[Chem. Pharm. Bull. 25(7)1574—1581(1977)]

UDC 547.466.08.09 : 543.52.06

# Incorporation Pattern of L-, D-, and DL-Amino Acids into the Pancreas of Mice

RENSUKE GOTO, MASAKATSU TEZUKA, and OSAMU TAMEMASA

*Shizuoka College of Pharmacy*[1]

(Received October 15, 1976)

For the development of amino acid derivatives as a new pancreas-scanning agent, comparative experiments were made on the *in vivo* incorporation of 18 kinds of $^{14}$C-labeled L-amino acid, and of D- and DL-forms of four selected radioactive amino acids into the trichloroacetic acid (TCA)-soluble and protein fractions of the pancreas and liver of mice.

Among the L-forms tested, tryptophan, valine, methionine, and leucine, in this order of decreasing incorporation, showed a relatively high incorporation into the pancreas 30 min after intravenous injection. Pancreas/liver ratio of the radioactivity of methionine, valine, and leucine determined 15, 30, and 60 min after injection were 6 to 10. Although all of the amino acids were not predominantly high in pancreas/liver ratio compared with selenomethionine-$^{75}$Se, the three amino acids seem a possible mother compound for introducing $\gamma$-emitters as a pancreas-scanning agent.

In the TCA-soluble fraction of the pancreas, radioactivity of DL- or D-amino acids tested was higher than that of the corresponding L-amino acid. In particular, the almost whole radioactivity of D-leucine was found in the TCA-soluble fraction, and the activity due to D-leucine-$^{14}$C itself. The incorporation of D-leucine into the pancreas was much the same as L-leucine.

Based on these results, $\gamma$-radiating derivatives of amino acids might be useful as a new pancreas-scanning agent.

**Keywords**——amino acid; D- and DL-amino acid; incorporation; pancreas; pancreas-scanning agent; trichloroacetic acid-soluble fraction

Selenomethionine-$^{75}$Se is often used for the isotope scanning of pancreas as a supplemental tool for diagnosis. However, it is desirable to develop better pancreas-scanning agents which show more pancreas-specific localization and less radiation hazards than selenomethionine-$^{75}$Se.

Pancreas is known to have a high ability to incorporate amino acids into its cells and to utilize the acids for the synthesis of pancreatic proteins and enzymes.[2] On the basis of the preferential uptake of amino acids by pancreas, several radioactive iodine-, selenium-, and fluorine-substituted amino acids were tentatively tested for the scanning agent, but these derivatives, except selenomethionine-$^{75}$Se, have not shown a favorable result.[2c,3] On the other hand, Berlinguet, *et al.*[4] and Sherman, *et al.*[5] have reported the high localization of $^{14}$C-1-aminocyclopentanecarboxylic acid in the pancreas of mice, which suggests the incorporation of an unnatural amino acid into the trichloroacetic acid (TCA)-soluble fraction rather than into the protein fraction of the tissue.

1) Location: *2–1, Oshika 2-chome, Shizuoka.*
2) *a*) F. Friedberg, H. Tarver, and D.M. Greenberg, *J. Biol. Chem.*, **173**, 355 (1948); *b*) E. Hansson, *Acta Physiol. Scand.* **46**, *Suppl.*, **161**, 99 (1959); *c*) M. Blau and R.F. Manske, *J. Nucl. Med.*, **2**, 102 (1961).
3) *a*) R.N. Melmed, J.E. Agnew, and I.A.D. Bouchier, *J. Nucl. Med.*, **10**, 575 (1969); *b*) R.E. Counsell, T.D. Smith, W. Diguilio, and W.H. Beierwaltes, *J. Pharm. Sci.*, **57**, 1958 (1968); *c*) V.B. Schatz, B.C. O'Brien, and W.R. Sandusky, *J. Med. Chem.*, **11**, 140 (1968); *d*) S. Kato, K. Kurata, Y. Sugisawa, and T. Wakebayashi, *Yakugaku Zasshi*, **90**, 1499 (1970); *e*) M.F. Cottrall, D.M. Taylor, and T.J. McElwain, *Brit. J. Radiol.*, **46**, 277 (1973); *f*) R.M. Lambrecht, H. Atkins, H. Elias, J.S. Fowler, S.S. Lin, and A.P. Wolf, *J. Nucl. Med.*, **15**, 863 (1974).
4) L. Berlinguet, N. Bégin, and L.M. Babineau, *Can. J. Biochem. Physiol.*, **40**, 1111 (1962).
5) F.C. Sherman, A.M. Paredes, D.A. Chambers, and G.L. Nardi, *Can. J. Biochem.*, **43**, 1243 (1965).

