[1-^{11}C] DL-Valine, A Potential Pancreas-Imaging Agent

Lee C. Washburn, Bruce W. Wieland, Tan Tan Sun, Raymond L. Hayes, and Thomas A. Butler

Oak Ridge Associated Universities and Oak Ridge National Laboratory, Oak Ridge, Tennessee

There is a great need for a better pancreas-imaging agent. Studies with [1-^{11}C] DL-valine have shown this amino acid to have a high pancreatic specificity in the four animal species examined. The tissue distribution was almost optimal by 30 min after injection, and no carrier effect was observed through a dose of 5 mg/kg. [1-^{11}C] DL-Valine was synthesized in amounts up to 363 mCi using a rapid ($T_{1/2}$ = 20.4 min for C-11), high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis. Purification was by anion-exchange followed by cation-exchange chromatography. [1-^{11}C] DL-Valine was obtained in a 70% chemical yield with a total synthesis and purification time of 45 min. Studies in animals have demonstrated that it is a potentially useful new agent for clinical pancreatic imaging.

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One of the most important diagnostic problems in nuclear medicine is the need for an improved agent for pancreatic imaging (*1*). Carcinoma of the pancreas is fourth in the leading causes of cancer deaths in the United States (*2*), being responsible for approximately 20,000 deaths each year (*3*). The 5-yr survival rate for patients with pancreatic carcinoma is only 1% for males and 2% for females. Moreover, the incidence of this type of cancer unfortunately appears to be increasing (*3*). The bleak survival prospects for patients having cancer of the pancreas are possibly due to the lack of early diagnosis.

Currently the most reliable nuclear medical procedure for diagnosis of pancreatic carcinoma involves imaging the pancreas with the radiopharmaceutical [^{75}Se] selenomethionine together with the use of a Tc-99m sulfur colloid scan to permit computerized subtraction of interfering Se-75 radiation derived from the liver (*4*). However, [^{75}Se] selenomethionine suffers from a number of disadvantages (*5*). One problem is the high radiation dose to the patient. Selenium-75 has a long physical half-life (120 days) and [^{75}Se] selenomethionine in turn has a long biologic half-time (70 days). These two factors result in exposure of the patient to near maximum acceptable levels of diagnostic radiation in order to achieve adequate imaging statistics (*5*). The biggest problem, however, is the inability of the agent to delineate clearly neoplasms associated with the pancreas. Uptake of [^{75}Se] selenomethionine even by a normal pancreas is not uniform from patient to patient. Significant percentages of both false positives and false negatives result (*6,7*).

A number of extrastructurally labeled amino acids (i.e., tryptophan and phenylalanine labeled with F-18 or I-123) have been investigated as potential agents for pancreatic imaging (*8–10*), but, as with [^{75}Se] selenomethionine, the in-vivo tissue distributions of these labeled agents have generally differed greatly from those of the natural amino acids. This makes C-11 ($T_{1/2}$ = 20.4 min) an obvious choice for the labeling of amino acids for pancreatic imaging, since the biochemical behavior of the labeled compound should be nearly the same as that of the natural amino acid. (Labeling with N-13 would also provide comparable in-vivo behavior, but the 10-min half-life of N-13 would be more restrictive.) Since C-11 is a positron emitter, C-11-labeled amino acids can be imaged by coincidence-detection techniques, such as positron emission transaxial tomography (*11,12*).

Although most naturally occurring amino acids show a significant affinity for the pancreas, two of

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For reprints contact: L. C. Washburn, Medical and Health Sciences Div., Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37830.

them, valine and tryptophan, appear to have the highest degree of pancreatic specificity (*13,14*). In order to evaluate the potential of [1-^{11}C] DL-valine as a pancreas-imaging agent, we used [1-^{14}C] DL-valine to corroborate the pancreatic specificity reported for it by other workers and to evaluate the effects of various parameters on the tissue distribution of DL-valine. We then applied our rapid, high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis—which had been developed for [carboxyl-^{11}C] 1-aminocyclopentanecarboxylic acid (C-11 ACPC) (*15*)—to the synthesis of [1-^{11}C] DL-valine (*16*) and examined the latter agent in animals as a pancreas-visualizing agent.

