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# 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

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$^{123}$I-3-iodo-alpha-methyl-L-tyrosine ($^{123}$I-L-AMT) was selected and its characteristics on pancreas accumulation, metabolic selectivity and metabolic stability of $^{125}$I-L-AMT were studied. The studies on rat tissue slice as well as mouse biodistribution proved very high accumulation of $^{125}$I-labeled L-AMT in the pancreas, which was remarkably inhibited by the active transport inhibitor, ouabain. $^{125}$I-L-AMT does not enter into protein synthesis and general amino acid catabolism. Moreover, $^{125}$I-L-AMT was very stable against enzymatic deiodination. Thus, the above studies indicated that the $^{123}$I-labeled L-AMT was an "artificial amino acid" radiopharmaceutical to be used for the selective measurement of the membrane amino acid transport rate in the pancreas.

**Key words:** radioiodinated amino acid, amino acid transport, pancreas, radiopharmaceutical metabolic stability

## INTRODUCTION

WE HAVE ALREADY REPORTED VARIOUS RADIOPHARMACEUTICALS for functional diagnosis in pancreas (exocrine protein synthesis rate, amino acid transport rate).[1–6] Because of the high protein synthesis activity of the pancreas, amino acid transport is an important function of the pancreas. In our previous research, we have found that it was worthwhile to introduce radioiodine to form modified amino acids; radioiodinated amino acids have high affinity for membrane active transport.[5,6] Careful attention should be paid to design suitable radioiodinated amino acids so that the chemical can maintain characteristics as amino acids and metabolic stability, especially resistance to deiodination. Since D-amino acids show signs of pancreas accumulation,[7–9] we designed $^{123}$I-3-iodo-D-tyrosine ($^{123}$I-D-MIT). We reported that it showed signs of high pancreas accumulation and sufficient pancreas selectivity. We also reported that the accumulation was caused by affinity with an active transport system at the cell membrane of the pancreas and $^{123}$I-D-MIT was very stable against enzymatic deiodination.[6]

Meanwhile, we have found that $^{123}$I-3-iodo-alpha-methyl-L-tyrosine ($^{123}$I-L-AMT, Fig. 1) is useful as a radiopharmaceutical for cerebral amino acid membrane transport rate measurement, which showed signs of high cerebral accumulation by a similar membrane transport system to that of its mother amino acid, L-tyrosine.[10] In previous studies, we have confirmed that $^{123}$I-L-AMT had high resistance to enzymatic metabolism including deiodination, in spite of an L-configuration at the alpha-carbon. In addition, I-L-AMT is a derivative of L-tyrosine which has high pancreas accumulation, and is prepared by simple radioiodination under carrier-free conditions. In this research, we studied the application of $^{123}$I-L-AMT as a radiopharmaceutical for pancreatic amino acid membrane transport rate measurement.

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Radioiodinated I-L-AMT has already been reported as an imaging agent for the pancreas by U. Tisljar et al.,[11,12] however, they used I-L-AMT as a structural analogue of $^{14}$C-alpha-methyl-3,4-dihydroxyphenylalanine ($^{14}$C-alpha-methyl-DOPA), which highly accumulated in the pancreas, and studied only pancreas accumulation and selectivity *in vivo*.

We studied I-L-AMT accumulation in the pancreas, as well as its mechanism and its metabolic stability, especially its resistance to enzymatic deiodination compared with L-tyrosine and 3-iodotyrosine. We also discussed the fitness of our drug design for radioiodinated amino acids as radiopharmaceuticals used in functional diagnosis.

