N-[^{11}C-Methyl]Chlorphentermine and N,N-[^{11}C-Dimethyl]Chlorphentermine as Brain Blood-Flow Agents for Positron Emission Tomography

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N-[^{11}C-methyl]chlorphentermine ([^{11}C]NMCP) and N,N-[^{11}C-dimethyl]chlorphentermine ([^{11}C]NDMCP) were prepared from chlorphentermine and $^{11}CH_3I$ in DMF and evaluated in rats as brain blood-flow agents for positron emission tomography (PET). Tissue distribution of [^{11}C]NMCP showed that brain uptake was 2.70 ± 0.40% of injected dose per organ at 5 min with no change in radioactivity concentration up to 30 min after i.v. injection. Approximately 80% of the initial brain uptake remained at 60 min. On the other hand, initial brain uptake of [^{11}C]NDMCP (3.66 ± 0.31 and 3.63 ± 0.88% injected dose per organ at 5 and 15 min, respectively) was greater than that of [^{11}C]NMCP. The brain activity however, rapidly decreased to 2.38 ± 0.17 and 1.82 ± 0.32% at 30 and 60 min, respectively. Because of its longer retention in the brain compared with [^{11}C]NDMCP, [^{11}C]NMCP would be a potential brain blood-flow agent for quantitative PET studies.

J Nucl Med 27:532–537, 1986

Many brain diseases are characterized by changes in regional perfusion and metabolic patterns. Regional cerebral blood flow (rCBF) can be estimated by several imaging techniques (*1*). Despite the question of effectiveness and the complexity of the technique, the application of positron emission tomography (PET) to the measurement of rCBF would be a most valuable research and diagnostic tool. Several positron-labeled radiopharmaceuticals have been suggested for the measurement of rCBF; to date, however, no completely satisfactory technique has been developed (*2*).

Clinical evaluation of iodine-123 (^{123}I) labeled IMP using single photon emission computed tomography (SPECT) has shown the usefulness of this agent in the measurement of rCBF (*3,4*). We have recently developed a new brain blood-flow agent [^{131}I]iodophentermine (IP), based on the structure of phentermine, which showed good brain uptake (2.3% injected dose/organ) and prolonged activity retention in rats (*5*). A major advantage of using p-halo substituted phentermine analogs is the high level of unchanged compound in the brain, due to blockage of both parahydroxylation and deamination metabolic pathways (*6–8*). The anorectic drug, chlorphentermine (CP), has demonstrated these favorable characteristics in several studies including one using autoradiographic techniques to investigate tissue distribution (*9*). We report here the preparation and in vivo evaluation of the N-[^{11}C-methyl] analogs of chlorphentermine as possible brain blood-flow agents for PET studies.

Received June 19, 1985; revision accepted Dec. 11, 1985.

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MATERIALS AND METHODS

General Procedures

Melting points were determined on a capillary melting point apparatus* and are uncorrected. Elemental analysis was performed commercially† and all values are within ±0.4% of theoretic values. Proton nuclear magnetic resonance (NMR) spectra were assayed on a 60 MHz spectrometer‡ and the chemical shifts are reported relative to an internal tetramethylsilane standard. The radioactivity in the tissue samples was determined in an automatic gamma counter§. High pressure liquid chromatography (HPLC)¶ was carried out on an ion-exchange resin column**. Separation was monitored with both a uv detector and a NaI radioactive detector.

Flash chromatography was performed with silica gel[††] (230–400 mesh). All thin layer chromatography (TLC) analyses were done on silica gel 60 F254[‡‡] (aluminum sheet) and visualized by quenching of the 254 nm fluorescence.