Although, as cited above, there are a number of reports on the incorporation experiments of natural and unnatural amino acid into the pancreas, fundamental and comparative knowledges are lacking in most of the publications on the incorporation of amino acids into the organ and its adjacent liver. The present paper describes the *in vivo* incorporation pattern of 18 kinds of L-amino acids and of D- and DL-forms of four selected amino acids into the TCA-soluble and protein fractions of pancreas and liver of mice in order to acquire a detailed information on their amino acid incorporation. Since high pancreas/liver ratio is required for a good visualization of the pancreas adjacent to the liver, the incorporation experiments were carried out in comparison with that of the liver.

## Experimental

**Radioactive Amino Acids**——All L-amino acids uniformly labeled with $^{14}C$ except L-cysteine·HCl, DL-leucine[1-$^{14}C$] and DL-tryptophan[3-$^{14}C$] were products of Daiichi Pure Chemicals Co., Tokyo. L-Cysteine-[U-$^{14}C$]·HCl and L-tryptophan[3-$^{14}C$], DL-methionine[1-$^{14}C$] and D-tryptophan[3-$^{14}C$], DL-valine[1-$^{14}C$], and D-leucine[1-$^{14}C$] were products of the Radiochemical Centre, U.K., New England Nuclear, U.S.A., Schwarz BioResearch, Inc., U.S.A., and ICN Pharmaceuticals, Inc., U.S.A., respectively. D-Methionine[U-$^{3}H$] and D-valine[U-$^{3}H$] were prepared by the Wilzbach method[6] as follows: One gram of each D-amino acid was allowed to stand with 2 Ci of $^{3}H$ gas in a breakable ampule for 2 weeks.[7] After removal of labile tritium by the conventional method, the labeled material was purified by an ion exchange column chromatography (Amberlite CG-120 (Type 2), 1.5×60 cm; eluent, 2.5 N HCl) followed by paper chromatography (Toyo Roshi No. 51, 40×40 cm, *n*–BuOH–AcOH–$H_2O$ (4: 1: 2)). The specific activity of D-methionine-$^{3}H$ (yield, 0.6 g) and D-valine-$^{3}H$ (yield, 0.7 g) thus obtained was 0.23 and 1.12 mCi/mmol, respectively.

**Animals**——dd/Y male mice (18 to 20 g) were obtained from Shizuoka Agricultural Cooperative Association for Laboratory Animals, Hamamatsu. They were fed on a standard pellet diet, supplied by the Oriental Yeast Co., Tokyo, for 1 to 2 weeks before use.

***In Vivo* Incorporation**——Animals administered intravenously one of radioactive amino acids were killed by inhalation of ether gas after a given time. Excised pancreas (whole organ) and liver (approx. 200 mg wet weight, after homogenization in a mortar) were disintegrated thoroughly with a glass rod after addition of 2 ml of 5% TCA and further extracted twice with the same volume of the acid. TCA in the combined extracts was removed twice with 5 volumes each of $(C_2H_5)_2O$ for the determination of radioactivity of the aqueous layer. In advance it was confirmed that over 90% of radioactive substances transferable into the TCA-soluble fraction could be extracted by these three washings with 5% TCA. The residue after TCA extraction was washed with 2 ml each of 5% TCA once at 50° for 10 min and twice at the same temperature for 5 min, three times with 2 ml each of EtOH–$(C_2H_5)_2O$ (3: 1), and finally once with 2 ml of $(CH_3)_2CO$. The final product was designated as the protein fraction, which was weighed as the amount of protein after drying.

**Abundance of $^{14}C$-Labeled L-Amino Acid in the TCA-Soluble Fraction**——The proportion of unmetabolized $^{14}C$-labeled L-amino acid to the whole radioactivity in the TCA-soluble fraction of pancreas 30 min after administration was determined by the isotope dilution method. Furthermore, radioactive metabolites in the fraction were pursued both by paper radiochromatography (Toyo Roshi No. 51, 2×40 cm, *n*-BuOH–AcOH–$H_2O$ (4: 1: 2)) and autoradiography (Sakura X-ray film, exposure, 60 days).

**Effect of D-Amino Acid on Incorporation of L-Form into TCA-Soluble Fraction of Pancreas *in Vitro***——Mouse pancreas was sliced 0.2—0.5 mm thick with a tissue slicer. The sliced tissues (approx. 200 mg wet weight/incubation tube) were incubated with a mixture of a radioactive L-amino acid and the corresponding nonradioactive D-amino acid at various concentrations in $Ca^{2+}$-free Krebs-Ringer phosphate buffer (KRP-Ca), pH 7.2 at 37° for 1hr. After incubation, the tissues were washed three times with 2 ml each of ice-cold KRP-Ca, and extracted three times with 2 ml each of 5% TCA. The combined TCA-soluble fraction was treated with $(C_2H_5)_2O$ to remove TCA.