## MATERIALS AND METHODS

*Preparation of $^{125}$I-L-AMT and $^{123}$I-L-AMT*

$^{125}$I-NaI was obtained from Amersham Japan, and $^{123}$I-NaI was provided by Nihon Medi-Physics, Japan. All other chemicals used were of reagent grade. $^{125}$I-L-AMT and $^{123}$I-L-AMT were prepared by the conventional chloramine-T method as follows;[10] in the case of $^{125}$I-L-AMT, chloramine-T ($2.0\times10^{-8}$ mol in 10 $\mu l$ of 0.05 M phosphate buffer (pH 6.2), Aldrich) was added to a mixture of L-AMT ($1.0\times10^{-8}$ mol, Aldrich) and carrier free $^{125}$I-NaI (7.4–37 MBq) in 35 $\mu l$ of 0.4 M phosphate buffer (pH 6.2). As for $^{123}$I-L-AMT, L-AMT ($1.0\times10^{-6}$ mol in 25 $\mu l$ of 1N phosphoric acid) and chloramine-T ($2.0\times10^{-6}$ mol in 20 $\mu l$ of 0.4 M phosphate buffer) were added to 500 $\mu l$ of carrier free $^{123}$I-NaI (74–111 MBq) solution adjusted to pH 10. The resultant solution was allowed to stand for 2 min. at room temperature, and 20 $\mu l$ of 10% saturated sodium metabisulfite solution was added. The radioiodinated L-AMT was purified by Sephadex LH-20 (Pharmacia) column chromatography ($10\times200$ mm, eluant; ethyl acetate: methanol: 2N ammonia= 40: 10: 4).[13] Labeling efficiency and radiochemical purity was studied by Silica gel thin layer chromatography (TLC, MERCK; Art. 5553) using two solvent systems; namely methanol: acetic acid=100: 1 (Rf value; MIT: 0.50, $I^-$: 0.75) and methanol: 10% ammonium acetate=10: 1 (Rf value; MIT: 0.55, $I^-$: 0.80).

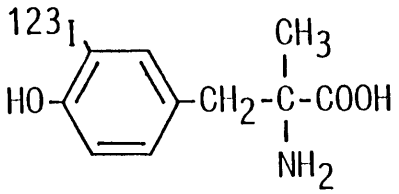


**Fig. 1** Structure of $^{123}$I-3-iodo-alpha-methyl-L-tyrosine ($^{123}$I-L-AMT).

As references, [U-$^{14}$C]-L-tyrosine (NEN; NEC-289E) as a labeled natural amino acid, $^{125}$I-3-iodo-L-tyrosine ($^{125}$I-L-MIT) and $^{125}$I-3-iodo-D-tyrosine ($^{125}$I-D-MIT) prepared by the same method mentioned above, were used in these studies.

In vitro *accumulation studies in rat tissue slices*

*In vitro* accumulation studies were conducted based on the method described by Fujibayashi et al.[1] Tissue slices of pancreas and liver as a reference were prepared. The liver has been claimed to be extremely likely to interfere with imaging of the pancreas.[14,15] Wistar male rats (250–300 g body weight, under fed conditions) were sacrificed by decapitation and the tissue was quickly dissected. The tissue was washed with cold HEPES buffer (pH 7.4) and sliced with a conventional Stadie-Riggs slicer. The slices (each weighing $100\pm5$ mg) were put into a vial containing 1.9 m*l* of HEPES buffer (pH 7.4) as the incubation medium. 0.1 m*l* of the buffer containing a radioactive amino acid was then added and incubation was performed at either 37°C or 4°C. As for the ouabain inhibition, tissue slices were preincubated at 37°C for 30 min in medium containing $5.0\times10^{-5}$ M of ouabain, before the addition of the radioactive sample, and then slices were incubated for 120 min. At the end of the incubation period, the slices were washed twice in 2 m*l* of cold HEPES buffer. The inhibition percentage of the dose accumulated per gram slice was calculated as follows:

$$\%\ \text{inhibition} = \frac{\text{control}(\%\,\text{dose/g}) - \text{ouabain loaded}(\%\,\text{dose/g})}{\text{control}(\%\,\text{dose/g})} \times 100$$

The final radioactive amino acid concentration was $2.7\times10^{-11}$ M (1.85 kBq/m*l*, non-carrier added) for $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{125}$I-D-MIT and $1.0\times10^{-7}$ M (1.85 kBq/m*l*) for $^{14}$C-L-tyrosine respectively.

