¹¹C-L-methionine for evaluation of pancreatic exocrine function

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SUMMARY Pancreatic uptake of a natural amino acid, L-methionine, was measured in 58 patients using a scintillation camera. This was possible by labelling L-methionine with ¹¹C, a short-lived isotope produced in a cyclotron. Time-activity-curves obtained in areas of interest selected over the pancreas in 25 normal subjects and in 14 alcoholic patients showed a plateau or a slight increase of activity with time. In contrast, in 19 patients with chronic pancreatitis an initial increase in radioactivity was followed by a decrease for 10 to 20 minutes and then by a plateau. The ratio of the height of the plateau at the 50th minute to the height of the peak was 0.74 ± 0.21 in these patients, whereas it was 0.96 ± 0.09 in the other subjects ($P < 0.001$). This result was compared with direct measurements of ¹¹C radioactivity and of amylase and bicarbonate in duodenal aspirate. The median amount of ¹¹C incorporated into protein at the 70th minute was 53% of total activity in the control group, 28% in alcoholic patients, and only 3% in chronic pancreatitis, the differences between these values were highly significant. The absence of a peak of radioactivity in the duodenal juice, and the existence of a correlation between total ¹¹C output and amylase output suggested that there was no release of protein in the duodenum in chronic pancreatitis. These results also suggested that the peak observed by external detection could be due to amino acid back-diffusion from the pancreas into the blood. External detection with ¹¹C-L-methionine could be used for the assessment of pancreatic dysfunction in man.

Uptake of radioactive labelled amino acids by the pancreas has been extensively studied in animals.¹ Few studies have been performed in humans, using ⁷⁵Se-L-methionine.²⁻⁴

However, this molecule is not a convenient tracer for at least two reasons. First, ⁷⁵Se has a relatively long half-life (120 days), which means that only small doses of radioactivity may be injected. As such, kinetic studies using external detection are impossible. Second, selenomethionine might have a metabolic pathway different from that of the natural amino acid L-methionine, as has been demonstrated in liver.⁵⁻⁶

In the present study patients were injected with (¹¹C-methyl)-L-methionine. Carbon ¹¹C is a short

half-life isotope (20.4 minutes) produced in a cyclotron. Its positron emission can be easily detected; moreover, it was previously shown that ¹¹C-L-methionine accumulates in the pancreas with a high pancreas/blood and pancreas/liver ratio.⁷ Kinetics of ¹¹C-L-methionine in the pancreas were studied by external detection using a conventional gamma camera in different patients and the results were compared with those obtained by duodenal aspirate. A combination of coerulein and secretin was used to stimulate the exocrine secretion.⁸

Method

Pancreatic uptake of ¹¹C-L-methionine was evaluated in 58 subjects. The study involved 25 control adults without organic disease of the alimentary tract and with no history of alcoholism or diabetes mellitus. A second group consisted of 19 patients with chronic pancreatitis; all had signs of irreversible pan-

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creatic damage assessed by the demonstration of calcifications on plain radiographs (11 patients) or by abnormalities seen on endoscopic retrograde pancreatography and ultrasound or at laparotomy. In addition, a third group involved 14 alcoholic patients (daily alcohol intake >150 g) in whom standard investigations showed no sign of pancreatitis. Among these 14 patients, five had cirrhosis, one a peptic ulcer, and three abdominal pains of unknown origin; the others were hospitalised for non-digestive diseases.

Informed consent was obtained from all patients.

MEASUREMENT OF KINETICS BY EXTERNAL DETECTION

Patients after an overnight fasting were sedated with diazepam and were placed in a supine position under the head of a gamma camera. A liver scan was first performed after injection of 1 mCi ^{99m}Tc sulphur colloid. The camera was next fitted with a collimator designed for the 511 KeV gamma rays and angled 10° cephalad. Patients were injected intravenously with 10–15 mCi (^{11}C -methyl)-L-methionine. The labelled molecule was synthesised for each patient in less than 30 minutes as previously described.⁹ Specific activity was very high (300 to 500 mCi/ μmol) and chemical purity (about 100%) was controlled by high pressure liquid chromatography just before injection. Data were acquired for 70 to 90 minutes using a data processing system. Several photographs were obtained at different times. Areas of interest were selected over the pancreatic area under the liver projection (Fig. 1). When necessary, the ^{11}C scan

Fig. 1 Normal pancreatic scan 15 minutes after injection of 12 mCi ^{11}C -L-methionine. P: pancreas. L: liver.

could be subtracted from the ^{99m}Tc liver scan in order to eliminate the superimposed liver image; but, in fact, the angulation of the collimator allowed a clear differentiation between the liver and the pancreas.

