RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

DL-[Carboxyl-^{11}C]tryptophan, a Potential Agent for Pancreatic Imaging; Production and Preclinical Investigations

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In animal studies, DL-[*carboxyl-*^{14}*C*]*tryptophan* [DL-*Try(C-14)*] ***showed a high specificity for the pancreas, which suggested the potential of*** DL-[*carboxyl-*^{11}*C*]*tryptophan* [DL-*Try(C-11)*] ***for clinical pancreatic imaging. The blood clearance and tissue uptake of the amino acid were very rapid, and no carrier effect was observed through a dose of 5 mg/kg. None of three transplanted hamster pancreatic adenocarcinomas that we studied showed a selective uptake of*** DL-*Try(C-14)* ***by the tumor, and none of the three enzymatic regimens investigated gave significant enhancement of the pancreatic specificity. Commercial*** L-*Try(C-14) gave slightly better pancreatic specificity than the analogous racemic compound but without enough improvement to warrant attempts at optical resolution.*** DL-*Try(C-11) was synthesized in amounts up to 325 mCi using a rapid, high-temperature, high-pressure modification of the Bücherer–Strecker amino acid synthesis. Yields ranged from 30–60%, and a total of 40 min was required for synthesis and chromatographic purification.* DL-*Try(C-11) thus appears to have significant potential as a clinical pancreas-imaging agent, particularly when used in conjunction with positron computerized transaxial tomography.*

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The selective affinity of amino acids for the pancreas, because of its high rate of protein synthesis, has prompted the development of labeled amino acids for pancreatic imaging. L-[^{75}Se]selenomethionine was one of the first such agents proposed for pancreatic imaging (*1*) and is still the most widely used tracer for that purpose (*2*). However, there are serious disadvantages associated with L-[^{75}Se]selenomethionine, including high liver uptake, suboptimal and variable pancreatic specificity, and long effective half-life (*3–5*).

In an attempt to avoid these disadvantages, other extrastructurally labeled amino acids have been investigated, such as phenylalanine, tryptophan, and tyrosine labeled with F-18 and radioiodine (*6–11*). However, as with L-[^{75}Se]selenomethionine, the in-vivo tissue distributions of these analogs have generally differed greatly from those of the natural materials.

Because most natural amino acids contain only carbon, hydrogen, nitrogen, and oxygen, the short-lived positron emitters 20.4-min carbon-11, 10-min nitrogen-13, and 2-min oxygen-15 are the only potential externally detectable radionuclides for la-

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beling these compounds without altering their biochemical properties. Due to their decay by positron emission, these nuclides offer the added advantage of detection by coincidence techniques, such as positron computerized transaxial tomography (*12,13*). Carbon-11-labeled DL-valine (*14*), DL-phenylalanine (*15*), DL-phenylglycine (*15*), N-13-labeled L-alanine (*16*), L-glutamic acid (*16,17*), and L-glutamine (*16*) have all been studied as agents for pancreatic imaging.

In a study of 17 C-14-labeled natural amino acids, Busch and coworkers (*18*) found tryptophan to have by far the greatest specificity for rat pancreas. Other workers (*1,7,19*) have likewise observed the striking pancreatic specificity of C-14-labeled tryptophan. In fact, Taylor and Cottrall (*7*) theorized that tryptophan labeled with C-11 or N-13 would be an "ideal" radiopharmaceutical for pancreas scanning. However, difficulties in synthesis have prevented its investigation. Enzymatically labeled L-[^{13}N]tryptophan has also been proposed (*20*), but its synthesis has not been reported.

We used DL-[carboxyl-^{14}C]tryptophan [DL-Try(C-14)] to corroborate the pancreatic specificity reported by other workers. We then adapted our rapid, high-temperature, high-pressure Bücherer-Strecker amino acid synthesis (*21*) to the synthesis of C-11-carboxyl-labeled DL-tryptophan, which was studied in animals as a pancreas-imaging agent.

