

*Alimentary tract and pancreas***Comparison of  $^{11}\text{C}$ -L-methionine uptake by the parotid gland and pancreas in chronic pancreatitis studied by positron emission tomography**

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**SUMMARY** L-methionine uptake by the parotid gland and pancreas has been compared in 27 patients using a non-invasive methodology. L-methionine was labelled with  $^{11}\text{C}$ , a positron emitter with a short half life produced in a cyclotron.  $^{11}\text{C}$ -L-methionine concentration was measured in the parotid glands and in the pancreas by external detection using a positron emission tomographic system.  $^{11}\text{C}$ -L-methionine uptake by the parotid glands was  $4.3 \times 10^{-3} \pm 1.9 \times 10^{-3}\%$  of the injected dose per millilitre of tissue (mean  $\pm$  SD) in a group of 11 normal non-alcoholic subjects. The uptake was  $3.6 \pm 1.3 (\times 10^{-3})$  in a group of nine alcoholic subjects without pancreatic disorder and it was  $4.9 \pm 1.5 (\times 10^{-3})$  in a third group of seven patients with chronic pancreatitis. These values did not significantly differ. In contrast median pancreatic uptake of  $^{11}\text{C}$ -L-methionine was nil in chronic pancreatitis and was lower than that seen in normal subjects ( $15.3 \times 10^{-3}\%$  ml,  $p < 0.001$ ) and in alcoholic subjects ( $11.5 \times 10^{-3}\%$  ml,  $p < 0.002$ ). Thus neutral long chain amino acid transport in the parotid gland appears to be independent of that in the exocrine pancreas in chronic pancreatitis. This absence of relationship between the parotid gland and the pancreas in pancreatic disease is in contradiction with the demonstration made in animals of an interaction between these two glands. These results, however, are in agreement with the conclusions drawn from the data collected from the saliva test used by several authors.

The existence of a direct interaction between the pancreas and the parotid gland has been put forward by Kakizaki *et al.*<sup>1</sup> Using parabiotic rats, they suggested that the parotid gland was altered in the case of pancreatitis by transmission of a humoral factor.<sup>2</sup> As a consequence the same authors proposed the parotid saliva test as a diagnostic test for evaluation of the exocrine pancreas.<sup>3</sup> The clinical usefulness of such a test appeared questionable for other authors although some parallelism between the pattern of secretion of the parotid and the pancreas was observed.<sup>4,5</sup> Furthermore, recently Dóbrilla *et al* could not find any correlation between the results of the saliva test and those of the secretin pancreozymin pancreatic test.<sup>6</sup> Positron emission tomography could answer this

question definitively because it offers the unique possibility of measuring *in vivo* the uptake of a L-amino acid by external detection. The uptake of neutral amino acids by the salivary glands and the pancreas involves carrier mediated transport systems before the amino acid is incorporated into proteins;<sup>7,8</sup> therefore L-methionine appears to be an ideal marker of the function of these glands.<sup>9</sup> Labelling L-methionine with the short life isotope  $^{11}\text{C}$  (half-life, 20 minutes) allows measurement of its radioactive concentration within a known volume of the organ using a positron camera.<sup>10</sup> The purpose of the present study was to compare the uptake of  $^{11}\text{C}$ -L-methionine by the parotid gland and the pancreas in patients with chronic pancreatitis.

**Methods****PATIENTS**

Twenty-seven consenting patients in which a final

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diagnosis was obtained were studied. Diagnostic evidence of normality or abnormality was established on the basis of clinical findings and of imaging data (plain radiographs, endoscopic retrograde pancreatography, ultrasound). Diagnosis was obtained by means of surgical exploration of the abdomen and/or post-mortem investigation in eight patients. They were classified in three groups. Eleven patients had no organic disease of the pancreas and no history of alcoholism. Nine patients were alcoholic subjects (daily alcohol intake > 150 g). Among these nine patients, two showed enlargement of the parotid glands and three had cirrhosis. The third group involved seven patients with chronic pancreatitis. These seven patients with chronic pancreatitis were all alcoholic male subjects with ages ranging from 41 to 68 years. Four out of seven had a calcified pancreatitis. Endoscopic retrograde pancreatography was performed in the three patients with non-calcified pancreatitis and in one of the patients for whom calcifications were shown on plain radiographs. Moderate changes were seen in two cases and major lesions were seen in the other cases (including the case with calcifications). Ultrasonography was performed in all the patients but adequate visualisation was obtained in only five patients. Ultrasonography was abnormal in all five cases. Duodenal intubation with stimulation of pancreatic secretion by a continuous infusion of secretin and caerulein was abnormal in the four patients for whom it was made (including the three without calcifications).