MATERIALS AND METHODS

Production and purification of [1-^{11}C] DL-Valine. The C-11 used in this study was produced by bombarding a B_2O_3 target with 22-MeV protons in the Oak Ridge National Laboratory's 86-inch cyclotron. A helium sweep gas moves the resulting mixture of ^{11}CO and $^{11}CO_2$ from the target assembly and they are converted catalytically, on line, to H^{11}CN (*15*). [1-^{11}C] DL-valine is synthesized and purified by procedures analogous to those used for the production of C-11 ACPC (*15*), except that 35 μl (27.8 mg) of isobutyraldehyde, replaces the cyclopentanone used in the C-11 ACPC synthesis. As in the latter, purification is accomplished by anion-exchange followed by cation-exchange chromatography.

The purity of the [1-^{11}C] DL-valine product was assessed by thin-layer chromatography using silica-gel chromatogram sheets* developed in butanol-water-acetic acid (100:10:5 by vol). Chromatographic patterns were viewed either by ninhydrin development or, when the original reaction mixture had been spiked with K^{14}CN, through the use of a spark chamber.† As a further check on the purity of the product, we also compared the tissue distributions in test animals with those obtained using [1-^{14}C] DL-valine (see below).

Animal studies. Tissue distribution, blood clearances, and decarboxylation studies in animals were carried out using [1-^{14}C] DL-valine. The specific activity was 0.47 mCi/mg. The labeled amino acid was dissolved in 0.9% NaCl before administration, and all animals were injected intravenously. For studies of the effect of carrier DL-valine on the tissue distribution, the appropriate quantity of unlabeled DL-valine was added before injection.

Tissue distribution studies with [1-^{14}C] DL-valine were made in male Buffalo rats, male Fischer 344 rats, male Golden Syrian hamsters, female New Zealand white rabbits, and mongrel dogs of both sexes (in which the results were pooled, since no sex difference in tissue distribution was evident).

Each experimental group consisted of four animals. Rats were administered 10 μCi [1-^{14}C] DL-valine per kg, and hamsters, rabbits, and dogs received 12.5 μCi per kg. At the desired time intervals the animals were killed; rats and hamsters were exsanguinated after light ether anesthesia, whereas rabbits and dogs were given an i.v. overdose of sodium pentobarbital. Weighed tissue samples were dissolved in NCS tissue solubilizer‡ and assayed by liquid-scintillation counting.

Blood clearance studies were performed using four male Fischer 344 rats injected through the tail vein. The animals received 20 μCi (= 42 μg) [1-^{14}C] DL-valine per kg. Blood samples were taken from the tail vein at various times after injection, and the samples were processed as were the tissue samples described above.

Decarboxylation studies with [1-^{14}C] DL-valine were carried out using male Buffalo rats injected as above through the tail vein. Immediately after injection the animal was placed into an airtight cage, which was then continuously flushed with a stream of air. After various intervals, samples containing the exhaled $^{14}CO_2$, which had been trapped in NCS tissue solubilizer, were removed and assayed by liquid-scintillation counting.

Whole-body retention studies of [1-^{11}C] DL-valine were made with male Fischer 344 rats. A geometry-independent small-animal whole-body counter (*17*) was used to obtain whole-body counts of the animals at various times after tail-vein administration, allowing, after decay correction, for computation of the total metabolic loss (by both decarboxylation and urinary excretion) of C-11 radiolabel.

An evaluation was made of the effect of various feeding protocols on the quality of rectilinear pancreas scans obtained with [1-^{11}C] DL-valine in the same normal mongrel dog. The agent (10–40 mCi) was administered through the cephalic vein, and all scans were begun 40 min after injection. The feeding protocols used were: (a) animal fasted for 24 hr; (b) animal fasted for 24 hr and then administered 10 g of glucose intravenously 30 min before [1-^{11}C] DL-valine administration; (c) animal fasted for 24 hr and then given 100 g of Gevral protein supplement (60% protein, 2% fat, and 24.2% carbohydrates) by mouth 30 min before tracer administration; (d) animal fasted for 24 hr and then given 40 g of lard ($\sim$ 100% fat) by mouth 30 min before tracer administration; and (e) animal fasted for 24 hr and then given 800 g of commercial high-protein dog food (16% protein, 5% fat) by mouth 30 min before tracer administration. All of the scans were