MATERIALS AND METHODS

Production and purification of DL-[carboxyl-^{11}C] and DL-[carboxyl-^{14}C]tryptophan. Oak Ridge National Laboratory's 86-inch cyclotron was used to produce a mixture of C-11 oxides by internal bombardment of a B_2O_3 target with 22-MeV protons. The mixture of ^{11}CO and $^{11}CO_2$ was converted on line catalytically, via $^{11}CH_4$, to H^{11}CN (*21,22*), which was trapped in 0.005 *N* NaOH. Our rapid, Bücherer-Strecker synthesis of DL-Try(C-11) using 3-indoleacetaldehyde bisulfite addition compound as a precursor, has been reported (*21*). We have recently found, however, that using a reaction temperature of 240°C for both steps and cutting the time for the first step to 5 min gives higher and more reproducible yields. The agent was purified by column chromatography on Porapak Q* followed by a final purification using cation-exchange chromatography (*21*). DL-Try(C-14) was prepared similarly, with K^{14}CN as the radioactive precursor.

Thin layer chromatography using silica gel chromatogram sheets with fluorescent indicator‡, developed in butanol:water:acetic acid (94:5:1 v/v), was used to establish the purity of the C-11- and C-14-labeled preparations of DL-tryptophan. Chromatographic patterns were assessed by visual examination under ultraviolet light, by ninhydrin development, or, when K^{14}CN had been added, by use of a spark chamber§. The tissue distributions of DL-Try(C-11) and DL-Try(C-14), prepared by the Bücherer-Strecker method, were also compared in rats with that of commercial DL-Try(C-14) (see below).

Animal studies. Tissue distribution studies with synthetic DL-Try(C-14) were made in male Fischer 344 rats, female New Zealand white rabbits, mongrel dogs of both sexes (results pooled), and male Golden Syrian hamsters bearing transplanted pancreatic adenocarcinomas (islet-cell adenocarcinoma 2309V, duct adenocarcinoma 46710, and adenocarcinoma Pan. No. 1) (*23*). Dogs were fasted overnight and then given a high-protein meal 30 min before agent administration; all other animals were fed ad libitum. For studies of the effect of carrier DL-tryptophan on the tissue distribution, the appropriate quantity of unlabeled DL-tryptophan was added to the injection solution. Animals received intravenous doses of 3–10 μCi of C-14-labeled DL-tryptophan per kg. After the desired intervals the animals were killed by exsanguination after light ether anesthesia (rats and hamsters), or by a lethal i.v. dose of sodium pentobarbital (rabbits and dogs). Weighed tissue samples were dissolved in NCS tissue solubilizer¶ and assayed by liquid-scintillation counting.

A similar study was done to compare the tissue distributions of several labeled tryptophan preparations in rats at 30 min after injection. The agents studied were DL-Try(C-11), synthetic DL-Try(C-14), commercial DL-Try(C-14), and L-Try(C-14). Rats were injected through the tail vein with 400 μCi/kg of C-11-labeled DL-tryptophan and 10 μCi/kg of the C-14-labeled agents.

Blood clearance studies were carried out using two- and eight-month-old male Fischer 344 rats injected through the tail vein with 15 μCi/kg of DL-Try(C-14). At various times after injection, blood samples were taken from the tail vein, weighed, dissolved in NCS tissue solubilizer, and assayed by liquid-scintillation counting. Male Fischer 344 rats, injected through the tail vein, were used with DL-Try(C-14) for decarboxylation studies and with DL-Try(C-11) for whole-body retention studies. The methods have been reported previously (*14*).

The effect of enzymatic stimulation of the pancreas on the tissue distribution of DL-Try(C-14) in rabbits was also studied. One group of animals was administered three Watson-Crick units/kg each of pancreozymin and secretin intravenously, 1 hr before administration of the amino acid (*24*). Another group received 0.5 Watson-Crick units of secretin per kg, 1 hr before injection, and 0.04 μg of Kinevac

sincalide** per kg, 30 min before injection (*25*). A third group received 5 Watson-Crick units/kg of pancreozymin and 1 mg/kg of bethanechol chloride (urecholine) intravenously, 15 min before injection (*26*). A fourth group served as controls. All animals were killed 30 min after administration of the DL-[carboxyl-^{14}C]tryptophan.