**Identification of the Optical Form of Incorporated Leucine-$^{14}C$ in the TCA-Soluble Fraction of Pancreas**——The optical form of free leucine in the pancreas 30 min after administration of D-leucine[1-$^{14}C$] was identified according to the procedure of Tamemasa, *et al.*[8] About 100 mg of nonradioactive L- or D-leucine was recrystallized from $H_2O$ with an aliquot of the TCA-soluble fraction (TCA was previously removed with $(C_2H_5)_2O$). The specific activities of leucine were measured after repeated recrystallizations.

**Measurement of Radioactivity**——(a) In the experiments on $^{14}C$-labeled L- and DL-amino acids, TCA-soluble fractions were measured as follows: An aliquot of the aqueous layer after removal of TCA was

6) K.E. Wilzbach, *J. Am. Chem. Soc.*, **79**, 1013 (1957).
7) S. Okada and O. Tamemasa, *Radioisotopes*, **14**, 42 (1965).
8) O. Tamemasa, S. Iwasaki, and M. Tezuka, *Radioisotopes*, **17**, 31 (1968).

placed on a disk and dried under an infrared lamp. Protein fractions were dissolved in 2 ml of 1 N $NH_4OH$, placed on the disk, and dried under the lamp. Radioactivity of the samples was counted with a $2\pi$ gas-flow counter (Aloka). (b) In the experiments on $^3H$- or $^{14}C$-labeled D-amino acids, TCA-soluble fractions were measured with a liquid scintillation counter (Aloka 602) by the use of a scintillation cocktail containing 2,5-diphenyloxazole (6.5 g), 1,4-bis[2-(5-phenyloxazolyl)]-benzene (0.13 g), naphthalene (104 g), dioxane (0.5 l), toluene (0.5 l), and MeOH (0.7 l). Protein fractions were lyophilized and treated with an automatic sample oxidizer (Packard). (c) The activity of $^{14}C$-labeled L-amino acids in an experiment by the isotope dilution method and of recrystallized leucine-$^{14}C$ for the determination of optical form was measured in a liquid scintillation counter by using the scintillator mentioned above.

## Results

### *In Vivo* Incorporation

As indicated in Fig. 1, a large portion of each radioactivity of 18 kinds of $^{14}C$-labeled L-amino acid 30 min after intravenous injection was found in the protein fraction of mouse pancreas except methionine and glycine. Also, many of the amino acids tested were incorporated into the protein fraction of the liver. The total incorporation (TCA-soluble fraction +protein fraction) into mouse pancreas was high in tryptophan, valine, methionine, leucine, and glycine, and radioactivity of these four amino acids except glycine was 6- to 9-fold higher than that into the liver.

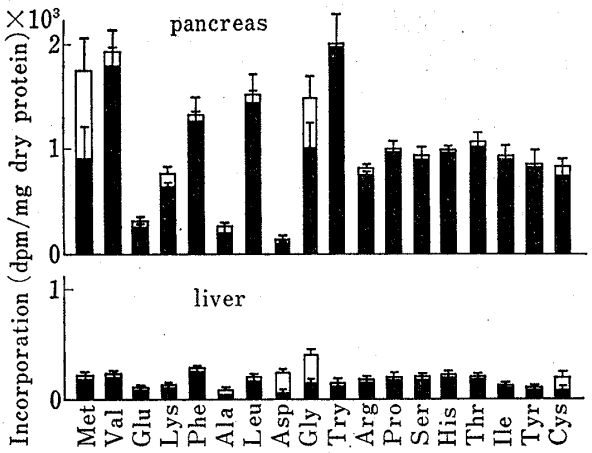


Fig. 1. *In Vivo* Incorporation of $^{14}C$-Labeled L-Amino Acids into TCA-Soluble and Protein Fractions of Pancreas and Liver of Mice

Three mice intravenously injected 1 $\mu$Ci (189 nmol/mouse) of each $^{14}C$-labeled L-amino acid were killed by inhalation of ether gas at 30 min. Approximately 200 mg of excised pancreas and liver were treated.
□: TCA-soluble fraction, ■: protein fraction,
I : standard deviation.