Curves of activity in these areas of interest were plotted against time.

MEASUREMENTS IN DUODENAL ASPIRATE

Duodenal aspirate was performed simultaneously with the external measurements in 36 patients (14 normal subjects, 10 with chronic pancreatitis, and 12 alcoholic patients). Intubation was carried out three hours before the injection of ^{11}C -L-methionine, which was made with the patient lying under the gamma camera. The tube was positioned radiologically so that the aspiration holes were sited in the descending duodenum. A nasogastric tube was placed with its tip in the antrum. Duodenal and gastric contents were aspirated manually with intermittent insufflation of air in order to maintain patency of the tubes.

Stimulation of pancreatic secretion was obtained by a continuous intravenous infusion of secretin (1 CU/kg/h) and coerulein (70 ng/kg/h). Purified porcine secretin was obtained from the GIH Laboratory, Karolinska Institute, Stockholm, and coerulein was obtained from Farmitalia Research Laboratories, Milan. Infusion, begun with the instantaneous injection of ^{11}C -L-methionine, was maintained for 30 minutes. Duodenal aspirate was collected at intervals of five minutes for 50 minutes and at intervals of 10 minutes for the 20 following minutes. Samples were collected over ice. Volumes were measured and the radioactive concentration of the juice was rapidly measured in a gamma counting system. After precipitation with 10% trichloroacetic acid the protein fraction was analysed for ^{11}C radioactivity. Bicarbonate was measured in an automatic analyser using the enzymatic reaction phosphoenolpyruvate carboxylase (E.C.4.1.1.31) malate dehydrogenase (E.C.1.1.1.37) and amylase activity was measured using a chromogenic substrate.¹⁰ When comparing the three groups of patients, radioactive concentration of ^{11}C -L-methionine was expressed as a percentage of the injected dose per 100 ml of duodenal aspirate at the 70th minute and radioactive output in percentage of the injected dose per minute at the 70th minute. The fraction of the amino acid incorporated into proteins was also the value calculated at the 70th minute. This 70th minute figure was selected in order to prevent excessive discomfort in patients. The other results were expressed in terms of peak bicarbonate and amylase concentration, and peak bicarbonate and amylase output.

STATISTICS

In order to compare results from external detection between groups, an analysis of variance was first performed. When the F-statistics indicated the significance of differences between groups, modified *t* tests

were performed using the mean and sample size for each group and the mean square within groups. For each comparison the critical value for the modified *t* statistics was calculated from the Bonferroni method. Because the distribution of the concentrations and outputs of bicarbonate, amylase, and radioactivity and the distribution of the fractions of amino acid incorporated into proteins were not Gaussian, statistical analyses were performed using the Kruskal-Wallis one-way analysis of variance.¹¹ If the differences between groups were significant, multiple comparisons were performed. The Spearman rank correlation coefficient was used to measure correlations; its degree of significance was obtained from the one-tailed *t* test.¹¹

Results

KINETICS OF ¹¹C-L-METHIONINE OBTAINED BY EXTERNAL DETECTION

Curves obtained by external detection over the pancreatic region strongly differed in normal subjects and in patients with chronic pancreatitis (Fig. 2). In

Fig. 2 Activity vs. time curve obtained in an area of interest selected over the pancreas (same normal subject (N) as in Fig. 1). The curve shows a plateau. Curve obtained in the same region in a patient with chronic pancreatitis (CP). The plateau is preceded by a peak. The plateau/peak ratio is equal to 0.76.

normal patients the radioactivity rapidly increased within a few minutes and then remained as a plateau or slightly increased with time. In contrast, in patients with chronic pancreatitis, an initial increase in radioactivity was followed by a more or less important decrease for 10 to 20 minutes and then by a plateau. To compare these patterns quantitatively, we measured the ratio of the height of the plateau at the 50th minute to the height of the initial peak.

This ratio was equal to 0.96 ± 0.09 (mean $\pm$ SD) in 25 normal subjects. It was identical in the group of 14 alcoholic patients (0.96 ± 0.09) but was significantly lower in the group of 19 patients with chronic pancreatitis (0.74 ± 0.21) (Fig. 3).