#### MEASUREMENT OF $^{11}\text{C}$ -L-METHIONINE IN THE PANCREAS AND THE PAROTID GLAND

$^{11}\text{C}$ -L-methionine concentration in parotid glands was evaluated in all 27 patients; an evaluation of the amino acid concentration in the pancreas was simultaneously performed in 10 of these 27 patients.

$^{11}\text{C}$ -L-methionine was synthesised for each patient in about 30 minutes. The preparation used the production of  $^{11}\text{CO}_2$  in a cyclotron and the reaction of  $^{11}\text{C}$ -methyl iodide on L-homocysteine.<sup>11</sup> Specific activity was high (300–700 mCi/ $\mu\text{mol}$ ) and chemical purity was assured by high pressure liquid chromatography just before injection.

Cross-sectional imaging of the parotid glands and of the pancreas was obtained using the Orsay positron-emission computed tomograph.<sup>12</sup> Three adjacent transverse slices of the head corresponding to the location of the parotid glands and at least four slices of the abdomen starting 4 cm above the umbilicus were obtained. After recording transmission images using a  $^{68}\text{Ge}/^{68}\text{Ga}$  source for subsequent correction of photon attenuation, 10–20 mCi (370–740 MBq)  $^{11}\text{C}$ -L-methionine were

injected intravenously. The emission data collection began five minutes after injection and lasted for about 45 minutes. The total counts in the image averaged two to three million. Each slice was 2 cm thick and the spatial resolution was 18 mm in the medium resolution mode. Whole body irradiation was 1.8 mGy.

Regions of interest corresponding to the parotid glands and the pancreas were automatically outlined at the 90% and 80% isocount contour of the parotid and pancreatic image.  $^{11}\text{C}$ -L-methionine concentrations were measured between 20 and 30 minutes after injection. Radioactive concentrations were expressed as per cent of the injected dose per millilitre of tissue. The calibration factor for converting counts per millilitre of the positron emission tomography slices to Bq/ml was measured every week using a cylinder filled with  $^{68}\text{Ga}$ .

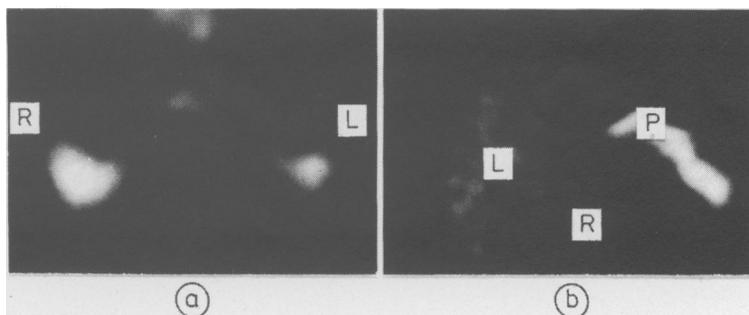
#### STATISTICS

A one way analysis of variance was performed to study the overall comparison of  $^{11}\text{C}$ -methionine concentrations in the parotids of the three groups of patients. The F-ratio of the mean square between groups to the mean square within groups was compared with the tabulated critical value before using modified *t* tests. The sign test was used to compare concentrations of left and right parotid gland within each individual.<sup>13</sup> The Kruskal-Wallis test was used to compare pancreas radioactive concentrations between groups because some distributions were not normal.<sup>13</sup>