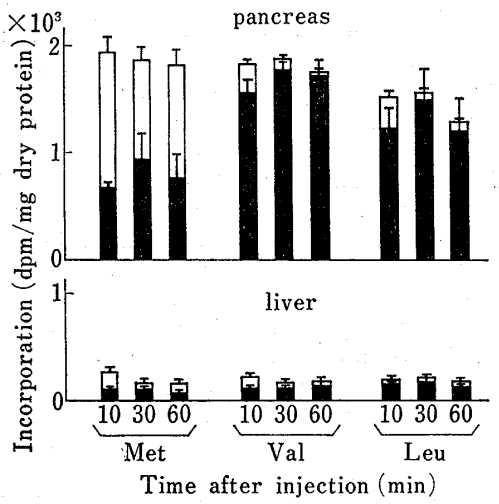


Fig. 2. Time-Course of *in Vivo* Incorporation of $^{14}C$-Labeled L-Methionine, L-Valine, and L-Leucine into TCA-Soluble and Protein Fractions of Pancreas and Liver of Mice

Experimental procedure was the same as described in the legend to Fig. 1, except that three mice were used for one determination of each amino acid.
□: TCA-soluble fraction, ■: protein fraction,
I : standard deviation.

Time-course of the incorporation of methionine, valine, and leucine into the pancreas and liver of mice is shown in Fig. 2. The radioactivity of the three amino acids in the TCA-soluble fraction of pancreas attained its maximum within 10 min, and it gradually decreased after that, while that of the protein fraction came to a maximum at 30 min. A somewhat similar tendency was observed in the liver.

At any period, the total incorporation per mg dry protein of the cells was over six times higher in the pancreas than in the liver. This result was similar to that of selenomethionine-$^{75}Se$.[9]

9) R. Goto, M. Tezuka, K. Ishigami, and O. Tamemasa, *Kakuigaku*, **11**, 453 (1974).

Fig. 3 shows the incorporation of DL-form of leucine, valine, methionine, and tryptophan which exhibited a relatively high total incorporation into the pancreas. In these experiments, the amount of each DL-amino acid used was twice that of L-amino acid having the same specific radioactivity.