A normal mongrel dog was fasted for 24 hr and then given a high-protein meal 30 min before administration of 10 mCi of DL-Try(C-11) through the cephalic vein. Rectilinear scanning was begun 40 min after injection, using an 88-hole focusing collimator with a diameter of 5.5 in. and a focal length of 4 in. No correction was made for radionuclide decay during the approximately 20-min scanning period.

RESULTS AND CONCLUSIONS

A maximum of 325 mCi of DL-[carboxyl-^{11}C]tryptophan was produced from 2.5 Ci of Na^{11}CN using the modified Bücherer-Strecker technique. The chemical yield for the two-step synthesis from Na^{11}CN to purified DL-Try(C-11), which required ~40 min, was typically 30-40%, though sometimes as high as 59%. The specific activity of the C-11-labeled amino acid at the completion of synthesis and column purification was 15-30 mCi/mg.

Thin-layer chromatograms of DL-Try(C-11) and DL-Try(C-14) prepared by the modified Bücherer-Strecker procedure were identical to those obtained with commercial DL-Try(C-14). A single spot of R_f 0.25 was visualized by observing the fluorescence under ultraviolet light, by ninhydrin development, or, when K^{14}CN had been added, by use of a spark chamber. We have not observed radiolytic decomposition of DL-Try(C-11).

The purity of the DL-Try(C-11) and DL-Try(C-14) produced by our method was also established by comparing the tissue distributions of these preparations with that of commercial DL-Try(C-14) in rats at 30 min after i.v. injection (Table 1). Significant anomalies between the three groups were found only for the pancreas-to-kidney ratio with commercial DL-Try(C-14), and the pancreas-to-blood ratio with synthetic DL-Try(C-14). The great difference in pancreas-to-kidney ratios ($p < 0.01$) is probably due to group variabilities in the excretory process. The reason for the small difference in pancreas-to-blood ratios ($0.02 < p < 0.05$) is unknown.

The tissue distribution of commercial L-Try(C-14), however, was quite different from those of the three racemic preparations. The absolute concentration in the pancreas for the L-amino acid was much higher ($p < 0.01$) than that for any of the three DL-amino acid preparations, and the pancreas-to-tissue ratios were significantly higher ($p < 0.05$) in all cases for kidney, blood, spleen, and bone marrow. The pancreas-to-liver ratios were significantly higher only in comparisons of the L-amino acid with the commercial racemic preparation, and the pancreas-to-lung ratios were different only for comparison of the L-tryptophan with the C-11-labeled and the commercial C-14-labeled DL-tryptophan preparations.

The blood clearance of intravenously administered DL-Try(C-14) in the rat was quite rapid (Fig. 1). (It was assumed that blood comprises 7% of the body weight.) The percentage of the administered dose remaining in the blood was significantly lower

TABLE 1. TISSUE DISTRIBUTION OF VARIOUS LABELED TRYPTOPHAN PREPARATIONS IN RAT AT 30 MIN AFTER I. V. ADMINISTRATION

Tissue	DL-[carboxyl-^{11}C] tryptophan*	Synthetic DL-[carboxyl-^{14}C] tryptophan†	Commercial DL-[carboxyl-^{14}C] tryptophan†	Commercial L-[carboxyl-^{14}C] tryptophan†
	Percent administered dose/g‡§			
Pancreas	12.1 (11.2-12.8)	12.8 (12.1-13.9)	11.0 (9.2-13.5)	18.3 (16.3-20.5)
	Pancreas-to-tissue concentration ratio‡			
Liver	9.3 (8.8-10.1)	9.9 (9.1-10.7)	8.6 (8.0- 9.9)	11.8 (9.4-14.0)
Spleen	14.8 (13.4-16.5)	15.1 (14.3-16.6)	14.8 (12.1-17.7)	22.2 (18.2-27.0)
Kidney	7.7 (6.8- 8.3)	7.8 (7.2- 8.3)	5.3 (4.3- 6.3)	14.4 (13.2-16.0)
Lung	19.0 (14.0-23.9)	22.4 (19.4-25.0)	17.6 (12.2-21.2)	27.6 (22.8-35.5)
Muscle	54.5 (49.6-57.4)	49.6 (47.6-52.8)	47.9 (42.9-58.0)	62.1 (49.8-84.5)
Small intestine	7.6 (5.8- 9.6)	6.8 (5.5- 8.2)	7.4 (6.4- 9.2)	7.6 (3.6-10.6)
Marrow	—	13.2 (12.0-14.1)	13.7 (11.5-15.1)	19.0 (13.9-23.0)
Blood	32.3 (30.3-35.0)	37.8 (34.8-41.3)	30.2 (26.0-36.0)	70.3 (57.2-81.1)

* Dose contained ~0.1 mg stable DL-tryptophan per kg.
† Dose contained 0.2 mg stable DL-tryptophan per kg.
‡ Mean of four animals and range.
§ Normalized to body weight of 250 g.