#### Results

The image of the parotid glands was always clearly seen as two circular or triangular zones of intense radioactivity (Fig. 1a). The other salivary glands were also apparent although less radioactive. The criteria used for assessing a normal pancreatic image have been previously defined.<sup>14</sup> In each patient,  $^{11}\text{C}$ -L-methionine concentration was measured in the left and in the right parotid gland. In 19 out of 27 patients the values were higher in the left parotid gland than in the right one. This asymmetry was very significant ( $p < 0.005$ ). The arithmetic mean was used to show individual values in the three groups of patients (Fig. 2a).  $^{11}\text{C}$ -L-methionine parotid concentration expressed as per cent of the injected dose per millilitre was  $4.3 \times 10^{-3} \pm 1.9 \times 10^{-3}$  (mean  $\pm$  SD) in the group of 11 patients without pancreatic disease. The concentration was  $3.6 \times 10^{-3} \pm 1.3 \times 10^{-3}$  of the injected dose per millilitre in the group of nine alcoholic patients and it was  $4.9 \times 10^{-3} \pm 1.5 \times 10^{-3}$  in the group of seven patients with chronic pancreatitis. It must be noticed

Fig. 1a, b <sup>11</sup>C-L-methionine tomographic transverse scans of parotid glands (a) and pancreas (b) in normal subject. (a) Left (L) and right (R) parotid glands are seen as zones of intense activity. Body and tail of pancreas (P) is seen in front of rachis (R) which shows up as non-radioactive zone. Right lobe of liver (L) is also seen. Each slice is 2 cm thick. Scans were recorded between 20 and 30 minutes after injection of 17 mCi <sup>11</sup>C-L-methionine.



that the measured values in the parotid are lower than the true values because of the partial volume effects owing to the small size of the gland compared with the spatial resolution of the positron camera. The recovery factor could be estimated to be 0.45-0.50 (unpublished data), as a consequence the true L-methionine concentration was about  $9 \cdot 10^{-3}$  in the group with pancreatitis. The F-ratio was 1.12 with degrees of freedom 2.24 and the groups were not significantly different.

Figure 2b shows the concentration values of the patients who had a pancreatic scan at the same time as the parotid scan. Medians were  $15.3 \times 10^{-3} \%$  ml in the group of four normal subjects,  $11.5 \times 10^{-3}$  in the group of six alcoholic subjects and nil in the

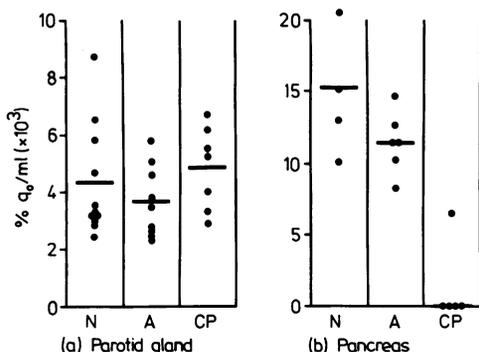


Fig. 2a, b <sup>11</sup>C-L-methionine uptake values measured in parotid glands (a) and pancreas (b) in three groups of subjects: normal (N), alcoholics (A) and chronic pancreatitis (CP). Heavy lines indicate the mean values in parotid glands and median values in pancreas. No significant difference was observed for uptake values in parotid glands. In pancreas, uptake was significantly much lower in group of patients with chronic pancreatitis than in two other groups.

group of five patients with chronic pancreatitis.

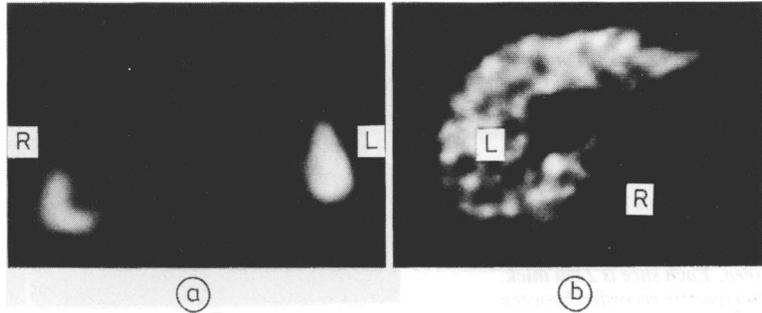
Values observed in the last group were significantly lower than those measured in the normal group ( $p < 0.001$ ) and in the alcoholic group ( $p < 0.002$ ). Fig. 3 illustrates this result; a normal image of the parotid glands contrasts with the absence of pancreatic image.