TABLE 1. TISSUE DISTRIBUTION OF [1-^{14}C] DL-VALINE AND [1-^{11}C] DL-VALINE IN DOG AND RAT 30 MIN AFTER I.V. ADMINISTRATION

	Dog*		Rat*	
Tissue	[1-^{14}C] DL-valine	[1-^{11}C] DL-valine	[1-^{14}C] DL-valine	[1-^{11}C] DL-valine
	Percent administered dose/g†			
Pancreas	0.10 (0.07– 0.13)	0.10 (0.09– 0.11)	6.47 (5.51– 8.22)	5.52 (4.68– 6.37)
	Pancreas-to-tissue concentration ratio			
Liver	6.4 (4.2 – 9.3)	3.9 (2.9 – 4.8)	9.8 (9.3 –10.4)	8.7 (8.0 – 9.6)
Spleen	8.6 (6.6 –11.5)	4.8 (4.1 – 5.9)	12.5 (9.1 –17.5)	8.1 (5.7 – 9.3)
Kidney	4.7 (3.9 – 5.9)	3.0 (2.1 – 3.8)	12.0 (10.0 –15.7)	5.9 (4.7 – 7.8)
Lung	8.0 (6.9 –10.1)	5.0 (4.0 – 6.3)	15.3 (13.3 –20.5)	10.9 (7.4 –14.0)
Muscle	12.9 (9.9 –16.3)	10.4 (9.0 –12.4)	33.2 (19.7 –44.7)	23.5 (20.2 –30.9)
Small intestine	4.4 (2.2 – 6.3)	4.1 (2.7 – 5.6)	5.7 (4.7 – 6.9)	6.6 (4.7 – 8.7)
Marrow	12.0 (4.9 –18.7)	—	7.8 (6.9 – 9.7)	—
Blood	9.6 (8.9 –10.8)	7.7 (5.5 – 9.8)	20.3 (14.3 –32.0)	22.3 (18.6 –28.1)
Thymus	8.1 (6.3 –10.3)	—	—	—
Adrenal	5.7 (4.2 – 7.4)	—	—	—
Urine	0.4 (0.1 – 0.8)	0.3 (0.1 – 0.4)	—	—
Heart	8.8 (6.9 –11.5)	—	—	—
Lymph node	4.6 (3.1 – 6.7)	—	—	—

* Mean of four animals and range.
† Normalized to body weight of 10 kg for dog and 250 g for rat.

carried out with an 88-hole, 5.5-in. diam., focusing collimator with a focal length of 4 in. No correction was made for radionuclide decay during the scanning, which required approximately 20 min.

RESULTS AND CONCLUSIONS

Cyclotron bombardment at a beam current of 175 μA for 30 min produced a maximum of 5 Ci of $^{11}CO_2$ and ^{11}CO, and their on-line conversion through $^{11}CH_4$ to H^{11}CN occurred with approximately 75% yield. The chemical yield for the two-step synthesis from H^{11}CN to purified [1-^{11}C] DL-valine was approximately 70% and gave 363 mCi as the maximum C-11 yield obtained to date. The specific activity of the [1-^{11}C] DL-valine was 15–35 mCi/mg at the completion of synthesis and purification, which required approximately 45 min. By overlapping various steps of the cyclotron production, chemical synthesis, purification, and column regeneration, we have been able to produce routinely 100 to 200-mCi batches of [1-^{11}C] DL-valine and/or other amino acids at production intervals of 1 hr or less (*16*).

The thin-layer chromatographic pattern obtained on a test sample of [1-^{11}C] DL-valine (from a run spiked with K^{14}CN before synthesis) was identical to that of commercial [1-^{14}C] DL-valine. No evidence of impurities was seen upon visualization either using a spark chamber or by ninhydrin development. No radiolytic decomposition of [1-^{11}C] DL-valine has been observed.