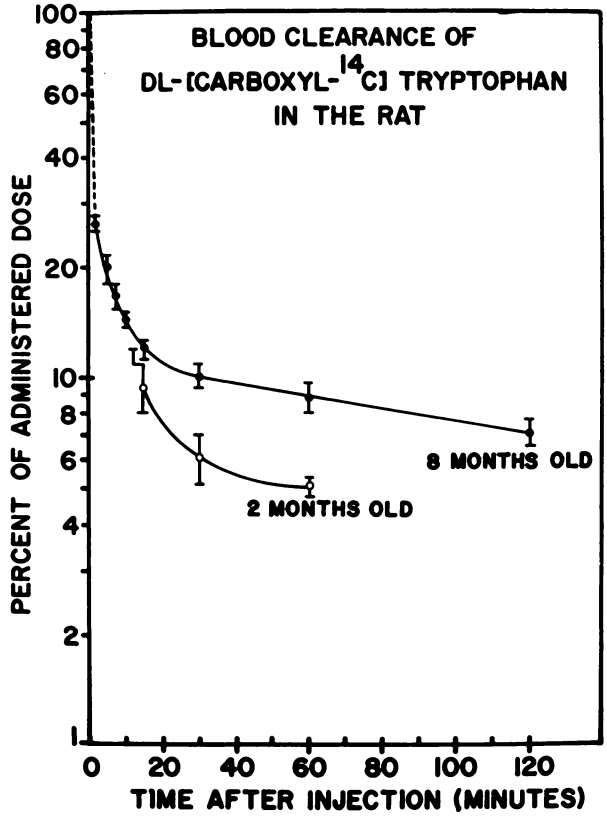

FIG. 1. Average blood clearance of intravenously administered DL-[carboxyl-^{14}C]tryptophan in 2- and 8-month-old male Fischer 344 rats (four animals per group). Doses contained 0.1 mg and 0.5 mg stable DL-tryptophan, respectively, per kg.

($p < 0.05$) for 2-month-old rats than for those 8 months old, for all three time intervals in which comparisons were made. In 2-month-old animals, only 9.4% of the injected dose remained in the blood at 15 min after injection.

Both the total excretion and the decarboxylative loss from intravenously administered carboxyl-labeled DL-tryptophan were appreciable in the rat (Table 2), but were much less than with DL-valine (*14*). The total excretion—including both urinary excretion and decarboxylative loss of $^{11}CO_2$ through the lungs—was measured using DL-Try(C-11), and amounted to 17.3% in 120 min. Decarboxylative loss alone, obtained using DL-Try(C-14), totaled 11.8% in 120 min.

TABLE 2. EXCRETION OF CARBOXYL-LABELED DL-TRYPTOPHAN IN MALE FISCHER 344 RATS

Time (min)	Total excretion* (%)	Decarboxylative loss† (%)
5	—	0.3 (0.0- 0.5)
10	—	0.8 (0.1- 1.6)
15	—	1.5 (0.2- 2.6)
20	4.9 (3.1- 6.4)	—
30	—	3.5 (1.3- 5.2)
40	9.4 (7.1-10.6)	—
60	11.7 (10.0-13.0)	6.9 (4.2- 9.2)
90	15.5 (13.6-17.6)	9.7 (8.3-10.3)
120	17.3 (14.8-21.6)	11.8 (11.0-12.8)

* Mean of five animals and range, obtained using DL-[carboxyl-^{11}C]tryptophan, containing ~0.02 mg stable DL-tryptophan per kg.