Synthesis of Chlorphentermine, *N*-Methyl Chlorphentermine and *N,N*-Dimethylchlorphentermine (Scheme 1)

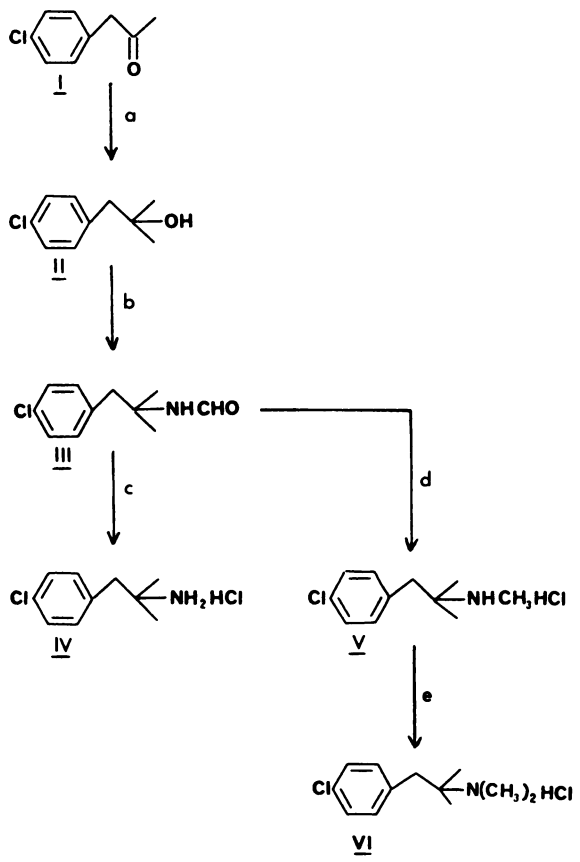
1-(p-Chlorophenyl)-2-methyl-2-propanol (II). To a solution of p-chlorophenylacetone[§§] (I) (5 g, 29.7 mmol) and 20 ml of dry ether, methyl magnesium bromide[§§] in ether (10 ml of a 3.2*M* solution, 32 mmol) was added dropwise. After completion of the addition, the mixture was heated and refluxed gently for 3 hr and stirring was continued overnight at ambient temperature. The reaction mixture was quenched with 30% NH_4Cl solution and extracted with ether. The organic phase was washed with water and brine. It was then dried over Na_2SO_4, filtered, and evaporated to dryness. The pale yellow oil (5.0 g, 27.1 mmol) was then purified by flash chromatography ($CHCl_3$) to yield 4.2 g of the product (76.6% yield). Boiling point 68–70°C/0.125 mmHg, (b.p.$_{lit.}$ 115–118°C/3 mmHg (*10*)). TLC ($CHCl_3$): Rf = 0.34; NMR ($CDCl_3$: δ(ppm) 1.10 (s, 6H), 1.65 (s, 1H), 2.80 (s, 2H), 7.45 (AB, 4H, J = 8Hz).

N-Formyl-1-(p-chlorophenyl)-2-methyl-2-propylamine (III). To a suspension of NaCN (1.03 g, 21 mmol) in 5 ml of glacial acetic acid, a mixture of 5 ml of glacial acetic acid and 3.5 ml of concentrated H_2SO_4 was added, followed by the tertiary alcohol (II) (3.54 g, 19.2 mmol). The reaction mixture was heated at 70°C for 2 hr, cooled to room temperature and poured onto ice water (200 ml). It was then basified by adding solid Na_2CO_3 and extracted with ether. The organic layer was washed with 1 N NaOH, H_2O, and brine. The solution was dried over Na_2SO_4, filtered, and evaporated to dryness. The yellow oil was then purified by flash chromatography (MeOH:$CHCl_3$, 3:97, v/v) to yield 1.2 g (5.67 mmol) of the product (III) (30% yield). Melting point 60–63°C, (b.p.$_{lit.}$ 163–165°C/4 mmHg (*10*)). TLC (MeOH:$CHCl_3$, 3:97, v/v):Rf = 0.27; NMR ($CDCl_3$): δ(ppm) 1.45 (s, 6H), 2.85 and 3.20 (s, 3H), 7.50 (AB, 4H, J = 8Hz), 8.5 (m, 1H).