The purity of the [1-^{11}C] DL-valine produced was also evaluated by comparing the tissue distributions of our [1-^{11}C] DL-valine preparations with those of the commercially available [1-^{14}C] DL-valine in both dogs and rats after i.v. administration (Table 1). Significant ($P < 0.05$) differences in tissue distribu-

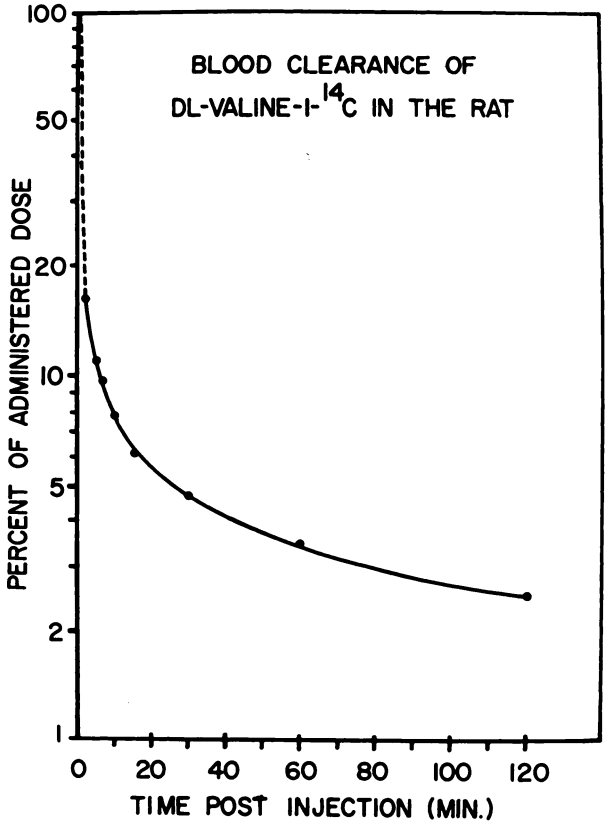

FIG. 1. Average blood clearance (semilog) of intravenously administered [1-^{14}C] DL-valine in four male Fischer 344 rats.

TABLE 2. EFFECT OF TIME ON TISSUE DISTRIBUTION OF [1-^{14}C] DL-VALINE (0.021 mg/kg) IN RAT

Tissue	Percent administered dose/g*		
	15 min	30 min	60 min
Pancreas	5.84 (5.37–6.85)	6.47 (5.51–8.22)	6.86 (6.74–7.17)
Liver	0.67 (0.62–0.69)	0.66 (0.58–0.84)	0.55 (0.52–0.57)
Spleen	0.68 (0.62–0.75)	0.54 (0.43–0.64)	0.58 (0.51–0.64)
Kidney	0.68 (0.62–0.76)	0.54 (0.52–0.57)	0.55 (0.52–0.57)
Lung	0.54 (0.47–0.62)	0.43 (0.40–0.45)	0.35 (0.34–0.37)
Muscle	0.24 (0.23–0.26)	0.21 (0.15–0.28)	0.16 (0.14–0.17)
Marrow	0.77 (0.69–0.87)	0.82 (0.75–0.89)	0.81 (0.74–0.85)
Small intestine	1.14 (1.10–1.25)	1.14 (0.98–1.21)	1.03 (0.85–1.17)
Blood	0.46 (0.31–0.59)	0.34 (0.26–0.38)	0.27 (0.25–0.31)

* Mean of 4 animals and range; normalized to a body weight of 250 g.

tion between the C-11- and C-14-labeled agents were seen in spleen, kidney, and lung in the dog, and kidney alone in the rat. Since the excretory process at 30 min after injection is subject to great variability, the kidney discrepancies are not too surprising. The other anomalies seen in the dog may be because we used mongrel dogs and gave no special attention to the feeding protocol, a factor later shown to be very important (see below).

The very rapid blood clearance of intravenously administered [1-^{14}C] DL-valine in the rat is shown in Fig. 1. (It was assumed that blood comprises 7% of the body weight.) By 15 min after injection only 6.2% of the injected radioactivity remained in the blood. The uptake of [1-^{14}C] DL-valine by the tissues was likewise very rapid (Table 2) and entirely compatible with the possible clinical use of C-11. The uptake of the agent by rat pancreas was almost maximum at 15 min after injection; it appeared to increase slightly (though the increase was not statistically significant, $P > 0.10$) between 15 and 60 min after injection, whereas the concentration in most other tissues diminished. In view of the half-life of C-11, 30 min after injection will perhaps be the best time for scanning in man, assuming that DL-valine behaves similarly in man and rat.