† Mean of four animals and range, obtained using DL-[carboxyl-^{14}C]tryptophan, containing 0.2 mg stable DL-tryptophan per kg.

Uptake of DL-Try(C-14) by rat tissues was very rapid (Table 3). Pancreatic uptake was high even at 15 min after injection and appeared to increase slightly through 60 min, although the increase was not statistically significant. Likewise, the pancreas-to-tissue concentration ratios generally showed a slight increase with increasing time after injection. The increase between 15 and 30 min was significant ($p < 0.05$) only for the pancreas-to-kidney and pancreas-to-blood ratios, whereas between the 15- and 60-min values the increase was significant ($p < 0.05$) for the ratios of pancreas-to-kidney, -lung, -muscle, and -blood.

The level of stable DL-tryptophan present in the DL-Try(C-14) injection solution was unimportant in the carrier range 0.1–5.0 mg/kg (Table 4). Three carrier levels (0.1, 1.0, and 5.0 mg/kg) were studied, and the absolute pancreatic uptakes were statistically equivalent in the three groups. The pancreas-to-tissue ratios were also generally the same, with small differences ($0.02 < p < 0.05$) found in the pancreas-to-kidney ratios in the 0.1- to 5.0-mg/kg comparison, and in the pancreas-to-muscle ratios in the 1.0- to 5.0-mg/kg comparison. The difference in pancreas-to-kidney ratios is again probably due simply to group variabilities in the excretory process.

In order to assess the pancreatic specificity of DL-Try(C-14) in a larger animal species, we studied its tissue distribution in normal mongrel dogs at 30 min after injection. The dogs were fasted overnight and then given a high-protein meal 30 min before the injection of the amino acid. The agent was taken up quite selectively by the pancreas (Table 5), although the pancreas-to-tissue concentration ratios were somewhat lower than in similar studies in rats.

Figure 2 shows a rectilinear pancreas scan, obtained with DL-Try(C-11) in a normal mongrel dog. A high-protein meal, which was found to stimulate pancreatic uptake in previous studies with DL-[1-^{11}C]DL-valine (*14*), was administered 30 min before the amino acid. The typical arch-shaped dog's pancreas was clearly delineated.

None of the three transplanted hamster pancreatic adenocarcinomas that we studied showed a selective affinity for DL-Try(C-14) (Table 6). There was a difference, however, in the tumor uptake of the agent by the three tumor types. The pancreatic

TABLE 3. EFFECT OF TIME ON TISSUE DISTRIBUTION OF DL-[CARBOXYL-^{14}C]TRYPTOPHAN* IN RAT

Tissue	15 min	30 min	60 min
		%dose/g†‡	
Pancreas	8.4 (7.5- 9.5)	9.8 (7.8-11.7)	10.9 (8.1-13.0)
		Pancreas/tissue concentration ratio†	
Liver	7.8 (7.0- 9.0)	8.5 (6.7- 9.4)	10.2 (7.6-12.4)
Spleen	14.9 (13.4-17.2)	15.2 (12.6-18.0)	18.5 (15.0-20.9)
Kidney	4.9 (4.4- 6.2)	6.4 (5.3- 7.0)	8.0 (6.1- 9.5)
Lung	16.5 (11.4-20.3)	19.2 (13.9-27.3)	28.2 (23.0-30.2)
Muscle	38.2 (31.6-44.7)	44.9 (36.2-55.0)	51.6 (39.3-60.0)
Small intestine	11.1 (8.4-17.9)	8.0 (6.6-10.1)	9.1 (7.6-10.6)
Marrow	11.3 (9.9-13.8)	11.1 (9.6-12.1)	11.7 (9.4-13.7)
Blood	16.2 (11.5-20.7)	28.6 (19.4-32.9)	37.2 (27.7-43.4)
Urine	3.3 (0.9- 4.8)	5.9 (4.5- 7.8)	—
Brain	70.4 (52.3-86.9)	70.3 (54.6-87.8)	66.7 (48.5-77.7)

* Containing 0.1 mg stable DL-tryptophan per kg.
† Mean of four animals and range.
‡ Normalized to body weight of 250 g.