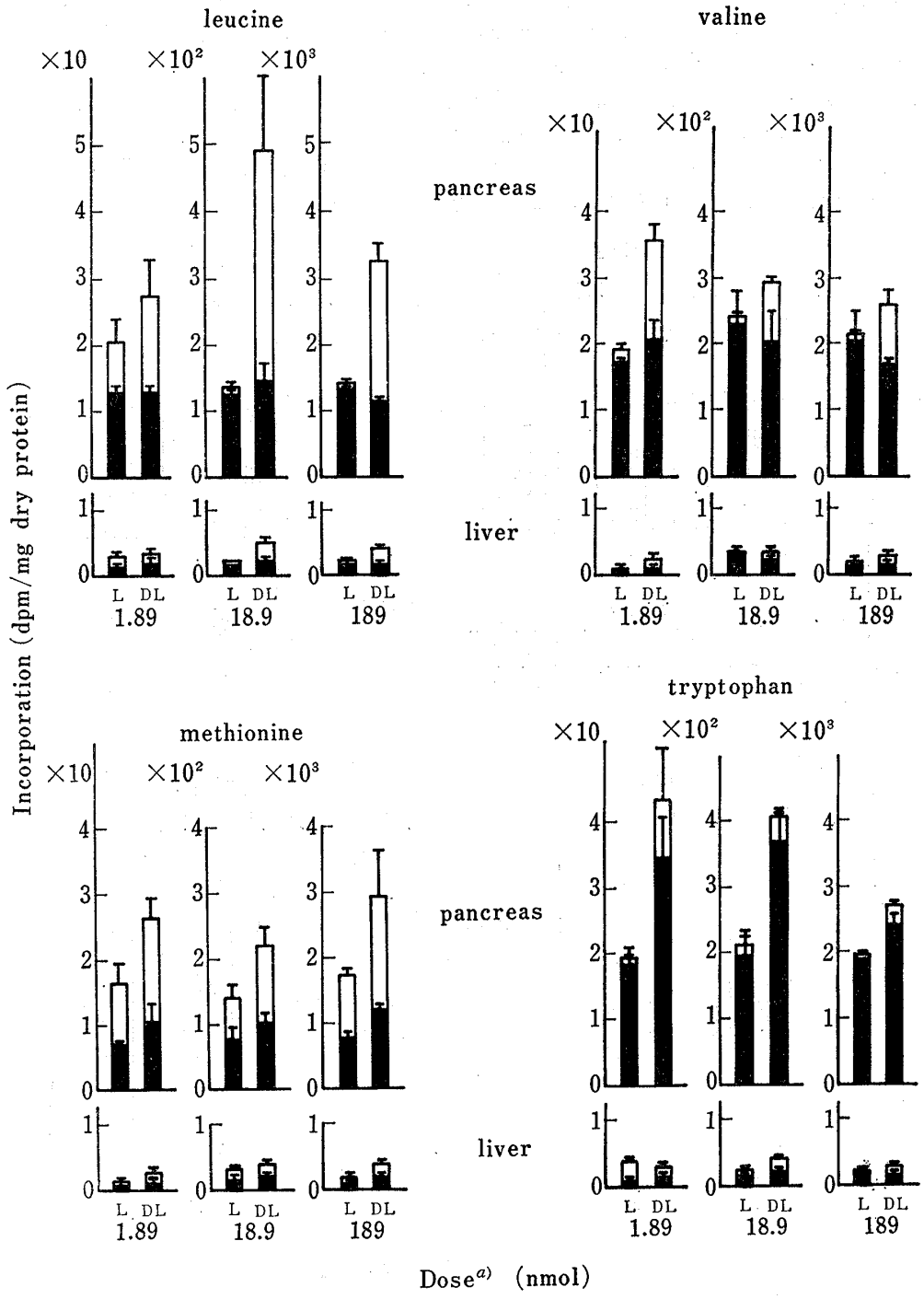


Fig. 3. Comparison of *in Vivo* Incorporation of L- and DL-Forms of $^{14}$C-Labeled Leucine, Valine, Methionine, and Tryptophan into TCA-Soluble and Protein Fractions of Pancreas and Liver of Mice at Different Doses

Three mice intravenously injected 0.01 μCi (1.89 nmol), 0.1 μCi (18.9 nmol), or 1 μCi (189 nmol) per mouse of each $^{14}$C-labeled L-amino acid were killed by inhalation of ether gas at 30 min. In the case of $^{14}$C-labeled DL-amino acid, mice were given double the quantity of L-amino acid having the same specific activity. Approximately 200 mg of excised pancreas and liver were treated.
□: TCA-soluble fraction, ■: protein fraction, I: standard deviation.
*a*) The dose refers to the amount of L-amino acid only.

Radioactivity of each of the four DL-amino acids in the TCA-soluble fraction of the pancreas 30 min after administration was considerably higher than that of the corresponding L-forms. This tendency was noteworthy in mice administered DL-leucine in 18.9 and 189 nmol/mouse referred to the amount of L-form only, in which the total incorporation was twice or above that of L-leucine. This result supported the fact that D-leucine uptake by the organ was almost the same as that of L-leucine.

To ascertain the above result, the uptake of four D-amino acids labeled with $^{3}H$ or $^{14}C$ was measured. These results are shown in Fig. 4.

As expected, the total incorporation of D-leucine was the same as or above that of L-leucine. Most of the radioactivity was found in the TCA-soluble fraction contrary to L-leucine which was incorporated almost exclusively into the protein fraction. The total incorporation of other three D-amino acids was less than that of the corresponding L-amino acids.