1-(p-Chlorophenyl)-2-methyl-2-propylamine HCl (IV). The N-formyl derivative (III) (1.1 g, 5.2 mmol) was dissolved in 10 ml of a mixture of concentrated HCl and EtOH (1:2) and heated for 4 hr at reflux. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under reduced pressure to dryness. The white residue was washed several times with ether, filtered and crystallized from iPrOH to yield 0.9 g (4.1 mmol) of crystalline product (IV) (78.8% yield). Melting point 229–230°C, (mp$_{lit.}$ 222°C (*10*)). TLC (MeOH:$CHCl_3$:NH_4OH, 10:90:1, v/v/v): Rf = 0.3; NMR (free base, $CDCl_3$): δ(ppm) 1.20 (s, 6H) 1.25 (s, 2H), 2.80 (s, 2H), 7.50 (AB, 4H, J = 8Hz).

N-methyl-1-(p-chlorophenyl)-2-methyl-2-propylamine HCl (V). The N-formyl derivative (III) (0.42 g, 2 mmol) was dissolved in 5 ml of dry THF, and a THF solution of lithium aluminum hydride[§§] (3 mmol) was added. The reaction mixture was then heated at reflux for 3 hr. The solution was quenched with H_2O and 10% NaOH in an ice-water bath, filtered and extracted with ether. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered. The solution was evaporated to dryness to yield 0.22 g (1.1 mmol) IV (56% yield). TLC (MeOH:$CHCl_3$:NH_4OH,10:90:1, v/v): RF = 0.29. The HCl salt V obtained by adding a methanol solution of HCl gas was crystallized from iPrOH. Melting point 185–188°C, (mp$_{lit.}$ 181–183°C (*11*)). NMR ($CDCl_3$, free base): δ(ppm) 1.05 (s, 6H), 1.10 (s, 1H), 2.40 (s, 3H), 2.70 (s, 2H), 7.40 (AB, 4H, J = 8Hz). Elemental analysis C H N.

N,N-dimethyl-1-(p-chlorophenyl)-2-methyl-2-propylamine HCl (VI). Methyliodide (0.14 g, 1.0 mmol) was added to a mixture of compound V (0.24 g, 1.0 mmol), K_2CO_3 (0.28 g, 2.0 mmol) and 5 ml of CH_3CN. The mixture was stirred at room temperature overnight. The



SCHEME 1
Synthesis of CP and NMCP. a: Methylmagnesium bromide in ether. b: Ritter reaction, NaCN, H_2SO_4 and HOAc. c: Acid hydrolysis. d: Reduction, lithium aluminum hydride (LAH) in THF. e: Methylation with CH_3I in presence of base and chromatographic separation

solvent was evaporated under reduced pressure, and the residue was dissolved in 0.1 N NaOH and extracted with ether (2 × 20 ml). The ether layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The solution was evaporated to dryness to yield 0.150 g of yellowish oil. The free base of the desired compound VI was purified by flash chromatography (MeOH:$CHCl_3$:TEA 10:90:1, v/v). Compound VI was obtained by passing HCl gas into the ether solution of the free base (40 mg, 16% yield). TLC (MeOH:$CHCl_3$:NH_4OH, 10:90:1, v/v/v): Rf = 0.39. mp 206–208°C (dec), ($mp_{lit.}$ 183–185°C as oxalic acid salt (*12*)). NMR ($CDCl_3$, free base): δ(ppm) 1.00 (s, 6H), 2.40 (s, 6H), 2.50 (s, 2H), 7.38 (AB, 4H, J = 8Hz).

Radiolabeling with $^{11}CH_3I$

With slight modifications $^{11}CH_3I$ was produced according to the published procedure (*13*). $^{11}CO_2$ was produced by the nuclear reaction, $^{10}B(d,n)^{11}C$ in the MGH cyclotron and collected in a copper coil that was cooled in liquid nitrogen. It was then transferred into 0.5 ml of a 1*M* solution of lithium aluminum hydride (LAH) in THF under a gentle stream of He. The THF was evaporated by heating and the reaction vial was then evacuated (10 mmHg) for 2 min to remove traces of solvent. $^{11}CH_3I$ was generated by the dropwise addition of 0.5 ml of 57% HI solution to the cooled $AlLi(O^{11}CH_3)_4$ complex. The mixture was heated at 140°C and $^{11}CH_3I$ was distilled through a tube containing $KClO_4$ into the reaction vial containing 3 mg of chlorphentermine (IV) and 0.3 ml of dry DMF at −10°C. The reaction mixture was then heated at 140°C for 5 min with stirring. To the cooled solution was added 1.5 ml of 0.1 N NaOH. The reaction mixture was extracted with ethyl ether (2 × 1.5 ml), and the combined ether layers were evaporated to dryness after adding one drop of 0.1 N HCl.