TABLE 4. EFFECT OF CARRIER DL-TRYPTOPHAN ON TISSUE DISTRIBUTION OF DL-[CARBOXYL-^{14}C] TRYPTOPHAN IN RAT AT 30 MIN AFTER INJECTION

Tissue	0.1 mg/kg	1.0 mg/kg	5.0 mg/kg
		%dose/g*†	
Pancreas	9.8 (7.8-11.7)	9.3 (8.3-10.7)	8.6 (7.6- 9.8)
		Pancreas/tissue concentration ratio*	
Liver	8.5 (6.7- 9.4)	8.8 (7.0-10.1)	8.4 (7.1- 9.8)
Spleen	15.2 (12.6-18.0)	16.8 (13.3-18.9)	14.0 (11.1-17.4)
Kidney	6.4 (5.3- 7.0)	7.2 (6.4- 8.0)	8.2 (7.1- 9.3)
Lung	19.2 (13.9-27.3)	18.0 (10.6-25.2)	21.0 (15.6-28.1)
Muscle	44.9 (36.2-55.0)	44.2 (39.1-50.2)	36.9 (33.1-39.9)
Small intestine	8.0 (6.6-10.1)	8.2 (6.8- 9.1)	8.4 (7.4-10.5)
Marrow	11.1 (9.6-12.1)	11.7 (9.5-12.7)	10.8 (7.7-13.7)
Blood	28.6 (19.4-32.9)	26.2 (22.2-31.6)	23.4 (21.8-26.2)
Urine	5.9 (4.5- 7.8)	2.2 (0.9- 3.9)	5.6 (2.7- 9.7)
Brain	70.3 (54.6-87.8)	63.6 (47.1-65.6)	57.3 (51.9-64.9)

* Mean of four animals and range.
† Normalized to body weight of 250 g.

TABLE 5. TISSUE DISTRIBUTION OF DL-[CARBOXYL-^{14}C]TRYPTOPHAN* IN DOG AT 30 MIN AFTER I.V. ADMINISTRATION

Tissue	%dose/g†‡	Pancreas/tissue concentration ratio†	Total percent in organ†
Pancreas	0.187 (0.117-0.307)	—	4.6 (3.9- 6.3)
Liver	0.028 (0.024-0.037)	6.5 (4.6- 8.8)	9.7 (7.4-11.7)
Spleen	0.017 (0.010-0.029)	11.6 (6.7-16.6)	0.6 (0.4- 0.7)
Kidney	0.036 (0.027-0.043)	5.4 (3.2- 9.0)	1.9 (1.4- 2.9)
Lung	0.015 (0.013-0.018)	12.5 (8.4-17.0)	1.3 (1.1- 1.5)
Muscle	0.007 (0.006-0.010)	24.9 (20.4-32.1)	—
Small intestine	0.023 (0.013-0.037)	8.0 (6.7- 9.9)	—
Marrow	0.027 (0.023-0.030)	6.8 (4.7- 9.8)	—
Blood	0.012 (0.009-0.014)	16.0 (12.9-24.1)	—
Urine	0.606 (0.325-1.110)	0.4 (0.1- 0.6)	7.9 (4.6-11.3)
Heart	0.012 (0.011-0.014)	15.7 (10.9-21.5)	0.8 (0.7- 0.9)
Lymph node	0.033 (0.018-0.061)	6.3 (4.9- 8.6)	—
Thymus	0.017 (0.015-0.019)	11.0 (7.8-15.6)	—
Adrenal	0.021 (0.018-0.028)	8.8 (6.7-10.5)	—

* Containing 0.1 mg stable DL-tryptophan per kg.
† Mean of four animals and range.
‡ Normalized to body weight of 10 kg.