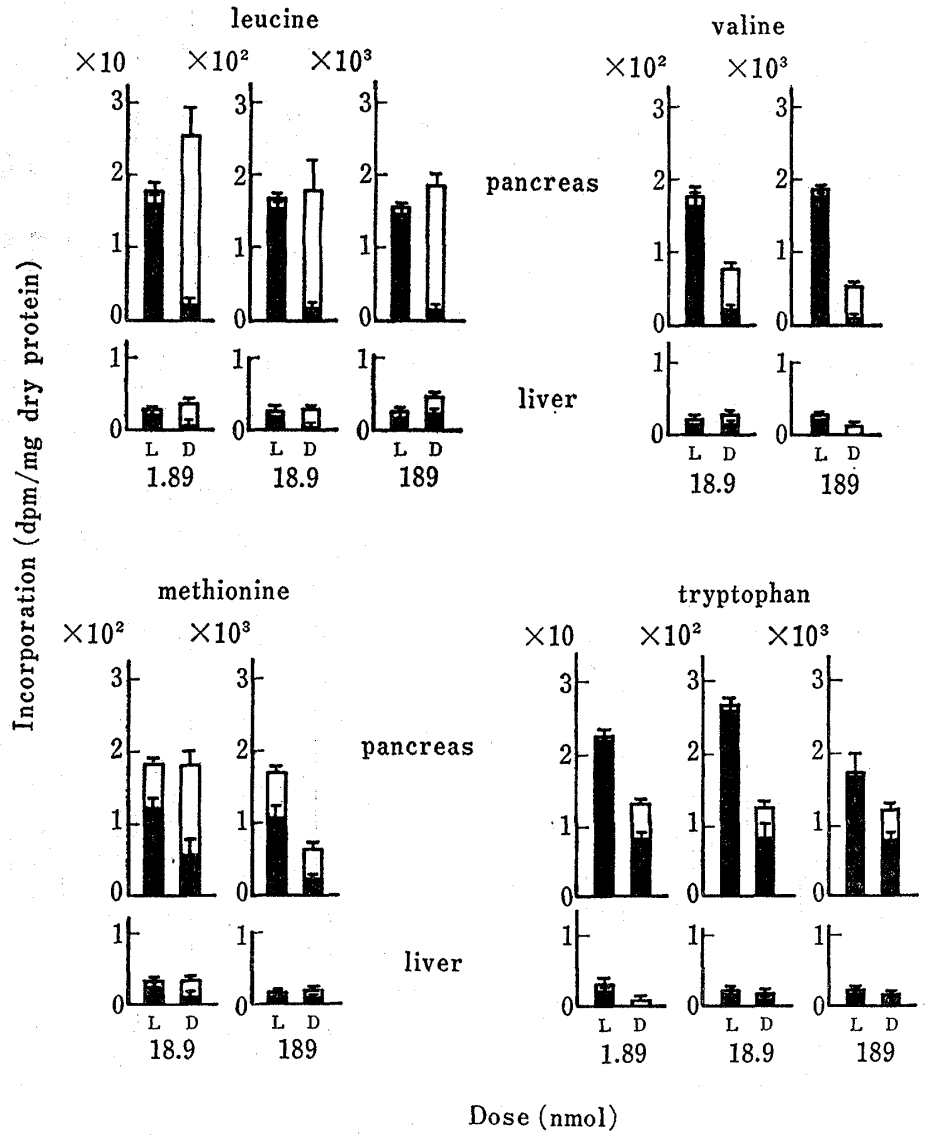


Fig. 4. Comparison of *in Vivo* Incorporation of L- and D-Forms of $^{3}H$- or $^{14}C$-Labeled Leucine, Valine, Methionine, and Tryptophan into TCA-Soluble and Protein Fractions of Pancreas and Liver of Mice at Different Doses

Three mice intravenously injected 0.01 $\mu$Ci (1.89 nmol), 0.1 $\mu$Ci (18.9 nmol), or 1 $\mu$Ci (189 nmol) per mouse of each of $^{14}C$-labeled L- or D-amino acid were killed by inhalation of ether gas at 30 min. Doses per mouse of D-methionine-$^{3}H$ were 0.0043 $\mu$Ci (18.9 nmol) and 0.043 $\mu$Ci (189 nmol), and those of D-valine-$^{3}H$ were 0.021 $\mu$Ci (18.9 nmol) and 0.21 $\mu$Ci (189 nmol). Approximately 200 mg of excised pancreas and liver were treated. In the experiments with $^{3}H$-labeled amino acids, the data were corrected for specific activity of $^{14}C$-labeled L-amino acid for illustration.
□: TCA-soluble fraction, ■: protein fraction, I: standard deviation.

The incorporation pattern of an equimolar mixture of L- and D-forms of an amino acid was the same as that of the corresponding DL-amino acids mentioned above.

### Abundance of $^{14}$C-Labeled L-Amino Acids into the TCA-Soluble Fraction

Of L-amino acids indicated in Fig. 1, methionine, valine, and leucine were examined since they showed relatively high total incorporation into the pancreas compared with any other amino acids. The proportion of $^{14}$C-labeled L-amino acid to the whole radioactivity in the TCA-soluble fraction of the pancreas 30 min after injection was 8.9% in methionine, 55.1% in valine, and 16.1% in leucine. However, radioactive metabolites other than each L-amino acid could not be detected, either by paper radiochromatography and autoradiography because of low radioactivity on the chromatogram.

### *In Vitro* Effect of D-Amino Acids on the Incorporation of $^{14}$C-Labeled L-Amino Acid

Effect of concentration of the substrate and of the corresponding D-amino acid on the incorporation of $^{14}$C-labeled L-amino acid into the TCA-soluble fraction of mouse pancreas was examined. The results were plotted by the method of Lineweaver and Burk (Fig. 5).

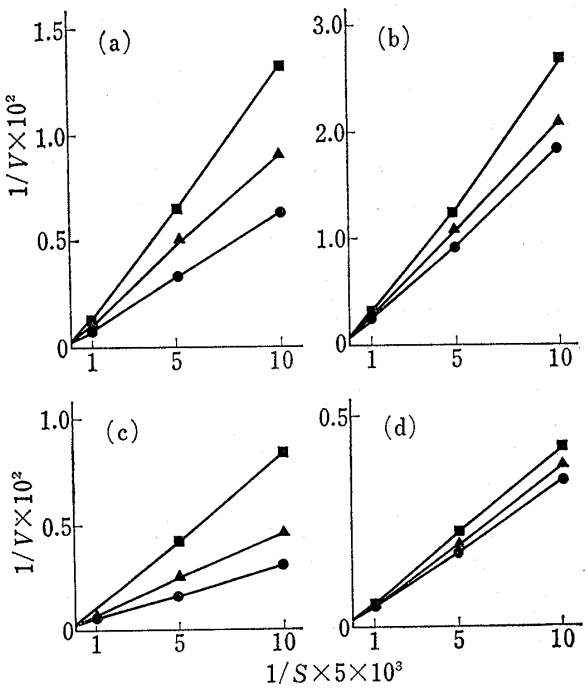


Fig. 5. Effect of Concentration of Substrate and of Corresponding D-Amino Acid on *in Vitro* Uptake of $^{14}$C-Labeled L-Amino Acid into TCA-Soluble Fraction of Mouse Pancreas

The sliced pancreas (approx. 200 mg wet weight/incubation tube) was incubated with a mixture of 0.5 ml of a radioactive L-amino acid (specific activity; 1 mCi/mmol) and 0.5 ml of the corresponding nonradioactive D-amino acid at various concentrations in KRP-Ca at 37° for 1 hr and treated by a procedure mentioned in the text.