In order to assess the importance of stable DL-valine on the tissue distribution of [1-^{11}C] DL-valine preparations, we studied the carrier effect on the tissue distribution of DL-valine-1-^{14}C in the rat. Added carrier DL-valine at levels up to 5 mg/kg had no statistically significant effect ($P > 0.10$) on the tissue distribution (Table 3). This is not surprising, since a significant amount of L-valine is found in rat blood—about 1.1 mg/kg body weight (*18*).

Determination of the tissue distribution of [1-^{14}C] DL-valine at 30 min after injection was carried out in four animal species (hamster, rat, rabbit, and dog) to test for any possible species differences and thus to indicate the potential of [1-^{11}C] DL-valine as a pancreas-imaging agent in man. All animals showed good pancreatic uptake, although the pancreatic specificity varied in the following order: hamster > rat > dog > rabbit (Fig. 2).

Significant excretion of carboxyl-labeled DL-valine was observed in the rat. The total loss of C-11 label due to both decarboxylative loss of $^{11}CO_2$ through the lungs and urinary excretion, obtained through a

TABLE 3. EFFECT OF CARRIER DL-VALINE ON TISSUE DISTRIBUTION OF [1-^{14}C] DL-VALINE IN RAT AT 30 MIN AFTER INJECTION

Tissue	Pancreas/tissue conc. ratio*		
	0.02 mg/kg	1.0 mg/kg	5.0 mg/kg
Liver	9.8 (9.3–10.4)	9.7 (8.6–10.4)	9.6 (7.9–10.4)
Spleen	12.5 (9.1–17.5)	10.1 (9.5–10.7)	10.3 (8.9–11.9)
Kidney	12.0 (10.0–15.7)	9.7 (8.8–10.3)	11.0 (9.4–12.3)
Lung	15.3 (13.3–20.5)	13.8 (12.0–15.0)	15.3 (13.6–16.6)
Muscle	33.2 (19.7–44.7)	29.5 (24.3–33.6)	27.9 (22.0–33.2)
Marrow	7.8 (6.9– 9.7)	8.2 (7.3– 9.9)	8.1 (7.2– 8.9)
Small intestine	5.7 (4.7– 6.9)	4.5 (3.9– 4.8)	6.6 (4.3–11.2)
Blood	20.3 (14.3–32.0)	24.5 (22.0–27.0)	24.5 (20.6–28.6)

* Mean of 4 animals and range.

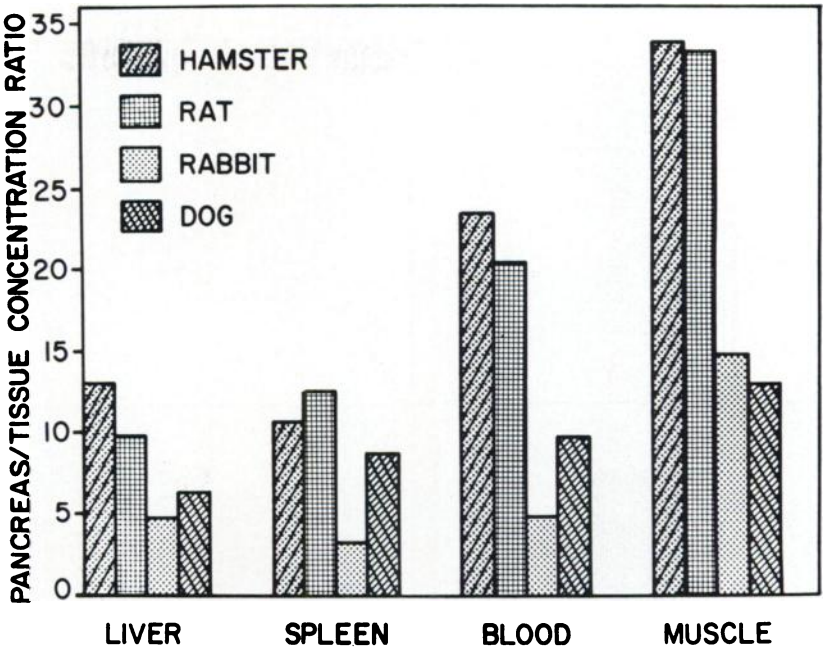

FIG. 2. Interspecies comparison of pancreas-to-tissue ratios for [1-^{14}C] DL-valine (0.02 mg/kg) at 30 min after injection. Each value is average of four animals.

total-body retention study with [1-^{11}C] DL-valine in male Fischer 344 rats, measured 27% at 30 min and 48% at 120 min (Table 4). Decarboxylative loss alone, obtained using the C-14-labeled amino acid in male Buffalo rats, amounted to 18% at 30 min and 34% at 120 min. Even though different strains of rats were used, it can be inferred from Table 4 that urinary excretion is significant, although not as great as loss by decarboxylation.