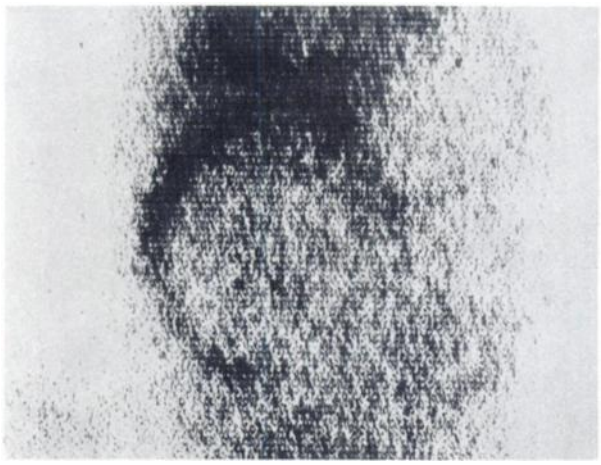

FIG. 2. Rectilinear pancreas scan of normal mongrel dog, begun 40 min after i.v. administration of 10 mCi of DL-[carboxyl-^{11}C]tryptophan containing ~1 mg of stable DL-tryptophan.

adenocarcinoma Pan. No. 1 showed significantly lower tumor uptake than either the pancreatic islet-cell adenocarcinoma 2309V or the pancreatic duct adenocarcinoma 46710. The reason for this difference is not fully known but may be related to the fact that the Pan. No. 1 tumor destroys blood vessels as it grows, thus outgrowing its blood supply (V. R. Risch, The Hahnemann Medical College and Hospital of Philadelphia, personal communication).

Enzymatic stimulation of the pancreas was investigated as a possible means of enhancing the pancreatic uptake of DL-Try(C-14) in rabbits (Table 7). None of the three enzymatic regimens that were studied—secretin plus pancreozymin, secretin plus sincalide, and pancreozymin plus urecholine—enhanced tissue distributions of the agent significantly above the controls. Although we did not verify that pancreatic stimulation had occurred, the enzymatic

TABLE 6. TISSUE DISTRIBUTION OF DL-[CARBOXYL-^{14}C]TRYPTOPHAN* AT 30 MIN AFTER INJECTION IN HAMSTERS BEARING TRANSPLANTED PANCREATIC ADENOCARCINOMAS

	%dose/g†		
Tissue	2309V‡	46710§	Pan. No. 1‡
Pancreas	11.24 (8.44–13.02)	13.48 (10.88–18.00)	15.96 (12.36–19.56)
Tumor	1.54 (1.16– 1.74)	1.12 (0.86– 1.56)	0.32 (0.14– 0.52)
Liver	2.04 (1.74– 2.34)	2.06 (1.62– 2.66)	3.02 (2.86– 3.26)
Spleen	1.34 (1.08– 1.56)	1.56 (1.28– 1.76)	2.28 (1.58– 2.66)
Kidney	2.26 (1.80– 2.76)	3.06 (2.06– 5.64)	2.98 (2.38– 3.62)
Lung	0.74 (0.64– 0.80)	0.86 (0.70– 0.96)	1.04 (0.96– 1.30)
Muscle	0.38 (0.34– 0.48)	0.44 (0.38– 0.52)	0.44 (0.36– 0.56)
Small intestine	1.96 (1.68– 2.32)	2.14 (1.06– 2.80)	3.20 (2.42– 3.70)
Marrow	1.68 (1.34– 2.06)	2.20 (1.94– 2.58)	2.58 (2.32– 2.74)
Blood	0.64 (0.56– 0.70)	0.80 (0.66– 0.92)	1.02 (0.90– 1.18)
Urine	16.72 (13.62–22.60)	25.74 (6.14–68.10)	20.58 (9.44–29.64)

* Containing 0.5 mg stable DL-tryptophan per kg.
† Normalized to a body weight of 125 g.
‡ Mean of four animals and range.
§ Mean of five animals and range.

TABLE 7. EFFECT OF ENZYMATIC STIMULATION OF THE PANCREAS ON TISSUE DISTRIBUTION OF DL-[CARBOXYL-^{14}C]TRYPTOPHAN* IN RABBIT AT 30 MIN AFTER INJECTION

