liver	12.3 (12.0–12.3)	22.0 (19.1–25.4)	15.9 (15.4–16.7)	7.29 (6.81–8.25)
Skin	8.60 (8.02–8.97)	11.7 (10.5–12.7)	10.3 (9.40–10.9)	18.3 (17.1–19.0)
Thyroid	0.17 (0.16–0.18)	0.03 (0.03–0.04)	0.17 (0.16–0.18)	0.18 (0.11–0.22)
Brain	2.77 (2.62–2.84)	0.26 (0.23–0.32)	1.79 (1.45–2.02)	0.42 (0.36–0.52)
Brain/Blood* ratio	1.86	0.42	0.95	0.39
Tc99m/I-125 Brain ratio	1.54 (1.40–1.81)	0.61 (0.54–0.65)		

* $\frac{\text{Brain \% dose/gram}}{\text{Blood \% dose/gram}}$.

min the brain uptake reaches its maximum (Fig. 4). The continued gradual decrease in brain activity demonstrated that the lipid-soluble Tc-99m complexes diffused out of the brain. The washout curve could be fitted with two components, $y = 52949\, e^{-0.069t} + 9152\, e^{-0.014t}$; $t_{1/2}$ (biological) = 10.32 min and 57.11 min, respectively.

The static image of this monkey 0–5 min after the i.v. injection clearly showed that the activity concentrated in brain, heart, and liver (Fig. 5).

Autoradiography. The regional distribution for one

TABLE 2. BRAIN UPTAKE OF Tc-99m BAT COMPLEXES (AVERAGE OF 3 RATS, AND RANGE)

	Tc-99m BAT-TM 2 min	Tc-99m BAT-TM 15 min	Tc-99m BAT-HM 2 min	Tc-99m BAT-HM 15 min	Tc-99m BAT-TE 2 min	Tc-99m BAT-TE 15 min
Brain (% dose/gram)	1.96 (1.82–2.11)	0.26 (0.18–0.33)	2.77 (2.62–2.84)	0.26 (0.23–0.32)	2.92 (2.62–3.44)	0.34 (0.29–0.39)
Brain/Blood* ratio	1.17	0.38	1.86	0.42	2.09	0.67
Tc99m/I-125† Brain ratio	1.58 (1.51–1.68)	0.64 (0.54–0.71)	1.54 (1.40–1.81)	0.61 (0.54–0.65)	1.92 (1.82–2.04)	0.78 (0.75–0.80)

* $\frac{\text{Brain \% dose/gram}}{\text{Blood \% dose/gram}}$.

† $\frac{\text{\% Dose of Tc-99m compound in brain}}{\text{\% Dose of I-125 IAP in brain}}$.

TABLE 3. PARTITION COEFFICIENT AND PROTEIN BINDING OF Tc-99m BAT COMPOUNDS

Compound	Partition coefficient pH = 7.0	Partition coefficient pH = 7.4	Protein binding (% free)
TM	82 ± 4	81 ± 9	40.7 ± 0.9
HM	212 ± 11	206 ± 8	30.2 ± 0.7
TE	541 ± 8	491 ± 11	16.9 ± 0.6

of the Tc-99m BAT compounds, BAT-HM, was evaluated using autoradiography. At 2 min after i.v. injection, a typical regional blood-perfusion pattern for the diffusible tracer was obtained (Fig. 6). The regional distribution pattern is very similar to those of IMP (*8*) and HIPDM (*4*): high in gray matter and low in white. At 15 min the autoradiograms, however, showed no regional concentration, reflecting the free diffusion across the BBB in both directions. Similar autoradiographic results have been reported for C-14-labeled antipyrine by Sokoloff et al. (*25*).

DISCUSSION

The biodistribution of Tc-99m BAT complexes has demonstrated that it is possible to prepare a neutral and lipid-soluble Tc-99m compound that crosses the BBB. In order for the Tc-99m BAT complexes to be useful as brain imaging agents—especially for SPECT, which requires longer imaging time—the retention time in the brain has to be increased. To improve brain retention, we intend to use the "pH shift" mechanism, which has been applied successfully in preparing other brain-imaging agents such as I-123 HIPDM. Monoamine and diamine derivatives of the BAT ligand will be synthesized. After labeling with Tc-99m, they may show high brain uptake and prolonged retention. This approach is currently under study in our laboratory.

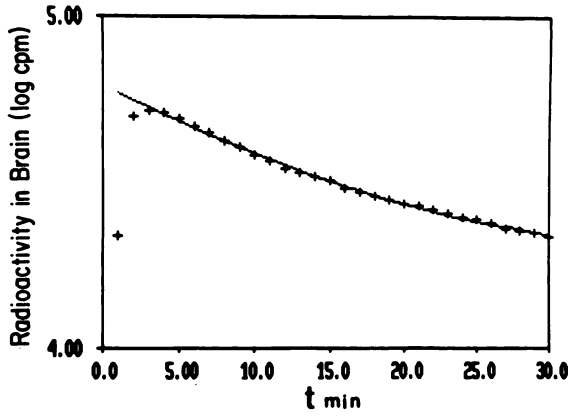

FIG. 4. Brain uptake and washout curve of Tc-99m BAT-HM in monkey after i.v. injection. Washout curve shows two components, 85% with $t_{1/2}$ = 10 min and 15% with $t_{1/2}$ = 57 min.

FIG. 5. Lateral view of monkey 0–5 min after injection with 5 mCi of Tc-99m BAT-HM. Brain, liver, and heart are visible.

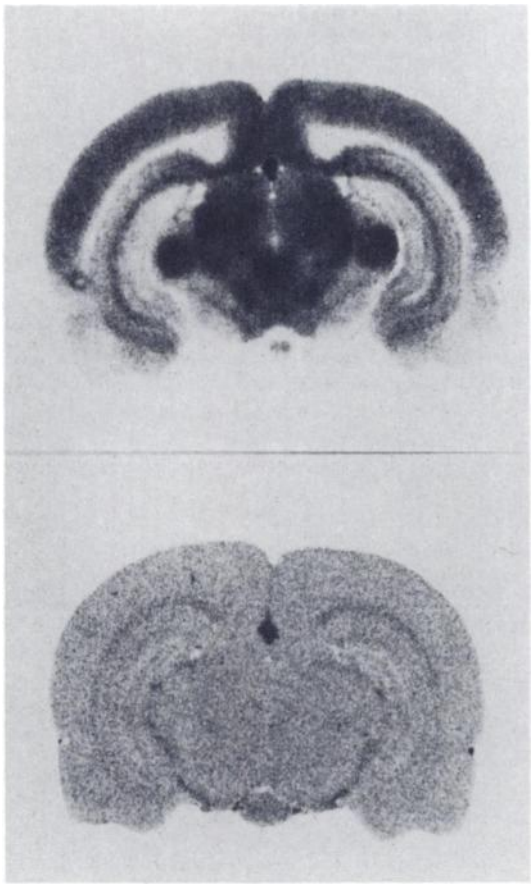

FIG. 6. Autoradiograms of rat brain sections, excised at 1 min (top) and 15 min (bottom) after i.v. injection of Tc-99m BAT-HM (~50 mCi).

In summary, three Tc-99m-labeled neutral lipid-soluble chelates are presented. This group of Tc-99m BAT compounds clearly showed in vivo stability and the ability to cross the BBB after an i.v. injection. Derivatives containing tertiary amine groups should have prolonged brain retention and might be suitable for SPECT studies of brain perfusion.

FOOTNOTES

* Varian.
† Fisher Scientific Company.

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