The residue was dissolved in saline (0.3 ml) and injected into a HPLC system equipped with a 0.2-ml sample loop. The column was eluted with a mixture of 40% 0.05*M* $NH_4H_2PO_4$ (pH 3.0) and 60% EtOH. Two radioactive fractions containing [^{11}C]NMCP and [^{11}C] NDMCP were collected and their radiochemical purity confirmed by the repeated injection of the isolated fractions into the HPLC system. The specific activity of the products was determined by assaying the total radioactivity of the sample in a dose calibrator, and calibrating its mass using a standard curve that plots uv absorbance at 254 nm compared with mass of NMCP or NDMCP.

Biodistribution studies in rats. After purification by HPLC, 0.1-ml aliquots (15–20 μCi) of radioactive solutions were injected into CD Fischer rats (175–225 g) through the tail vein. Rats were killed at 5, 15, 30, and 60 min after injection. Distribution of radioactivity in blood, heart, lung, liver, kidney, muscle, and brain was determined by a NaI(Tl) gamma well-counter, and the results were expressed as % injected dose per gram tissue and % injected dose per organ.

RESULTS AND DISCUSSION

Chlorphentermine HCl (IV) was prepared according to the synthetic route described by Simes (*10*) with the exception of the synthesis of the tertiary alcohol (II) as shown in Scheme 1. Instead of preparing chlorobenzyl magnesium chloride in the first step of the synthesis, II was obtained in high yield from commercially available methyl magnesium bromide[55] and p-chlorophenylacetone[55] (I). The Ritter reaction (14) at 70°C gave the N-formyl intermediate (III) which yielded IV upon acid hydrolysis and V upon reduction with LAH. N,N-dimethylchlorphentermine (VI) was obtained by further methylation of V with methyliodide.

After 30–40 min of bombardment with a 50 μA deuteron beam current, 50–80 mCi of $AlLi(O^{11}CH_3)_4$ complex was obtained. At the end of the distillation (~5–8 min from the EOB) the reaction vial contained 25–40 mCi of $^{11}CH_3I$.

Following radiolabeling, ether extraction and evaporation (30 min from EOB), the residue (6–10 mCi) was dissolved in saline and purified by HPLC (Fig. 1). Carbon-11 NMCP was eluted at a retention time of 5.34 min which corresponds to the retention time of the authentic NMCP (V). The repeated injection of the purified product into the HPLC system confirmed that the radiochemical purity was >99% and free of unreacted $^{11}CH_3I$ and DMF. The specific activity of [^{11}C] NMCP was 7–10 Ci/mmol at the end of the HPLC purification (40 min total synthesis time). Radiochemical yield of the product was 20% based on the activity of the $AlLi(O^{11}CH_3)_4$ complex and decay corrected. Carbon-11 NDMCP was eluted at a retention time of 7.92 min which corresponds to the retention time of the authentic NDMCP (VI). Approximately 25–50% of the total activity in the residue was due to [^{11}C] NDMCP. The specific activity of [^{11}C]NDMCP was ~14–20 Ci/mmol. Radiochemical yield of the product was 10–20%.

The data from tissue distribution studies in rats of both [^{11}C]NMCP and [^{11}C]NDMCP calculated as % injected dose per gram tissue and % injected dose per organ are shown in Tables 1–4. These values were not normalized to a standard body weight. The brain uptake of [^{11}C]NMCP was 2.70 ± 0.40, 2.67 ± 0.31 and 2.67 ± 0.35% ID/organ at 5, 15, and 30 min, respectively, and 80% of the initial activity remained in the brain at 60 min. Analysis of this data showed this difference to be statistically significant ($p<0.001$). Brain-to-blood ratios were 10.8, 15.2, and 13.6 at 5, 15, and 30 min, respectively, and the ratio decreased to 12.2 at 60 min