Figure 3 shows a study of the effect of various feeding protocols on the quality of rectilinear pancreas scans obtained with [1-^{11}C] DL-valine in the same normal mongrel dog. A comparison of the five scans illustrates the importance of a meal of protein and/or fat just before administration of the agent. In the scans made after fasting for 24 hr (Fig. 3A) or after fasting for 24 hr followed by administration of glucose intravenously 30 min before injection (Fig. 3B), no selective uptake by the pancreas could be seen. On the other hand, in the scans made after fasting for 24 hr followed by ingestion of Gevral protein supplement (Fig. 3C), lard (Fig. 3D), or commercial high-protein dog food (Fig. 3E) 30 min before [1-^{11}C] DL-valine administration, the typical arch-shaped dog's pancreas was easily visible.

TABLE 4 EXCRETION OF CARBOXYL-LABELED DL-VALINE IN RAT

Time (min)	Total excretion* (%)	Decarboxylative loss† (%)
15	12.6	9.8
30	27.1	18.2
60	41.3	28.1
90	44.5	31.7
120	48.1	34.1

* Average of five male Fischer 344 rats, obtained using [1-^{11}C] DL-valine.
† Average of two male Buffalo rats, obtained using [1-^{14}C] DL-valine.

DISCUSSION

These animal studies with [1-^{14}C] DL-valine corroborated the previously reported affinity of this amino acid for the pancreas, and further suggested the potential value of [1-^{11}C] DL-valine as a pancreas-imaging agent in man. Tissue distribution studies showed [1-^{14}C] DL-valine to have high pancreatic concentrations in all four animal species investigated. The rapid blood clearance and tissue uptake of the agent are quite favorable, compensating for the short half-life of C-11.

The absence of a carrier effect (through 5 mg/kg) on the tissue distribution of [1-^{14}C] DL-valine is important, since the chemical yield of amino acids by the modified Bücherer-Strecker synthesis is improved by the addition of small amounts of unlabeled potassium cyanide to the reaction mixture. Carrier-free C-11-labeled amino acids can be synthesized by this procedure, but the yields are only about half as high.

The rapid metabolic loss of significant amounts of radiolabel by both decarboxylation and urinary excretion in the rat represents a potential source of difficulty in the diagnostic use of [1-^{11}C] DL-valine. The decarboxylative loss poses a potential health-physics problem, since collection or venting of the $^{11}CO_2$ present in a patient's breath will be required