In vivo *mouse biodistribution studies and analysis of metabolites*

DdY male mice (25 g body weight, under fed conditions) received, through the tail vein, 0.1 m*l* of radioactive amino acids in saline ($^{125}$I-L-AMT, $^{125}$I-L-MIT, $^{125}$I-D-MIT: $1.6\times10^{-13}$ mol, 11.1 kBq, $^{14}$C-L-tyrosine: $4.0\times10^{-10}$ mol, 74 kBq) were sacrificed at various time intervals. Then radioactivity in each tissue was measured. An aliquot of the tissue ($150\pm10$ mg) was homogenized in 2.0 m*l* of Krebs-Ringer phosphate buffer (pH 7.4) containing 2.5 mM nicotinamide and 1.0 mM of thiouracil, and its 5% trichloroacetic acid precipitated fraction was trapped on a glass filter (Toyo; GC-50) to measure radioactivity incorporated in protein. Furthermore, its supernate was separated by TLC using the solvents mentioned above to examine the metabolites.

*Measurement of radioactivity*
For the measurement of radioactivity, a well-type scintillation counter (Aloka; ARC-300) was used for $^{125}$I and $^{123}$I-labeled compounds. As for $^{14}$C-L-tyrosine, 1 m*l* of NCS tissue solubilizer (Amersham) was added to each organ, incubated at 50°C for 3 hr, followed by the addition of 8 m*l* of toluene scintillator containing DPO and POPOP. The radioactivity was measured in a liquid scintillation counter (Aloka; ARC-900).

## RESULTS

*Preparation of $^{125}$I-L-AMT and $^{123}$I-L-AMT*
Non-carrier added $^{125}$I-L-AMT and $^{123}$I-L-AMT with radiochemical purities greater than 95% and radiochemical yields of 50–60% were obtained after purification.

*Accumulation in rat tissue slices and effects of ouabain*
Accumulation in rat pancreas and liver slices (%/g slice) at 37°C is shown in Fig. 2. Accumulation of $^{125}$I-L-AMT and $^{125}$I-L-MIT was increased time dependently. Within 30 min, the former accumulated in the pancreas at 95.0±13.6%/g and in the liver at 36.7±2.1%/g, and the latter, 94.0±5.0%/g and 36.9±3.5%/g respectively. Thus, both accumulated in the pancreas 2.5 times as much as in the liver. In the case of 4°C incubation, the accumulation of $^{125}$I-L-AMT in pancreas slices was suppressed by 53.5±7.3% at 60 min (data not shown in Fig.). Comparing the accumulation of $^{125}$I-L-AMT and $^{125}$I-L-MIT with that of $^{14}$C-L-tyrosine, lower level accumulation of the former two was observed in the pancreas and slightly higher level accumulation was observed in the liver.

The degree of ouabain inhibition of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in the pancreas and the liver is shown in Fig. 3. Ouabain, admitted as an inhibitor of an energy-dependent active transport system, suppressed accumulation of $^{125}$I-L-AMT in the pancreas by 28.7%, $^{125}$I-L-MIT by 24.7%, and $^{14}$C-L-tyrosine by 35.2%, respectively, while in the liver, inhibition in the above order was not significant.

*Biodistribution in mice and metabolic stability* in vivo
Figure 4 shows the biodistribution of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in mice (%/g tissue). In the pancreas, in the case of $^{125}$I-L-AMT, the highest accumulation which exceeded that of $^{14}$C-L-tyrosine was found 5 min after injection (41.5± 5.2%/g tissue), and then it rapidly decreased. On the other hand, the accumulation of $^{14}$C-L-tyrosine was increased until 15 min after injection (39.2±10.6%/g tissue), and it was retained until 30 min.$^{125}$I-L-MIT showed high accumulation in the pancreas after injection, but very rapid clearance was noted and there was hardly any indication of greater accumulation than in blood. In the liver, $^{14}$C-L-tyrosine showed the highest accumulation, and in blood $^{125}$I-L-MIT showed the highest. The high accumulation of $^{125}$I-L-MIT was seen in the stomach, in which free iodine selectively accumulated.

