Annals of Nuclear Medicine Vol. 9, No. 1, 47–50, 1995

Canine SPECT studies for cerebral amino acid transport by means of ^{123}I-3-iodo-α-methyl-L-tyrosine and preliminary kinetic analysis

Keiichi KAWAI,* Yasuhisa FUJIBAYASHI,** Yoshiharu YONEKURA,*** Kenichi TANAKA,* Hideo SAJI,** Junji KONISHI,*** Akiko KUBODERA* and Akira YOKOYAMA**

*Faculty of Pharmaceutical Sciences, Science University of Tokyo
**Faculty of Pharmaceutical Sciences and ***School of Medicine, Kyoto University

We have already reported that ^{123}I-3-iodo-α-methyl-L-tyrosine (^{123}I-L-AMT) is superior as a single-photon emitter labeled radiopharmaceutical reflecting cerebral amino acid transport. In this study, we investigated the distribution of ^{123}I-L-AMT in the canine head by means of SPECT and kinetically analyzed the data in the brain. As a result, clear SPECT images of the canine brain were obtained. Kinetic analysis with a 2-compartment model, including or expressing membrane transport of the amino acid, was performed with time-activity curves in the arterial blood and in the cerebral region. The results of the analysis coincided closely with the experimental data and the relevance of the model was strongly suggested. Therefore ^{123}I-L-AMT is considered to be useful as a single photon radiopharmaceutical which enables us to measure the cerebral amino acid transport rate.

Key words: cerebral amino acid transport, 3-iodo-α-methyl-L-tyrosine, kinetic analysis, SPECT

INTRODUCTION

QUANTITATIVE DIAGNOSIS with not only PET but also SPECT has recently come to be desired in nuclear medicine.[1] In our research on single photon emitter labeled radiopharmaceuticals, which offered wider applicability than positron emitter labeled ones, ^{123}I-3-iodo-α-methyl-L-tyrosine (^{123}I-L-AMT) was selected for the measurement of cerebral amino acid transport. As we have already reported, ^{123}I-L-AMT has shown high brain accumulation, rapid blood clearance, the affinity for the carrier-mediated and stereoselective active transport system of the brain, and stability against catabolism including enzymatic deiodination.[2] Therefore ^{123}I-L-AMT has appeared to be a useful radiopharmaceutical for the selective measurement of cerebral amino acid transport.

In the present study, imaging of the canine head with ^{123}I-L-AMT by SPECT and preliminary quantitative analysis were carried out. For this study, the time-activity curves in the cerebral region and in the arterial blood were obtained by SPECT and arterial blood collection, respectively. Kinetic analysis with these data was performed with a 2-compartment model considering only cerebral amino acid transport.

Received July 4, 1994, revision accepted October 3, 1994.

For reprint contact: Keiichi Kawai, Ph.D., Department of Radiopharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12 Ichigaya Funagawara-machi, Shinjuku, Tokyo 162, JAPAN.

MATERIALS AND METHODS

Preparation of ^{123}I-L-AMT

Non-carrier added ^{123}I-L-AMT (8.79×10^{12} Bq/μmol, theoretical) was prepared by the conventional chloramine-T method with Na^{123}I solution provided by Nihon Medi-Physics, Japan, previously reported.[2] All other chemicals used were of reagent grade.

Comparative canine SPECT studies with ^{123}I-L-AMT and ^{123}I-IMP

A male beagle dog (10 kg body weight, no fasting condition) was anesthetized with pentobarbital sodium (Nembutal®, Abbott Laboratories), and ^{123}I-L-AMT solution (48 MBq in saline) was injected through the femoral vein. Imaging was performed at 2.5 minutes intervals for 60 minutes with a ring-type SPECT machine (SET-030W, Shimadzu, FWHM: 12 mm, slice thickness: 24 mm, slice interval: 30 mm). Seven days after the experiment, ^{123}I-dl-N-isopropyl-p-iodoamphetamine hydrochloride (^{123}I-IMP 67 MBq, Nihon Medi-Physics) imaging was carried out in the same dog.