Concentrations of (a) D-leucine, (b) D-valine, and (c) D-methionine: ●—●: 0 M, ▲—▲: $5\times10^{-3}$ M, ■—■: $5\times10^{-2}$ M. Concentrations of (d) D-tryptophan: ●—●: 0 M, ▲—▲: $5\times10^{-4}$ M, ■—■: $5\times10^{-3}$ M.

$S$: molar concentration of substrate (L-amino acid).
$V$: incorporated radioactivity.

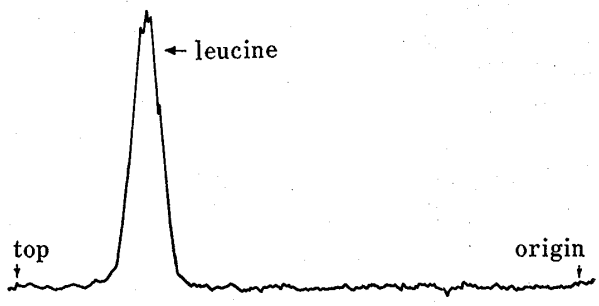


Fig. 6. Paper Radioscannogram of TCA-Soluble Fraction of Mouse Pancreas after Injection of D-Leucine[1-$^{14}$C]

Toyo Roshi No. 51, 2×40 cm.
Solvent: *n*-BuOH–AcOH–$H_2O$ (4:1:2).

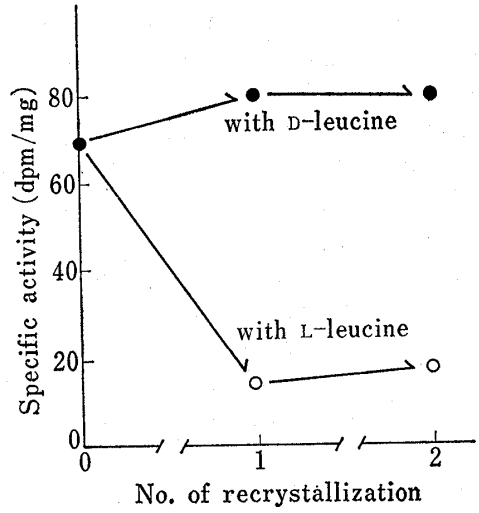


Fig. 7. Identification of Optical Form of Leucine-$^{14}$C Incorporated into TCA-Soluble Fraction

Changes in specific activity of leucine after repeated recrystallization are shown.

Each D-form of the four amino acids tested competed with the corresponding L-form for the incorporation into the TCA-soluble fraction. This suggested that the transport system of D-form into the mouse pancreas was identical with that of the L-form.

**Identification of the Optical Form of a Radioactive Amino Acid into TCA-Soluble Fraction after Injection of D-Leucine-$^{14}$C**

Paper radiochromatography was first carried out to identify radioactive metabolites in the TCA-soluble fraction of the pancreas 30 min after injection. Only one peak was detected on the chromatogram and its *Rf* value was identical with that of D- or L-leucine used as both internal and external standards (Fig. 6).

Optical form of leucine in the TCA-soluble fraction was examined by the recrystallization method. As indicated in Fig. 7, the specific activity, when recrystallized with nonradioactive D-leucine, was little altered. Contrary to this result, the specific activity decreased markedly with nonradioactive L-leucine. This indicated that the radioactive leucine was the D-form.

## Discussion

Of 18 kinds of L-amino acid tested, tryptophan, valine, methionine, and leucine, in this decreasing order of incorporation showed a relatively high total *in vivo* incorporation into the mouse pancreas 30 min after intravenous injection. Busch, *et al.*,[10] and Blau and Manske[2c] have already demonstrated the high localization of DL-tryptophan-$^{14}$C in the pancreas of Walker tumor-bearing and normal rats 60 min after injection. Among the above-mentioned four amino acids, about 50% of the radioactivity of L-methionine was found in the TCA-soluble fraction, while a large portion of L-tryptophan, L-valine, and L-leucine was detected in the protein fraction. The radioactivity of L-methionine, L-valine, and L-leucine in the TCA-soluble fraction attained its maximum within 10 min, as seen in selenomethionine-$^{75}$Se,[9] and it gradually decreased thereafter. The activity of protein fraction came to a maximum within 30 min. Hansson[2b] has shown that the radioactivity of methionine-$^{35}$S in the TCA-soluble fraction of mouse pancreas was already high 5 min after injection and attained its maximum at 10 min. He also pointed out that the activity of the protein fraction was also high at 5 min and it rose to a maximum at 80 min. This period for reaching the peak was very important for the decision of time of scanning.