Table 1 shows the ratios of accumulation in the pancreas versus that in other tissues, in mice. The

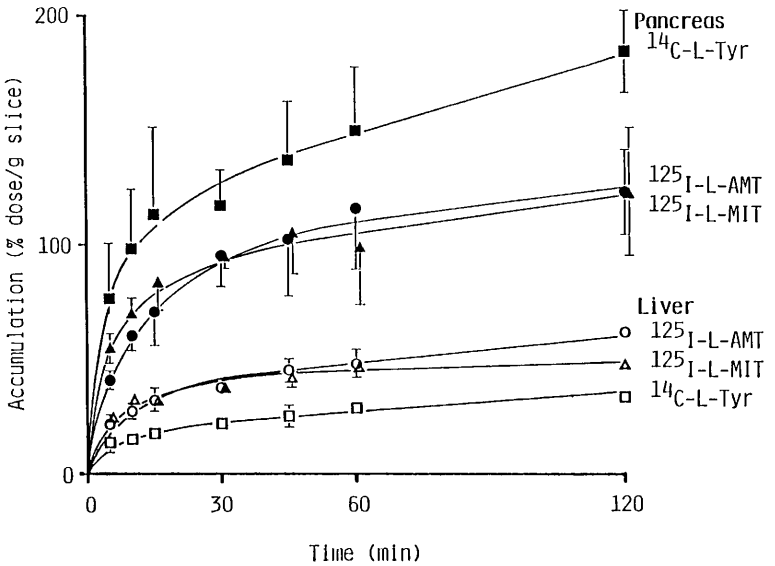


**Fig. 2** Accumulations of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in rat tissue slices at 37°C. Each point represents the mean±S.D. for four to five experiments (closed marks; accumulation in pancreas slices, opened marks; in liver slices).

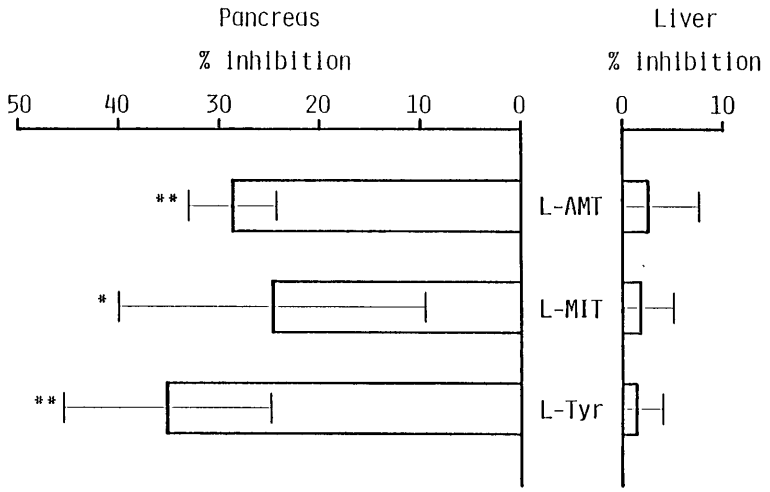


**Fig. 3** Effects of ouabain on the accumulation of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in rat tissue slices. Each bar represents the mean±S.D. for four to five experiments (left bars; % of inhibition on the accumulation in pancreas slices, right bars; in liver slices). *; $p<0.05$, **; $p<0.01$ compared to controls.