Canine SPECT studies of ^{123}I-L-AMT and kinetic analysis of cerebral amino acid transport

A male mongrel dog (12 kg body weight, no fasting condition) was injected with ^{123}I-L-AMT solution (26 MBq in saline) through a foreleg vein and head SPECT images parallel to the orbitomeatal (OM) line were obtained at 2.5 minutes intervals for 60 minutes with a ring-type SPECT machine (SET-030W, Shimadzu). Arterial blood samples were collected through the catheter set in the femoral aorta, weighed and radioactivity was measured with a well-type scintillation counter (ARC-300, Aloka). The time-activity curve in the cerebral region was calculated. The activity per 1 m*l* in the arterial blood was substituted in equation (1) and the constants P_1 to P_6 were calculated. With the obtained constants and the activity data per boxel in the cerebral region, the rate constants for cerebral amino acid transport, k_1 and k_2 in equation (2), were obtained. Both kinetic analyses were fitted by the Simplex method.

$$Cb = P_1 \times Exp(-P_2 t) + P_3 \times Exp(-P_4 t) + P_5 \times Exp(-P_6 t) \quad (1)$$

$$dCf/dt = k_1 Cb - k_2 Cf \quad (2)$$

where

Cb: radioactivity in the arterial blood (cpm/m*l* blood)
P_1–P_6: blood clearance parameters
Cf: radioactivity in the cerebral region (cpm/boxel)
t: time after intravenous injection (minutes)

RESULTS

Comparative canine SPECT studies with ^{123}I-L-AMT and ^{123}I-IMP

A canine head SPECT image added imaging data for 10 to 30 minutes after intravenous injection of ^{123}I-L-AMT solution is shown in Figure 1a. The high brain accumulation of ^{123}I-L-AMT was clearly visualized as a circle in the lower part of the photograph. The crescent-shaped accumulation may represent the salivary glands or the nasal mucosa. Figure 1b shows the head SPECT image of the same dog for 10 to 30 minutes after intravenous injection of ^{123}I-IMP solution at the same position. Only the brain was visualized by ^{123}I-IMP, which is well known as a brain-seeking amine with high lipophilicity.

Canine SPECT studies of ^{123}I-L-AMT and kinetic analysis of cerebral amino acid transport

A head SPECT image of another dog parallel to the OM line 10 to 30 minutes after intravenous injection of ^{123}I-L-AMT and a region of interest set in the SPECT image are shown in Figure 2. The high accumulation of ^{123}I-L-AMT in the brain was also visualized as a circle, and the time-radioactivity curve of the cerebral region was obtained (Fig. 3). The time-activity curve of the canine brain resembled that of the human cerebral cortex during ^{124}I-L-AMT PET studies.[3] The results of kinetic analysis by the Simplex method are shown in Figures 3 and 4. The 3 exponential equation (1) showed the best fit for the arterial blood clearance curve. The blood clearance parameters, P_1 to P_6, fitted to equation (1) were 1.441×10^5 cpm/m*l*, 1.318 minute^{-1}, 4.311×10^4 cpm/m*l*, 2.735×10^{-1} minute^{-1}, 3.367×10^4 cpm/m*l* and 7.292×10^{-3} minute^{-1}, respectively (r = 0.9999). These constants were introduced into equation (2). From the radioactivity data for the cerebral region, the rate constants k_1 and k_2 were converted to 7.28×10^{-6} m*l* blood/boxel/minute and 6.27×10^{-2} minute^{-1}, respectively. The obtained curves closely fitted the original time-radioactivity curve (r = 0.9573).

DISCUSSION

Various mental disorders have been associated with changes in cerebral amino acid metabolism; for example, a defect in tyrosine transport has been suggested in schizophrenic patients.[4] Some studies on the use of radiolabeled amino acids with cyclotron-produced short-lived radionuclides have been attempted,[5] but they are limited to PET centers; a radioiodinated amino acid, providing similar data, would offer wider applicability.

Radioiodinated AMT has already been reported as an imaging agent for pancreas,[6,7] melanoma,[8,9] and brain tumors.[3,10] We reported that ^{123}I-L-AMT showed high brain accumulation in mice and in rats.[2] The brain uptake index and brain slice studies indicated the affinity of ^{123}I-L-AMT for carrier-mediated and stereoselective active transport systems similar to ^{14}C-L-tyrosine, respectively. Langen et al. also reported saturation of ^{123}I-L-AMT uptake of human brain by loading L-amino acids.[11] The tissue homogenate analysis revealed that most of the accumulated radioactivity belonged to intact ^{123}I-L-AMT, an indication of its metabolic stability. The high brain accumulation of ^{123}I-L-AMT therefore indicated only cerebral L-tyrosine transport.