### Discussion

Positron emission tomography is a new non-invasive technique which allows simultaneous imaging and quantitation of a metabolic function inside an organ when using a molecule labelled with a positron emitting isotope. This technique has been used for pancreatic imaging by injecting patients with <sup>11</sup>C-labelled amino acids.<sup>14-16</sup> This technique has been performed very recently in both a qualitative and a quantitative manner in a series of 100 patients referred for possible pancreatic disease.<sup>10</sup>

In this work we have used the same methodology to compare the uptake of an amino acid by the parotid gland and the pancreas in order to investigate a possible interaction between these two glands in patients with pancreatic disease.<sup>1-3</sup> The tracer was a natural L-amino acid, L-methionine, labelled with <sup>11</sup>C because it has been shown that this tracer was incorporated into proteins and that it was a sensitive indicator of pancreatic dysfunction in man.<sup>9</sup> It should be pointed out that in the data reported by us in this study, the measurements reflect not only the methionine incorporated into protein but also the extravascular free methionine pool. The values of <sup>11</sup>C-L-methionine uptake by the pancreas have been measured by positron tomography in a series of 22 normal subjects and of 13 patients with chronic pancreatitis.<sup>10</sup> In the former group, the median concentration, expressed as a percentage of the injected dose, was  $13.4 \times 10^{-3} \%$  ml (range:  $8.2-31.1 \times 10^{-3}$ ) and in the latter group it

Fig. 3a, b  $^{11}\text{C}$ -L-methionine tomographic transverse scans of parotid glands (a) and pancreas (b) in patient with chronic pancreatitis.  $^{11}\text{C}$ -L-methionine uptake was normal in both parotid glands (a) whereas no uptake was seen in pancreatic region (b). Liver (L) is only visible.



was 0 (range:  $0\text{--}10.3 \times 10^{-3}$ ). In a smaller series of patients, we have found in this study similar results, the median uptake per millilitre was  $15.3 \times 10^{-3}\%$  in four normal subjects and the median was 0% in five patients with chronic pancreatitis. Positron emission tomography, as well as external detection with a scintillation camera, could not distinguish the alcohol subjects from the normal ones. In a previous study, however,<sup>9</sup> the percentage of  $^{11}\text{C}$  incorporated into proteins was measured as a function of time in samples of duodenal juice. In alcoholic subjects this percentage was intermediate (28%) between the control value (53%) and that measured in patients with chronic pancreatitis (3%). This suggests that, in alcoholic subjects, the protein synthesis rate is lowered although amino acid transport from the blood into the pancreatic tissue is not altered.

Contrasting with findings in the pancreas, measurements of  $^{11}\text{C}$ -L-methionine uptake by the parotid glands showed no significant difference between normal subjects and patients with chronic pancreatitis. This result is in agreement with the conclusion of Dobrilla *et al* who measured bicarbonate and amylase salivary concentration and output after stimulation with pilocarpine.<sup>6</sup> They found no correlation between the results of this test which was described by Kakizaki *et al*<sup>3</sup> and the results of the secretin-cholecystokinin-pancreozymin test or endoscopic retrograde pancreatography. Furthermore, we have not seen any significant difference between normal and alcoholic subjects. The two alcoholic patients with parotid hypertrophy had a  $^{11}\text{C}$ -uptake equal to 2.6 and  $5.8 \times 10^{-3}\%$  ml and could not be distinguished from the others.

These results indicate that, in patients with chronic pancreatitis, a normal parotid uptake of L-methionine contrasts with a zero pancreatic uptake. Thus they suggest that the interaction between the pancreas and the parotid gland shown experimentally in rats and dogs by Kakizaki does

not exist, at least in man. Although these authors have measured amylase and bicarbonate content in parotid gland and saliva and not amino acid uptake, they have found histological alterations in the parotid glands parallel to that observed in the pancreas. From the  $^{11}\text{C}$ -uptake values found in the pancreas of patients with chronic pancreatitis, we may infer that, if an interaction had existed, we should have observed reduced  $^{11}\text{C}$ -uptake values in the parotids of the same patients. Therefore, we may conclude that the exocrine pancreas function cannot be assessed by a saliva test.

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