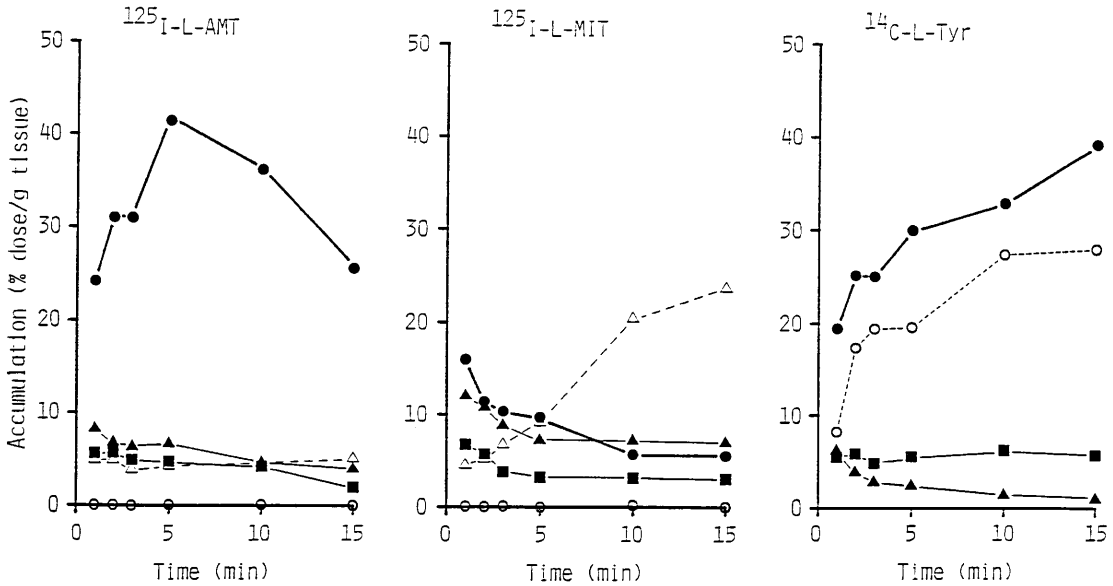


**Fig. 4** Biodistribution of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in mice. Each point represents the mean for three to five animals (●; accumulation in pancreas, ■; in liver, △; in stomach, ▲; $^{125}$I-labeled amino acids in blood and $^{14}$C-L-tyrosine in plasma, and ○; protein incorporation in pancreas).

pancreas to blood and the pancreas to kidney ratios of $^{125}$I-L-AMT were lower than those of $^{14}$C-L-tyrosine. However, at 10 min after injection, the pancreas to liver ratio, which is the most important when the pancreas is imaged, turned out to be 8.67±2.19, which exceeded 5.35±1.00 of $^{14}$C-L-tyrosine. The ratio of accumulation in the pancreas versus that in the stomach was also high enough with a value of 7.95±1.04 to exceed that of $^{125}$I-L-MIT, 0.28±0.09. These results on $^{125}$I-L-AMT agree with those of U. Tisljar et al.[11]

The chemical forms of the radioactive compounds in mouse pancreas 10 min after injection are shown in Fig. 5. In the pancreas of $^{14}$C-L-tyrosine injected mice, there was less than 10% L-tyrosine, while more than 80% of the radioactivity was found in protein precipitate. In the case of $^{125}$I-L-MIT, more than 75% of the radioactivity was found as free iodine. On the other hand, $^{125}$I-L-AMT was found to be more than 97% as free amino acids, and neither as protein nor as free iodine.