	Pancreas-to-tissue concentration ratio			
Tissue	Control†	Secretin+ pancreozymin†	Secretin+ sincalide†	Pancreozymin+ urecholine‡
Liver	6.9 (2.6–10.3)	6.7 (4.6–11.6)	6.4 (4.2– 8.3)	6.8 (6.3– 7.5)
Spleen	6.5 (2.7– 9.7)	5.9 (3.4–10.4)	7.0 (4.1– 9.6)	7.1 (6.2– 7.8)
Kidney	3.7 (1.6– 5.6)	3.8 (2.0– 7.2)	4.2 (2.7– 5.8)	4.0 (3.2– 4.6)
Lung	9.3 (2.6–15.3)	8.8 (5.8–16.3)	10.4 (6.3–15.0)	9.3 (7.8–11.1)
Muscle	21.8 (7.3–33.1)	19.9 (12.6–35.6)	22.1 (14.4–31.4)	26.1 (19.0–30.3)
Small intestine	5.0 (2.0– 7.8)	4.6 (3.6– 6.3)	5.5 (3.5– 6.9)	5.3 (4.6– 5.6)
Marrow	11.5 (8.8–15.5)	8.3 (4.2–14.3)	13.4 (5.8–20.0)	17.6 (11.4–29.6)
Blood	9.8 (3.1–14.2)	14.3 (7.4–25.8)	12.2 (7.2–17.2)	12.3 (10.1–14.4)
Urine	2.0 (0.5– 3.5)	0.9 (0.2– 1.5)	0.4 (0.2– 0.5)	1.8 (0.1– 3.1)

* Containing 0.1 mg stable DL-tryptophan per kg.
† Mean of four animals and range.
‡ Mean of three animals and range.

regimens used have been reported to stimulate the pancreas (*24–26*). We note that significant adverse reactions were observed in the treatment of rabbits with pancreozymin and urecholine according to protocols used previously in both rats and humans (*24*). Our four animals had excessive salivation and secreted a milky fluid from the eyes. The salivation started ~1 min after administration of the enzymes and continued until the animals were killed at 45 min after enzyme administration. The eye secretion was more transient, beginning ~5 min after enzyme administration and lasting for 5–10 min. In addition, three of the four animals developed diarrhea.

DISCUSSION

The synthesis of DL-Try(C-11) by the modified Bücherer–Strecker technique has made possible the evaluation of the long-recognized potential of a carbon-11-labeled tryptophan as an agent for pancreatic imaging (*7*). The production techniques used gave high yields of DL-Try(C-11). The purity of the agent was proven both by thin layer chromatography and by tissue distribution comparisons in animals. After final radiopharmaceutical processing, which included neutralization, microfiltration, and a rapid (15-min) check for pyrogenic contamination using the Limulus amebocyte lysate technique†† (*27*), the material was suitable for human use. We are currently supplying DL-Try(C-11) for clinical trials.

Tissue distribution studies in animals, using both DL-Try(C-14) and DL-Try(C-11), corroborated the literature reports of unusually specific uptake of this amino acid by the pancreas. Scanning studies with DL-Try(C-11) further verified the potential of this agent. Blood clearance and tissue uptake of the amino acid were both very rapid, which is necessary for use of the short-lived C-11.

The absence of a significant carrier effect (in the range 0.1–5.0 mg/kg) on the tissue distribution of DL-Try(C-14) is important, since attempts to scale down the quantities of reagents in the modified Bücherer–Strecker synthesis have presented difficulties. Very low and nonreproducible yields have been obtained at ½ to $^1/_{10}$ of the 0.1-millimole level normally used.

The lack of specific uptake of DL-Try(C-14) by three transplanted hamster pancreatic adenocarcinomas suggests that pancreatic carcinoma in man may be diagnosed by the presence of a defect in the normal pancreatic uptake of DL-Try(C-11). The use of positron computerized transaxial tomography with this agent should permit the diagnosis of smaller lesions than is possible using conventional two-dimensional pancreatic imaging with L-[^{75}Se]selenomethionine.

Although L-Try(C-14) showed somewhat greater pancreatic specificity than the analogous racemic compound, the improvement does not appear sufficient to warrant attempts at optical resolution of DL-Try(C-11), which would be hampered by the short half-life of C-11. The pancreas-to-tissue concentration ratios with DL-Try(C-11) should be high enough to permit excellent visualization of the pancreas, particularly when transaxial tomographic imaging is used.

FOOTNOTES

* Waters Associates, Inc.
‡ Eastman #13181.
§ Birchover Instruments, Bancroft, U.K.
¶ Amersham/Searle, Arlington Heights, IL.
** E. R. Squibb & Sons, New Brunswick, NJ.
†† Difco Laboratories, Detroit, MI.

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