It is thought that free (TCA-soluble fraction) or bound (protein fraction) amino acids in the pancreas may interfer with the amino acid incorporation level. However, no parallel correlation could be seen between the total incorporation level into the pancreas and the amino acid content[9] in both fractions of the organ of mice fed under the same conditions as in this experiment. This suggests that the incorporation level must be considered in correlation with the rate of transfer of amino acids into their pool and of their utilization for protein synthesis.

The pancreas/liver ratio of the total radioactivity of methionine, valine, and leucine incorporated into both fractions at 15, 30, and 60 min after injection were 6 to 10. These values were almost the same as that of selenomethionine-$^{75}$Se in dogs[11] and were a little higher than that in mice[11] and rabbits.[12] It has generally been estimated that the pancreas/liver ratio is required to be nearly over 10 for pancreatic scanning agents in man. Although all of 18 kinds of amino acid tested were not predominantly high in pancreas/liver ratio compared with selenomethionine-$^{75}$Se, the above-mentioned three amino acids seem a possible mother compound for introducing $\gamma$-emitters as a pancreas-scanning agent.

10) H. Busch, J.R. Davis, G.R. Honig, D.C. Anderson, P.V. Nair, and W.L. Nyhan, *Cancer Res.*, **19**, 1030 (1959).
11) T. Mizutani, *Nippon Igaku Hoshasen Gakkai Zasshi*, **26**, 1299 (1967).
12) H. Kakehi and Y. Tateno, *Nippon Rinsho*, **23**, 787 (1965).

Berlinguet, *et al.*[4] and Sherman, *et al.*[5] reported the localization of $^{14}$C-1-aminocyclopentanecarboxylic acid in a high concentration in the pancreas of mice, which suggests incorporation of an unnatural amino acid into the TCA-soluble fraction than into the protein fraction. This fact implies the significance of an incorporation into TCA-soluble fraction for the development of new pancreatic scanning agents. From this consideration, incorporation of DL- and D-forms corresponding to four L-amino acids mentioned above was examined. As a result, total incorporation of D-leucine into the pancreas was much the same as L-leucine. Other three D-amino acids were less incorporated than the corresponding L-forms. A large portion of the radioactivity of D-leucine was found in the TCA-soluble fraction, and the activity due to D-leucine itself (Fig. 6 and 7), in contrast to L-leucine, which was mostly incorporated into the protein fraction and about 16% of the radioactivity in TCA-soluble fraction was attributable to the L-form. Unnatural amino acids showing higher localization in the TCA-soluble fraction than in the protein fraction might be useful for the radioscanning agents, because of less radiation hazards owing to possible rapid excretion of labeled amino acids from TCA-soluble fraction into urine.

On the other hand, in order to convert a nonradioactive amino acid to a pancreas-scanning agent, a $\gamma$-emitter such as $^{75}$Se, $^{125}$I, $^{131}$I, *etc.*, must be introduced into the amino acid. As such examples, 3-iodotyrosine-$^{131}$I,[2c] N-iodoacetyltryptophan-$^{131}$I,[2c] selenocystine-$^{75}$Se,[3a] iodophenylalanine-$^{131}$I,[3b,3c,3d] *p*-fluorophenylalanine-$^{18}$F,[3e] 4-iodophenylalanine-$^{123}$I,[3f] and 6-iodotryptophan-$^{123}$I[3f] have already been tentatively investigated, and they showed no satisfactoty results in experimental studies. The ineffectiveness of the iodine-substituted amino acid derivatives may be due to a significant alteration in the molecular size of their amino acids. In order to minimize change in the size, substitution of iodine atom for a terminal methyl group of an aliphatic amino acid would be favorable for a pancreas-scanning agent because the Van der Waals radius of an iodine atom (2.15 Å) resembles that of a methyl group (2.0 Å).

From these considerations, some iodine-substituted derivatives of L- and D-forms of leucine and valine are being studied following an example of the fraudulent incorporation of 5-iodouracil for thymine in nucleic acid synthesis.[13]

13) P. Roy-Burman, "Analogues of Nucleic Acid Components: Mechanisms of Action," Springer-Verlag Berlin, 1970, pp. 57—59.