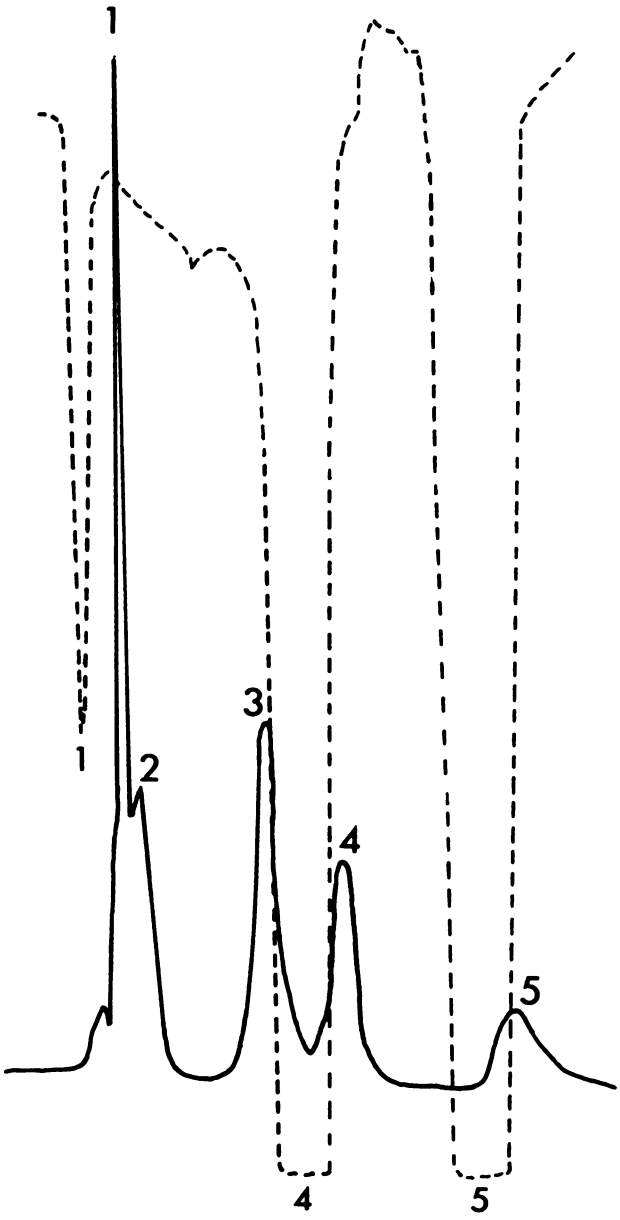


FIGURE 1
HPLC separation of typical reaction mixture, (—) radioactivity detector (NaI) and (—) uv absorbance detector at 254 nm. Residue obtained by ether extraction of reaction mixture was dissolved in saline and injected into HPLC system consisting of cation exchange resin column (4.6 mm × cm) and 0.2 ml sample loop. Flow rate was 2.0 ml/min. Peak 1 (Rt: 1.98 min) $^{11}CH_3I$, Peak 2 (Rt: 2.24 min) DMF, Peak 3 (Rt: 4.18 min) chlorphentermine (VI), Peak 4 (Rt: 5.34 min) [^{11}C]NMCP, and Peak 5 (Rt: 7.92 min) ([^{11}C]NDMCP)

after injection. Among the organs examined, initial uptake of [^{11}C]NMCP was highest in the lung (15.85 ± 2.90% ID/g tissue at 5 min), but cleared rapidly (4.33 ± 0.61% ID/g tissue at 30 min). Uptake in the liver increased slowly while the activity of the lung was continuously decreasing. The lung uptake of [^{11}C]NMCP was ~50% of the values obtained with [^{125}I]IMP and [^{125}I]IP at 30 min (*5,15*). Initial brain uptake of [^{11}C]NDMCP (3.66 ± 0.31 and 3.63 ± 0.88% ID/organ at 5 and 15 min respectively) was greater than that of [^{11}C]NMCP. The brain activity, however, rapidly decreased to 2.38 ± 0.17 and 1.82 ± 0.32% ID/organ at 30 and 60 min, respectively.