Fig. 3 Values of the plateau/peak ratio in normal (N) and alcoholic (A) subjects, and in patients with chronic pancreatitis (CP). Heavy lines indicate the mean values; lighter lines indicate standard deviations. *F* value was 17.78 with (2,55) degrees of freedom, $p < 0.001$. Differences between normal and chronic pancreatitis were significant at the level of 0.001 and differences between alcoholic and CP at the level of 0.005.

MEASUREMENTS IN DUODENAL JUICE

In normal patients ¹¹C radioactive concentration began to increase 15 to 20 minutes after ¹¹C-L-methionine was injected. No plateau was reached during the 70 minute sampling period and there was no decrease in activity until the end of stimulation (Fig. 4a). In patients with chronic pancreatitis there was no significant increase in radioactivity. Only low radioactivity was detected, due to free amino acid released in the duodenum. On the other hand, in normal patients there was a parallel increase in the fraction of ¹¹C activity incorporated into proteins and in ¹¹C total concentration. ¹¹C incorporation into proteins continued to increase until the end of the sampling period (Fig. 4c).

Median concentrations and outputs and ranges of radioactivity, bicarbonate and amylase are given in Table 1.

Median total ¹¹C radioactive concentration in duodenal juice was significantly lower in patients with chronic pancreatitis (0.096% of the injected dose/100 ml) than in normal subjects (0.154%/100

Fig. 4 (a) ^{11}C radioactive concentration expressed as a percentage of the injected dose per 100 ml of duodenal aspirate as a function of time in a normal subject (No) and in a patient with chronic pancreatitis (CP●). (b) ^{11}C radioactivity output expressed as a percentage of the injected dose per minute as a function of time. (c) Fraction of total ^{11}C radioactivity found in the trichloroacetic acid precipitable fraction as a function of time. This percentage corresponds to ^{11}C -L-methionine incorporated into proteins. Same patient as in (a) and (b).

Table 1 Median values and ranges of concentrations and outputs measured in duodenal aspirate

	^{11}C -radioactivity		Amylase		Bicarbonate	
	Concentration $\times 10^3$	Output $\times 10^3$	Concentration	Output	Concentration	Output
Normal subjects						
Median	153	1188	250	1657	97	526
Range	84-387	579-1914	176-820	825-11059	64-117	317-1106
Number	7	7	14	14	13	13
Alcoholic patients						
Median	124	473	170	1080	85	400
Range	79-244	244-2636	18-270	120-2169	30-108	236-1102
Number	7	7	12	12	12	12
Chronic pancreatitis						
Median	96	266	29	108	50	165
Range	44-245	22-930	2-82	33-410	21-62	46-260
Number	9	9	10	10	10	10

^{11}C -Radioactivity is expressed as a percentage of the injected dose per 100 ml of aspirate or per minute at the 70th minute. Amylase is expressed in IU/ml or IU/min and bicarbonate in mmol/l or $\mu\text{mol}/\text{min}$. Amylase and bicarbonate are the peak values.

ml), $P < 0.02$, but it was not significantly different between groups of alcoholic subjects and patients with chronic pancreatitis (Fig. 5a).

However, ^{11}C output was significantly different between the three groups, median outputs being equal to 1.19, 0.47, and 0.27% of the injected dose per minute ($\times 10^2$) in the three groups of patients—normal, alcoholic, and chronic pancreatitis—

respectively (Fig. 5b). Significance levels are shown in Table 2.

Individual results for amylase and bicarbonate in all patients studied are shown in Figs 6 and 7. Median concentrations and outputs are indicated in Table 1. Significant differences for these values were observed when comparing normal or alcoholic subjects with patients having chronic pancreatitis but no

Fig. 5 Median ¹¹C concentration (a) and output (b) measured at the 70th minute in the three groups of patients, normal (N), alcoholic (A), and chronic pancreatitis (CP).

Table 2 Comparisons between normal, alcoholic, and chronic pancreatitis subjects

Comparisons	¹¹ C-radioactivity		% of ¹¹ C-L-methionine incorporated in proteins	Amylase		Bicarbonate	
	Concentration	Output		Concentration	Output	Concentration	Output
Normal—chronic pancreatitis	<0.02	<0.01	<0.01	<0.001	<0.01	<0.001	<0.01
Normal—alcoholic	NS	<0.05	<0.05	<0.05	NS	NS	NS
Alcoholic—chronic pancreatitis	NS	<0.02	<0.02	<0.05	<0.01	<0.005	<0.01

The Kruskal-Wallis one-way analysis of variance was significant for all the variables studied, thus allowing multiple comparisons. Significance levels from non-parametric tests are shown for each variable. NS: non-significant.

difference was seen between normal and alcoholic subjects except for amylase concentration (Table 2).