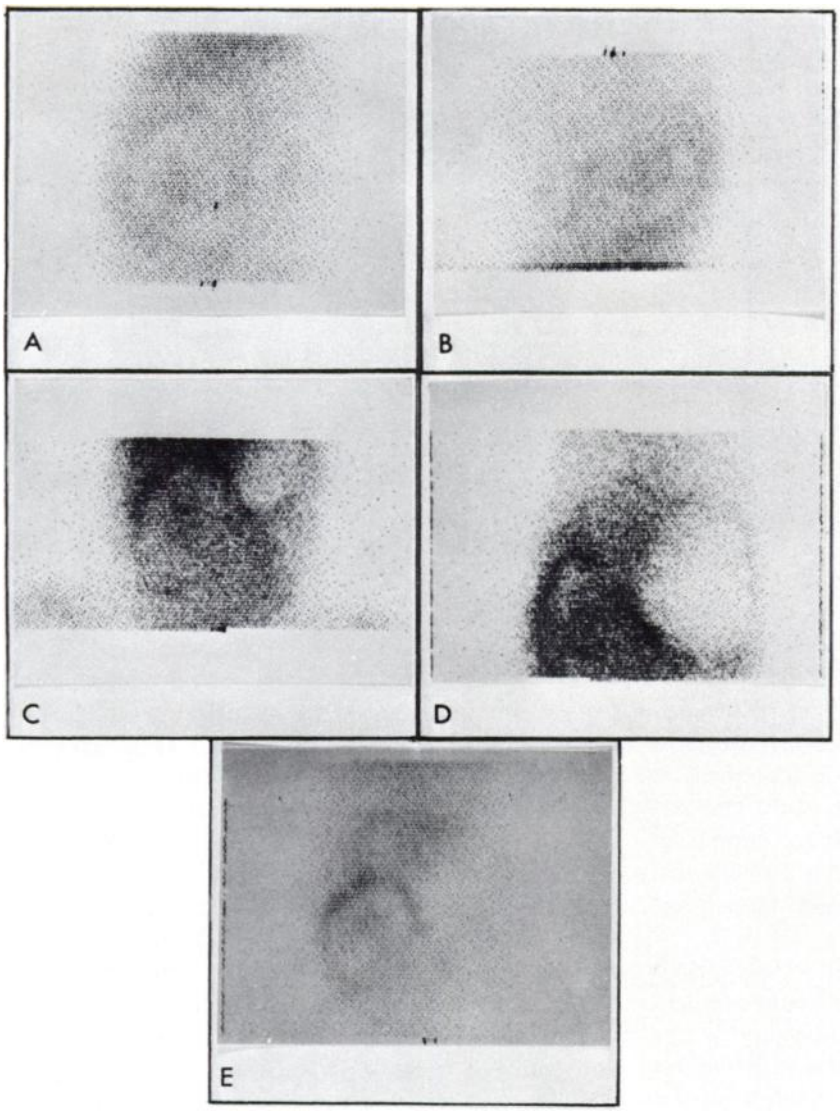

FIG. 3. Effects of various feeding protocols on quality of pancreas scans obtained in same normal mongrel dog with intravenously administered [1-^{11}C] DL-valine. All scans were started 40 min after injection. Feeding protocols used were: (A) animal fasted for 24 hr; (B) animal fasted for 24 hr and then administered glucose intravenously 30 min before [1-^{11}C] DL-valine administration; (C) animal fasted for 24 hr and then given Gevral protein supplement by mouth 30 min before [1-^{11}C] DL-valine; (D) animal fasted for 24 hr and then given lard by mouth 30 min before [1-^{11}C] DL-valine; and (E) animal fasted for 24 hr and then given commercial high-protein dog food by mouth 30 min before [1-^{11}C] DL-valine.

to protect the personnel performing a scan, assuming that comparable decarboxylation occurs in man. The rapid urinary excretion suggests that activity in the kidneys, in close anatomical proximity to the pancreas in man, might tend to obscure the pancreatic image. On the other hand, no evidence of kidney activity was seen in the dog scans (Fig. 3).

The toxicity of [1-^{11}C] DL-valine should present no problems. L-valine, of course, is one of the essential, naturally occurring amino acids, and as such it is present to the extent of 2.4 (2.0–2.9) mg per 100 ml of normal human blood (*18*). Assuming that blood comprises 7% of the body weight of man, there is, therefore, $\sim$ 120 mg of L-valine in the blood pool of a normal 70-kg human. The LD_{50} for intraperitoneally administered L-valine in the rat is reported to be 5.38 g/kg, and the D-isomer is reported to be even less toxic (*19*).

The radiation dose to patients from [1-^{11}C] DL-valine should likewise be minimal because of the short half-life of C-11. The estimated radiation doses in Reference Man from i.v. administration of [1-^{11}C] DL-valine are only 0.009 rads/mCi to the total body, 0.150 rads/mCi to the pancreas, 0.027 rads/mCi to the liver, and 0.032 rads/mCi to the kidney (*20*). These estimates are based on the 30-min tissue distribution of [1-^{14}C] DL-valine in the dog following i.v. administration of 0.02 mg/kg and assume immediate uptake by the organs, followed by complete decay in situ.

The uptake of [1-^{11}C] DL-valine by dog pancreas was not stimulated by i.v. glucose administration but was stimulated by ingestion of both protein and fat. The importance of a meal of protein and/or fat just before [1-^{11}C] DL-valine administration is thus clearly evident.

FOOTNOTES

* Eastman #13179.
† Birchover Instruments, Bancroft, U.K.
‡ Amersham/Searle.

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