In Table 2, *in vivo* metabolic stability of $^{125}$I-L-

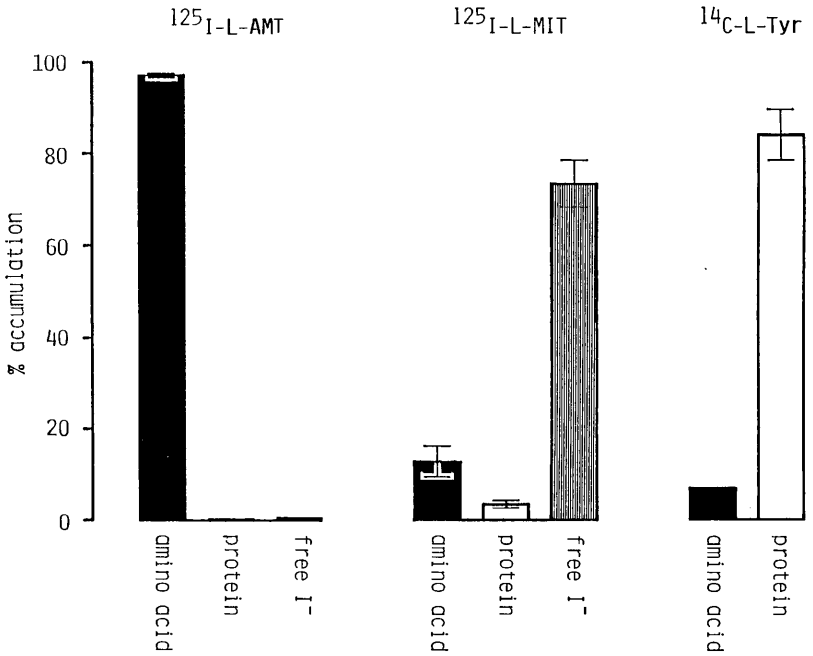


**Fig. 5** Fate of $^{125}$I-L-AMT, $^{125}$I-D-MIT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in mouse pancreas, 10 min after injection. Each bar represents the mean±S.D. for three to five animals. The result for the amino acid fraction of $^{14}$C-L-tyrosine is from only one animal (closed bars; amino acid fraction, opened bars; protein fraction, striped bars; free $I^-$ fraction).

**Table 1** Biodistribution of $^{125}$I-L-AMT, $^{125}$I-L-MIT and $^{14}$C-L-tyrosine in mice—Ratio of pancreas to other tissue[a]—

| | $^{125}$I-L-AMT | $^{125}$I-L-MIT | $^{14}$C-L-tyrosine |
|---|---|---|---|
| Pancreas/Liver | 8.67 (2.19) | 1.83 (0.13) | 5.35 (1.00) |
| Pancreas/Blood | 7.56 (1.47) | 0.82 (0.07) | 22.58 (7.87)[b] |
| Pancreas/Kidney | 0.48 (0.08) | 0.80 (0.07) | 5.58 (0.75) |
| Pancreas/Stomach | 7.95 (1.04) | 0.28 (0.09) | |

[a] Ratio of accumulation % injected dose per gram of slice. The mean (S.D.) of three to four animals, 10 min after injection

[b] Pancreas/Plasma

AMT, $^{125}$I-D-MIT and $^{125}$I-L-MIT is shown for comparison. In the kidney and urine as well as in the pancreas, $^{125}$I-L-AMT showed higher stability than $^{125}$I-D-MIT, which is resistant to enzymatic deiodination.[6] Free iodine was less than 5% in all tissues. In the case of $^{125}$I-L-MIT, MIT was less than 15% in the pancreas, liver and kidney as well, while free iodine was more than 65%. In urine, more than 90% of $^{125}$I-L-MIT was detected as free iodine. Thus, the above results showed that $^{125}$I-L-MIT is easily deiodinated.

## DISCUSSION

I-L-AMT is a modified amino acid of L-tyrosine with iodination and alpha-methylation. Modified amino acids have been known as a "non-metabolizable amino acid" with selective affinity for membrane transport system.[16,17] Also in nuclear medicine, some modified amino acid radiopharmaceuticals, such as [1-$^{11}$C]-aminocyclopentancarboxylic acid[18,19] and [1-$^{11}$C]-alpha-aminoisobutylic acid,[20] have been developed and amino acid transport measurement *in vivo* has been attempted.[21] However, since cyclotron-produced ultra short-lived radionuclides are not suitable for routine use, we have sought the development of a radioiodinated amino acid labeled