In these studies, the high accumulation of ^{123}I-L-AMT in canine brain was clearly visualized similar to that of ^{123}I-IMP. The salivary glands or the nasal mucosa might also be imaged in contrast with ^{123}I-IMP, it might be an example that ^{123}I-L-AMT showed the characteristics as an amino acid. The higher regional accumulation of ^{123}I-L-AMT in rat striatum and midbrain reported by Yoshizumi et al.[12] was not observed in these canine cerebral SPECT images. Even if there were greater accumulation of ^{123}I-L-AMT in these regions, the canine brain is too small to image the specific accumulation in these regions. Based on previous results, 2-compartment kinetic model shown in Figure 5 was applied to the kinetic analysis of canine SPECT data for cerebral amino acid transport. The time-a

b

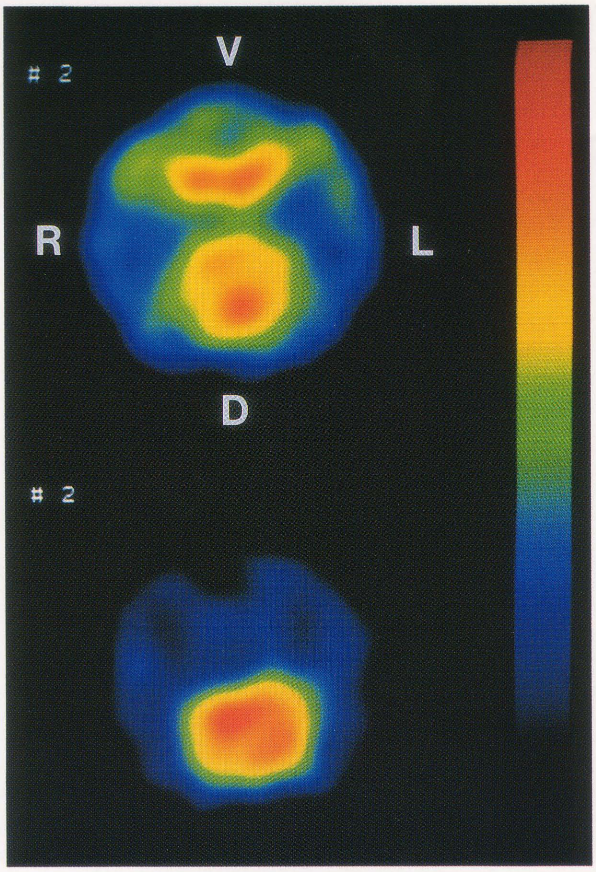


Fig. 1

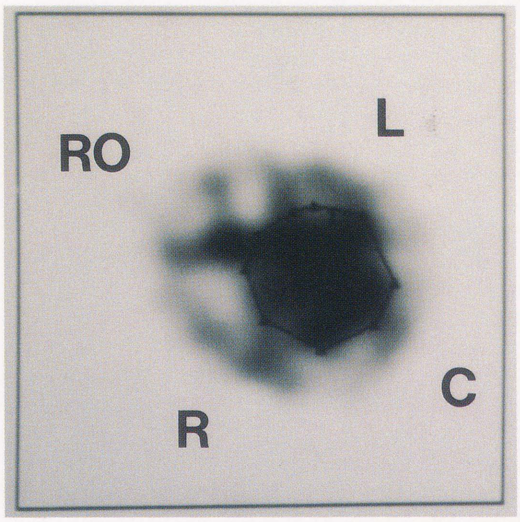


Fig. 2

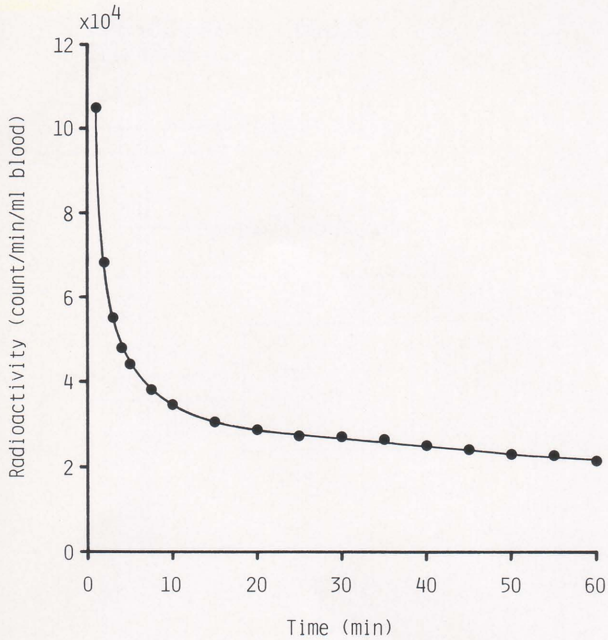


Fig. 3

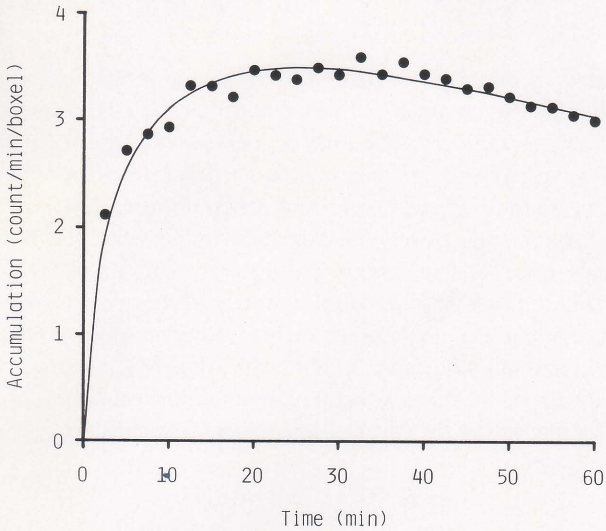


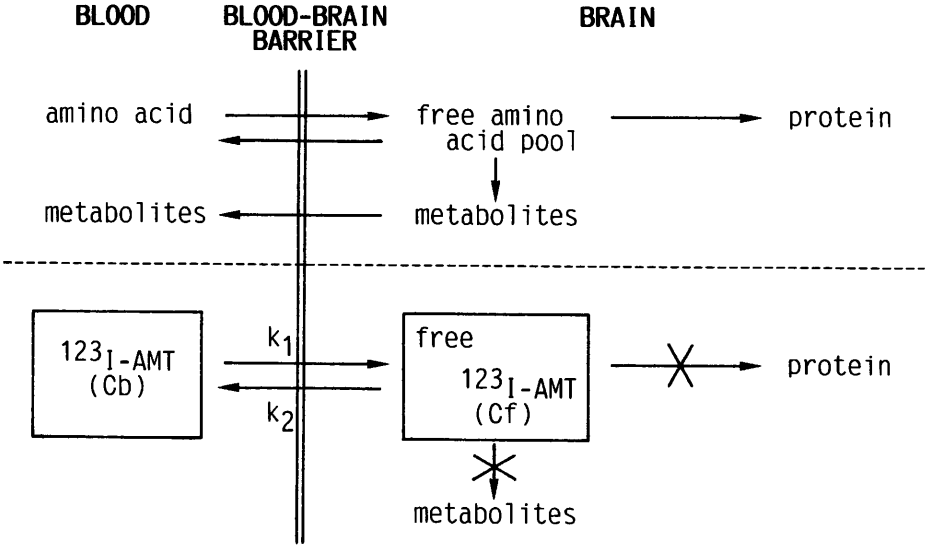
Fig. 4

Fig. 1 a. A canine head SPECT image added 10 to 30 minutes after intravenous injection of ^{123}I-L-AMT. The high brain accumulation of ^{123}I-L-AMT was clearly visualized as a circle in the lower part of the photograph. The crescent-shaped accumulation may represent the salivary glands or the nasal mucosa. b. A head SPECT image of the same dog 10 to 30 minutes after intravenous injection of ^{123}I-IMP at the same position. Only the brain was visualized by ^{123}I-IMP. (D: dorsal, V: ventral, L: left, and R: right side)

Fig. 2 A head SPECT image of a dog parallel to the orbitomeatal line 10 to 30 minutes after intravenous injection of ^{123}I-L-AMT and the region of interest for the brain. The high accumulation of ^{123}I-L-AMT in the brain was visualized as a circle. (RO: rostral, C: caudal, L: left, and R: right side)

Fig. 3 Arterial blood clearance of ^{123}I-L-AMT in the dog and the result of kinetic analysis by the Simplex method. The experimental data (●) are compared with the theoretical curve (line).