The oxidative N-dealkylation reaction catalyzed by the cytochrome P-450 monooxygenase system is commonly observed for many drugs containing the N-alkyl moieties (*16*). McMahon reported that, in general, the maximum rate (V_{max}) of demethylation is greater for tertiary amines than for secondary amines (*17*). This finding was also observed in vitro by Miwa et al. (*18*); during the initial rate conditions (15 min), the N-demethylation of N,N-dimethylphentermine to N-methylphentermine and formaldehyde was seen but no phentermine metabolite was detected under these conditions. Our biodistribution data for [^{11}C]NMCP in rats are in good agreement with the in vitro studies using rat liver microsomes.

The rapid washout which seems to be due to a loss of one of the $^{11}CH_3$ moieties from [^{11}C]NDMCP, coincided with the increased activity in the liver at the 15- and 30-min time periods. After 30 min, the rates of washout of the two compounds appeared to be identical. In general, the ratios of brain-to-blood of [^{11}C] NDMCP were greater than those obtained with [^{11}C] NMCP. For both compounds, the ratios were highest at 15 min (15.2 for [^{11}C]NMCP and 24.8 for [^{11}C] NDMCP). Thus, it appears that both [^{11}C]NMCP and [^{11}C]NDMCP are useful agents for measuring the regional brain blood flow. In particular, the activity of [^{11}C]NMCP was higher than that of radioiodinated IMP and HIPDM (*15,19*) and was completely retained in the brain for a period of 30 min.

The usefulness of [^{123}I]IMP has been demonstrated in the diagnosis of several cerebral diseases (*3,4*), and quantitative measurement of rCBF has been explored by Kuhl et al. using the IMP-SPECT method (*20*). Their study concluded that after i.v. injection, IMP was nearly completely extracted on first pass through the brain, where it was bound in proportion to rCBF. This microsphere-like property of [^{123}I]IMP allows quantitative measurement of rCBF using SPECT. Although the use of IMP presents some problems, such as redistribution phenomena within the brain (*21*), it is a promising radiopharmaceutical for assessing rCBF.

Phentermines are closely related to amphetamine in their molecular structure and pharmacologic characteristics. In addition, the high initial brain uptake and prolonged retention of concentration in the brain suggest that [^{11}C]NMCP would possess the microsphere-like properties that are essential to quantitative measurement of rCBF using PET techniques. Because of the absence of an alpha-hydrogen atom, phentermines are

TABLE 1
Tissue Distribution of [^{11}C]NMCP in Rats*

Tissue	5 min	15 min	30 min	60 min
Blood	0.14 ± 0.03	0.10 ± 0.01	0.11 ± 0.02	0.10 ± 0.05
Heart	1.71 ± 0.37	0.64 ± 0.13	0.48 ± 0.08	0.40 ± 0.05
Lung	15.85 ± 2.90	6.37 ± 1.10	4.33 ± 0.61	3.67 ± 0.57
Liver	0.91 ± 0.21	1.42 ± 0.16	1.84 ± 0.37	1.73 ± 0.31
Kidney	2.19 ± 0.30	1.80 ± 0.37	1.64 ± 0.17	1.37 ± 0.11
Muscle	0.42 ± 0.15	0.43 ± 0.09	0.34 ± 0.06	0.31 ± 0.05
Brain	1.51 ± 0.11	1.52 ± 0.18	1.50 ± 0.13	1.22 ± 0.07
Brain/Blood	13.1	15.2	13.6	12.2

* Values shown represent mean % injected dose/g tissue ± s.d. for n = 6.

TABLE 2
Organ Distribution of [^{11}C]NMCP in Rats*

Tissue	5 min	15 min	30 min	60 min
Blood	1.59 ± 0.27	1.51 ± 0.19	1.70 ± 0.29	1.43 ± 0.29
Heart	1.08 ± 0.25	0.51 ± 0.08	0.36 ± 0.04	0.32 ± 0.10
Lung	17.36 ± 4.06	8.72 ± 1.74	5.89 ± 0.98	4.91 ± 1.46
Liver	5.14 ± 1.10	10.92 ± 0.93	14.02 ± 2.19	12.86 ± 1.69
Kidney	3.02 ± 0.34	3.01 ± 0.68	2.55 ± 0.28	2.20 ± 0.15
Muscle	25.45 ± 7.53	35.41 ± 7.86	28.74 ± 3.94	25.55 ± 4.21
Brain	2.70 ± 0.40	2.67 ± 0.31	2.67 ± 0.35	2.16 ± 0.11

* Values shown represent mean % injected dose/organ ± s.d. for n = 6.