The fraction of ¹¹C-L-methionine incorporated into proteins reflected the amount of newly synthesised proteins and their excretion. Median fractions and ranges measured at the 70th minute were 53% of total activity in normal subjects (20–84), 28% in alcoholic patients (3–60), and only 3% in patients with chronic pancreatitis (0–33) (Fig. 8). As shown in Table 2 these values were significantly different for all comparisons between the three groups of patients.

The last variable measured was the ratio of output of ¹¹C incorporated into proteins to amylase output. This ratio was only an approximation of ¹¹C-protein

specific activity, as protein concentration was not measured. Expressed in arbitrary units, median ratios calculated at the 70th minute were 0.48, 0.30, and 0.25 for the three groups—normal, alcoholic, and pancreatitis—respectively. Individual values were relatively dispersed and these medians were not statistically different.

A positive and highly significant correlation was found between ¹¹C output and amylase output; the higher the amylase output, the greater the ¹¹C uptake and transport; $r_s = 0.791$, $n = 20$, $P < 0.001$ (Fig. 9) Correlation between ¹¹C output and bicarbonate output was also good ($r_s = 0.683$, $n = 20$, $P < 0.005$), as was the correlation between bicarbonate and amy-

Fig 8 Median ^{11}C fraction incorporated into proteins. The ^{11}C -protein fraction was precipitated by adding 10% trichloroacetic acid to the duodenal juice at the 70th minute.

lase output ($r_s = 0.725$, $n = 20$, $P < 0.001$). However, no correlation was found between the plateau-to-peak ratio evaluated by external detection and the fraction of ^{11}C -L-methionine incorporated into proteins.

Discussion

Several studies have recently underlined the potential value of the use of amino acids labelled with carbon ^{11}C for imaging the pancreas with emission computed positron tomography.^{7 12 13} The interest of this short-lived carbon isotope is that it is possible to inject a patient with 10 to 20 mCi of a labelled amino acid without exposing him to a large dose of radiation, thus making possible repeated studies. An injection of 15 mCi ^{11}C -L-methionine gives a dose of 1.35 mGy to the whole body, which is low compared with a standard barium x-ray examination. Different ^{11}C labelled amino acids have been used; some were racemic as D-L-valine or D-L-tryptophan,^{12 13} others were L-isomer as L-methionine.⁷ Morphological data obtained in different pancreatic diseases with these molecules were comparable¹³ but blood kinetics were different because of an high renal elimination of the D-amino acid. Furthermore, using the natural amino acid L-methionine seems better than using the racemic amino acid, as rates of uptake in the pancreas depend on stereospecific transport systems.¹⁴

In this paper, we have used a conventional gamma camera instead of a positron camera to obtain a continuous record of activity as a function of time for 70 minutes. A positron camera would not have recorded the first 10 minutes of the curves in most

Fig. 9 Correlation between ^{11}C total output and amylase output measured in 20 patients. The Spearman rank correlation coefficient r_s was equal to 0.791 ($P < 0.001$).

patients, as it is impossible to determine the exact location of the pancreas before tracer injection. Such a study was not possible when using selenomethionine, as about 20 minutes were necessary to get an image because of the low activity injected. Pancreatic scanning with ^{75}Se -L-selenomethionine is only a qualitative functional test; however, a normal scan virtually eliminates the presence of chronic pancreatic insufficiency.¹⁵

Activity vs. time curves computed over the pancreatic area corresponded to the uptake, metabolism, and transport of ^{11}C -methionine and of newly synthesised proteins or other labelled products of catabolism. These curves have been taken to reflect the overall exocrine pancreatic response to secretin and coerulein—that is, secretory capacity rather than synthetic capacity. Curves exhibited two different patterns according to the group of patients. By comparison, curves obtained over an intestinal area of interest were identical in normal subjects and in patients with chronic pancreatitis, ^{11}C activity remained constant as a function of time. Therefore the presence of an initial peak of activity during 10 to 20 minutes in patients with chronic pancreatitis could not be explained by ^{11}C activity of the surrounding tissues. It could be due to a rapid leakage of free amino acid in the duodenum, attributable to the destruction of the acinar cells. According to this hypothesis, a peak of activity should be detected in duodenal aspirate after some delay; but, in fact, a significant increase in ^{11}C activity was never observed. ^{11}C -L-methionine might be passively transported in a pancreatic volume of distribution and this might be followed by a back-diffusion from this space into the blood, possibly because of duct obstruction.¹⁶ ^{11}C radioactivity not associated with the proteins was detected quickly in the duodenal juice. Such activity has been also observed after injection of selenomethionine and could be due to gastric or biliary contamination.² Such non-protein-bound radioactivity was also observed in animals and in isolated pancreas after injection of labelled amino acids.^{17, 18} This was explained by an amino acid flux through the intercellular spaces of the pancreas.¹⁸ Measurements in subjects with T-tube have shown that radioactivity in the TCA-precipitable fraction originates essentially in the pancreas.³ The delay of 15–30 minutes between the injection of ^{11}C -L-methionine and the appearance of ^{11}C -labelled proteins under constant infusion of secretin and coerulein seems to be shorter than that observed after injection of selenomethionine and stimulation by a Lundh test meal² or by pancreozymin and secretin.³ No inflection of the curve was observed within 70 or 90 minutes: this conforms with findings in animals which show that the maximum incorporation is