Fig. 4 Accumulation of ^{123}I-L-AMT in the dog brain and the result of kinetic analysis by the Simplex method. The SPECT experimental data (●) are compared with the theoretical curve (line).



$$Cb = P_1 \times \exp(-P_2 t) + P_3 \times \exp(-P_4 t) + P_5 \times \exp(-P_6 t)$$

$$dCf/dt = k_1 \times Cb - k_2 \times Cf$$

Fig. 5 Kinetic model for evaluation of cerebral amino acid transport.

activity curves in the cerebral region and in the arterial blood were obtained by SPECT and arterial blood collection, respectively. The kinetic analysis with these data was performed by means of a 2-compartment model considering only cerebral amino acid transport. The result of the analysis closely fitted the experimental data and the relevance of this model was strongly suggested. The kinetic analysis of cerebral amino acid transport might provide useful information on brain tumors, schizophrenia and other diseases. Therefore ^{123}I-L-AMT is considered to be useful as a single photon radiopharmaceutical for measuring the cerebral amino acid transport rate.

ACKNOWLEDGMENTS

The authors wish to thank Nihon Medi-Physics Co. Ltd. for the generous supply of Na^{123}I solution.

REFERENCES

1. Wagner HN Jr. SPECT and PET advances herald new era in human biochemistry. *J Nucl Med* 27: 1227–1238, 1986.
2. Kawai K, Fujibayashi Y, Saji H, Yonekura Y, Konishi J, Kubodera A, et al. Strategy for the study of cerebral amino acid transport using iodine-123-labeled amino acid radiopharmaceutical: 3-iodo-alpha-methyl-L-tyrosine. *J Nucl Med* 32: 819–824, 1991.
3. Langen KJ, Coenen HH, Roosen N, Kling P, Muzik O, Herzog H, et al. SPECT studies of brain tumors with L-3-[^{123}I]iodo-alpha-methyltyrosine: comparison with PET, ^{124}IMT, and first clinical results. *J Nucl Med* 31: 281–286, 1990.
4. Hagenfeldt L, Venizelos N, Bjerkenstedt L, Wiesel FA. Decreased tyrosine transport in fibroblasts from schizophrenic patients. *Life Sci* 41: 2749–2757, 1987.
5. Foeler JS, Wolf AP. Positron emitter-labeled compounds: priorities and problems. *In* Positron emission tomography and autoradiography, principles and applications for the brain and heart, Phelps ME, Mazziotta JC, Schelbert HR (eds.), New York, Raven Press, pp. 391–450, 1986.
6. Tisljar U, Kloster G, Ritzl F, Stöcklin G. Accumulation of radioiodinated L-α-methyltyrosine in pancreas of mice: concise communication. *J Nucl Med* 20: 973–976, 1979.
7. Kawai K, Fujibayashi Y, Yonekura Y, Konishi J, Saji H, Kubodera A, et al. An artificial amino acid radiopharmaceutical for single photon emission computed tomographic study of pancreatic amino acid transports. ^{123}I-3-iodo-alpha-methyl-L-tyrosine. *Ann Nucl Med* 6: 169–175, 1992.
8. Kloss G, Leven M. Accumulation of radioiodinated tyrosine derivatives in the adrenal medulla and in melanomas. *Eur J Nucl Med* 4: 179–186, 1979.
9. Bockslaff H, Kloster G, Stöcklin G, Safi N, Bornemann H. Studies on L-3-^{123}iodo-α-methyl-tyrosine: a new potential melanoma seeking compound. *Nuklearmedizin* (suppl.) 17: 179–182, 1980.
10. Biersack HJ, Coenen HH, Stöcklin G, Reichmann K, Bockisch A, Oehr P, et al. Imaging of brain tumors with L-3-[^{123}I]iodo-α-methyl tyrosine and SPECT. *J Nucl Med* 30: 110–112, 1989.
11. Langen KJ, Roosen N, Coenen HH, Kuikka JT, Kuwert T, Herzog H, et al. Brain and brain tumor uptake of L-3-[^{123}I]iodo-α-methyl tyrosine: competition with natural L-amino acids. *J Nucl Med* 32: 1225–1229, 1991.
12. Yoshizumi H, Fujibayashi Y, Kikuchi H. A new approach to the integrity of dual blood-brain barrier functions of global ischemic rats. Barrier and carrier functions. *Stroke* 24: 279–285, 1993.