TABLE 3
Tissue Distribution of [^{11}C]NDMCP in Rats*

Tissue	5 min	15 min	30 min	60 min
Blood	0.15 ± 0.03	0.09 ± 0.01	0.08 ± 0.01	0.08 ± 0.03
Heart	1.15 ± 0.13	0.62 ± 0.12	0.38 ± 0.05	0.28 ± 0.06
Lung	9.33 ± 1.79	4.29 ± 0.65	3.53 ± 0.54	2.12 ± 0.64
Liver	0.86 ± 0.15	2.50 ± 0.47	3.59 ± 0.30	4.10 ± 1.56
Kidney	2.70 ± 0.21	1.98 ± 0.39	1.54 ± 0.12	1.40 ± 0.33
Muscle	0.55 ± 0.20	0.50 ± 0.12	0.36 ± 0.07	0.20 ± 0.06
Brain	2.30 ± 0.25	2.23 ± 0.45	1.53 ± 0.15	1.04 ± 0.18
Brain/Blood	15.6	24.8	19.1	13.0

* Values shown represent mean % injected dose/gram tissue ± s.d. for n = 5.

TABLE 4
Organ Distribution of [^{11}C]NDMCP in Rats*

Tissue	5 min	15 min	30 min	60 min
Blood	1.56 ± 0.34	0.90 ± 0.10	0.85 ± 0.11	0.87 ± 0.29
Heart	0.70 ± 0.06	0.33 ± 0.06	0.23 ± 0.03	0.17 ± 0.04
Lung	10.09 ± 2.24	4.90 ± 1.11	4.13 ± 1.28	2.54 ± 0.61
Liver	5.03 ± 0.64	14.63 ± 3.45	21.44 ± 1.96	24.85 ± 7.55
Kidney	3.82 ± 0.20	2.53 ± 0.52	1.98 ± 0.22	1.94 ± 0.50
Muscle	32.77 ± 12.52	29.40 ± 7.14	20.42 ± 3.36	11.81 ± 3.09
Brain	3.66 ± 0.31	3.63 ± 0.88	2.38 ± 0.17	1.82 ± 0.32

* Values shown represent mean % injected dose/organ ± s.d. for n = 5.

not a substrate of monoamine oxidase (MAO), whereas a major metabolic pathway of amphetamine is through deamination by MAO. It has been reported that the chlorphentermine found in the urine of rats was mostly unmetabolized (*6*). The N-demethylation of N-methyl chlorphentermine appear to be very slow, thus, should not affect the concentration of radioactivity in the brain during the time of the study. The slow metabolism of

phentermine derivatives is a major advantage over amphetamines in their use for the quantitative measurement of rCBF, since there would be minimal correction for the presence of extractable metabolites in the blood. In addition, the minimal change in the brain activity would improve the quantitative measurement of rCBF using high resolution images which require a long image collection time. Because of its longer retention in the brain compared with [^{11}C]NDMCP, [^{11}C]NMCP would be a potential agent for studying rCBF using PET.

FOOTNOTES

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† Galbraith Laboratories.

‡ Varian Associates, Inc., (T-60 Spectrometer) Palo Alto, CA.

§ LKB Instruments Inc., Gaithersburg, MD.

¶ LDC Division Milton Roy, Riviera Beach, FL.

** Whatman Chemical Separations, Inc., (Partisil-10 SCx 4.6 mm IDx 25 cmL) Clifton, NJ.

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§§ Aldrich Chemical Company, Milwaukee, WI.

ACKNOWLEDGMENTS

The authors thank J. Garneau, K. Anderton, W. Bucelewicz, and L. Beagle for excellent technical assistance. The authors also thank E. Garneau for preparation of this manuscript and to R. Taube for editing. This work was supported in part by the U.S. Dept. of Energy under Contract No. DE-AC02-76EV04115 and by R01 CA26371.

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