reached approximately two hours after injection.^{1, 17} Measurements, however were not prolonged because of the 20 minute half-life of ^{11}C . The 53% ^{11}C fraction incorporated into proteins found in this study seems to be higher than that measured with ^{75}Se ^{2, 3} but was similar to that obtained in animals after injection of ^{14}C labelled amino acids.¹⁷ A good separation was obtained between the three groups of patients. When comparing normal subjects and patients with chronic pancreatitis all the tests for amylase, bicarbonate, and ^{11}C -L-methionine were highly significant (with $P < 0.01$ except for one of them). These results were comparable with those derived from standard pancreatic function tests¹⁹ and from radioselenium tests. However, the discrimination in this study was more significant than in selenomethionine studies.²⁰ It can be seen, for example, that there was no overlap of individual values of ^{11}C protein-bound fractions when comparing normal subjects and chronic pancreatitis; furthermore, radioactivities were not cumulated; this may be due to less specific metabolic pathways for ^{75}Se -methionine than for ^{11}C -methionine.^{5–6} The possibility of an increase in demethylation of (^{11}C -methyl)-L-methionine cannot be excluded in pancreatic disease but no such data have been noted in the literature.

The correlation observed between ^{11}C output and amylase output tended to imply that in chronic pancreatitis the proteins could not be released into the duodenum even if they were synthesised. This could be explained by an obstruction of the pancreatic ducts by protein plugs or calculi which have been considered to be important in the mechanism of alcoholic chronic pancreatitis.²¹ This result could also be a further argument in favour of our interpretation of the peak observed by external detection in these patients as due to amino acid back-diffusion.

The 3% ^{11}C protein-bound fraction in patients with chronic pancreatitis compared with the 53% value in normal subjects could also suggest that, if an abnormal secretion of non-enzymatic proteins occurred in chronic pancreatitis,²² such synthesis might be small compared with normal secretion.

For some parameters studied—in particular, the ^{11}C fraction incorporated into proteins—the group of alcoholic patients could be differentiated from normal subjects and from patients with chronic pancreatitis. Protein synthesis has been found to increase in the chronic alcoholic rat²³ and by others to diminish.²⁴ In alcoholic patients pancreatic juice was more concentrated in proteins when the pancreas was not stimulated, but after injection of cholecystokinin-pancreozymin this difference diminished.¹⁶ In this study, after stimulation by secretin

and coerulein, the median percentage of ¹¹C incorporated into proteins in alcoholic subjects was intermediate (28%) between the control value (53%) and that measured in patients with chronic pancreatitis (3%); although the range of values was broad these values differed significantly. It is possible that some of these alcoholic subjects with low incorporation had early lesions of the exocrine pancreas; however, no abnormality was detected by ultrasound and endoscopic retrograde pancreatography. Nevertheless, it should be observed that this group of alcoholic subjects could not be differentiated from the control group using external detection; pancreatic images and curves were normal in both groups. This suggests that transport function might be diminished earlier than cellular uptake.

This work shows that ¹¹C-L-methionine fulfils the conditions of an ideal tracer for studying both morphology and function of the exocrine pancreas. External detection using a gamma camera exhibited a high sensibility and specificity for the assessment of pancreatic dysfunction in man; this non-invasive method could thus be used as a diagnostic test. However, this molecule cannot yet be proposed as a routine test, as its synthesis needs a cyclotron and a relatively complex chemistry, but this study proves its potential efficiency if the use of ¹¹C labelled molecules is more widely developed.

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