**Table 2** *In vivo* stability of $^{125}$I-L-AMT, $^{125}$I-D-MIT and $^{125}$I-L-MIT in mice[a]

| | $^{125}$I-L-AMT | | $^{125}$I-D-MIT | | $^{125}$I-L-MIT | |
|---|---|---|---|---|---|---|
| | AMT | Free $I^-$ | MIT | Free $I^-$ | MIT | Free $I^-$ |
| Pancreas | 97.2 | 0.6 | 85.1 | 4.5 | 13.3 | 76.4 |
| | (0.5) | (0.4) | (6.9) | (2.5) | (3.5) | (5.3) |
| Liver | 55.3 | 1.9 | 35.6 | 10.5 | 13.9 | 66.3 |
| | (7.1) | (1.3) | (8.6) | (5.7) | (2.9) | (5.4) |
| Kidney | 94.9 | 2.2 | 76.0 | 6.5 | 14.1 | 75.1 |
| | (1.4) | (1.5) | (11.2) | (2.8) | (4.6) | (6.1) |
| Urine | 93.1 | 3.8 | 35.7 | 62.2 | 4.8 | 94.2 |
| | (2.5) | (2.0) | (7.6) | (8.3) | (1.5) | (1.2) |

[a] The mean (S.D.) for three to four animals, 10 min after injection.
TLC analysis (MeOH: AcOH=100: 1).

with $^{123}I$, which can be widely used and offers good physical characteristics for nuclear medicine.

In spite of iodination and alpha-methylation of L-tyrosine, I-L-AMT showed high pancreas selectivity in both *in vitro* and *in vivo* studies (Figs. 2, 4, Table 1). Furthermore, unlike accumulation in the liver, the high accumulation in pancreas tissue was based on energy-dependent active transport (Fig. 3). It is known that the mechanism of transport of the mother compound, L-tyrosine, into cells is in the category of the mechanism of neutral amino acid active transport, especially the L-system (Leucine-mediation).[22,23] The pancreas selectivity and contribution to the active transport of I-L-AMT are comparable to those of L-tyrosine. This strongly suggested that the transport mechanisms of the above two cases are quite similar.

In regard to retention after accumulation in cells, however, unlike from L-tyrosine, I-L-AMT has no affinity for protein synthesis, which is the most likely retention mechanism in the pancreas (Fig. 5), and rapidly disappeared from the pancreas *in vivo* (Fig. 4). These results clearly indicated that I-L-AMT and the basic characteristics of a "non-metabolizable amino acid" with affinity for the membrane active transport system.

Generally, when radioiodinated radiopharmaceuticals are developed, it is necessary to give careful consideration to resistance to enzymatic deiodination. L-MIT, monoiodinated L-tyrosine, exists naturally as a metabolite of thyroid hormone in the body anr is known to be rapidly metabolized by deiodinase.[24,25] However, it was shown that I-L-AMT, which was methylated at the alphaposition of L-MIT, which was methylated at the alphaposition of L-MIT, was sufficiently resistant to being metabolized including deiodination in the pancreas (Fig. 5). However, in the liver, low molecular weight metabolites were observed, and no free iodine was found in any of the tissues studied. It is suggested that I-L-AMT was stable *in vivo* and was finally excreted as intact I-L-AMT (Table 2). The metabolism of I-L-AMT promoted the clearance of radioactivity from the blood, and brought about simple distribution, unlike the complicated metabolic action of natural amino acids such as L-tyrosine. The characteristics of I-L-AMT indicated that the modifications, iodination and alpha-methylation of L-tyrosine made it easier to analyze *in vivo* as well.

From the above facts, $^{123}I$-L-AMT, which can be easily labeled under non-carrier added conditions, shows high pancreas selectivity and has the biochemical characteristics suitable for membrane amino acid transport measurement. Furthermore, it is considered that $^{123}I$-L-AMT can be expected as a single photon amino acid radiopharmaceutical which has suitable characteristics for the metabolic stability fundamentally required in radioiodinated compounds.

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