Residual β-Cell Function Judged from Serum C-Peptide Immunoreactivity (CPR) in Patients with Chronic Pancreatitis.

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SUMMARY  In order to determine the B-cell function in the patients with chronic pancreatitis who had glucose intolerance, we measured C-peptide immunoreactivity (CPR) in plasma. In patients with chronic pancreatitis who are insulin requiring diabetics, concentrations of fasting plasma CPR were low as compared with those never treated with insulin. Concerning the CPR response to glucose ingestion, no significant peak was observed in the patients with chronic pancreatitis as a whole, and the CPR response is smaller than that of adult type diabetics in spite of the equal glucose changes. As for the patients with chronic pancreatitis, CPR/BS showed a higher score in those treated by diet than in those who had been treated by insulin.

On the other hand, the group with normal or low values in one factor of the pancreozymin-secretin test showed higher CPR responses than the group with low values in two or three factors of the pancreozymin-secretin test.

Introduction

C-peptide connects A and B chains of insulin within proinsulin molecule and is secreted in equimolar concentrations with insulin. As such, measurement of human C-peptide by a recently developed radioimmunoassay has provided an alternative means of measuring B-cell secretion and proved useful in the study of residual islet cell function especially in insulin treated diabetic patients, in whom exogenous insulin and circulating insulin antibodies interfere with quantitative measurements of endogenous insulin. On the other hand, the exocrine function of pancreas has been extensively studied in patients with chronic pancreatitis. Residual B-cell function however has not been sufficiently investigated in such patients with the inclusion of insulin requiring cases.

The purpose of this study is to confirm the residual B-cell functions in the patients with chronic pancreatitis who had glucose intolerance and to compare those...
observed in patients with diabetes mellitus. Our second object is to study the relationship between the endocrine and exocrine disturbances in patients with chronic pancreatitis.

Materials and Methods

The following subjects were investigated in this study; i.e. 12 subjects with no intestinal and no pancreatic complaints, and with no family history of diabetes mellitus or obesity (aged 20–59 years, 8 males and 4 females), 15 patients with both chronic pancreatitis, diagnosis of which was based on the roentgenographic finding of pancreatic calcification, and glucose intolerance (aged 35–50 years, 12 males and 3 females), 18 adult type diabetics who had been taking dietary treatment and/or oral hypoglycemic agents (aged 38–64 years, 9 males and 9 females) and 9 juvenile onset type diabetics treated with insulin (aged 21–33 years, 6 males and 3 females). All subjects were within ±10% of standard weight calculated by Broca index except 5 overweight adult onset type diabetics. Each subject fasted for more than twelve hours prior to the study and all hypoglycemic medications were stopped from the preceeding day. After a fasting blood specimen was obtained, 50g flavored glucose was given orally. Blood specimens were then obtained at 30, 60, 90, 120, 180 minutes. All blood specimens were separated by centrifugation within 30 minutes of collection, and then frozen at −20°C until assayed. Blood sugar was determined by glucose oxidase method adapted for autoanalyzer. CPR was determined by the C-peptide radioimmunoassay method, using C-peptide Kit “Daichi” (Daichi Radioisotope Labs., Ltd.) which has been described previously by Kaneko et al.\textsuperscript{5} CPR responses to oral glucose ingestion were expressed as \( \Sigma \text{CPR}/\Sigma \text{BS} \) (the ratio of the sum of CPR values to the sum of glucose values at each time from 0 to 180 minutes). Pancreozymin-secretin test was performed by inserting a Dreiling tube and used for both injections of cholecystokinin-pancreozymin and secretin. Cholecystokinin-pancreozymin (Boots Pure Drug Co. Ltd., England) was administered intravenously 1 unit/kg body weight, and after then duodenal juice was collected during 20 minutes with constant suction at a negative pressure. Then Secretin (Boots Pure Drug Co. Ltd., England) was injected intravenously 1 unit/kg body weight, and the aspirations were fractionated into 4 collection periods, the first two at 10 minute intervals and the last two at 20 minute intervals. Each aspiration was analyzed for volume, bicarbonate concentration, and amylase output. Controlled values ranged from 1.6 to 4.4 ml/kg for volume, 70 to 118 mEq/L for maximum concentration of bicarbonate, and 300 to 1000 I.U./kg for amylase output, respectively. Statistical analysis was carried out by means of student’s t-test.

Results

The mean fasting CPR in normal subjects (NS) was 2.6±0.2 ng/ml (mean±SE). In adult onset type diabetics (AD), a higher CPR level was observed as compared with the normal group (p<0.05), the mean value being 3.7±0.6 ng/ml. The mean level in chronic pancreatitis (CP) (2.0±0.6 ng/ml) was lower than in the above two groups (p<0.05 respectively, and that in juvenile onset type diabetics (JD) was very low (1.0±0.1 ng/ml) (Fig. 1). Fig. 2
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Fig. 1 Fasting serum CPR in normal subjects (NS), adult type diabetics (AD), juvenile type diabetics (JD) and patients with chronic pancreatitis (CP)

Table 1. Summary of CPR/BS in normal subjects (NS), adult type diabetics (AD), juvenile type diabetics (JD) and patients with chronic pancreatitis (CP). Values are mean ± SE.

<table>
<thead>
<tr>
<th>Group</th>
<th>Measurement (µg/ml)</th>
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<tbody>
<tr>
<td>NS (n=12)</td>
<td>1.11 ± 0.37</td>
</tr>
<tr>
<td>AD (n=18)</td>
<td>1.87 ± 0.48</td>
</tr>
<tr>
<td>JD (n=9)</td>
<td>0.34 ± 0.11</td>
</tr>
<tr>
<td>CP (n=15)</td>
<td>4.65 ± 0.60</td>
</tr>
</tbody>
</table>

Fig. 2 Response of blood sugar and CPR during 50g O-GTT

- NS: normal subjects, n=12
- AD: adult type diabetics, n=18
- JD: juvenile type diabetics, n=9
- CP: patients with chronic pancreatitis, n=15

shows the response of blood sugar and CPR during 50g O-GTT. During O-GTT, for NS, the blood sugar reached a peak, 140.2 ± 12.1 mg/dl at 30 minutes, while CPR reached a peak at 60 minutes, 7.2 ± 0.5 ng/ml. For AD, CPR after the ingestion of glucose showed a delayed and lower peak, 5.2 ± 0.8 ng/ml at 120 minutes. No significant peak was observed for CP, in spite of similar changes of blood sugar as shown in AD. On the other hand, no response to oral glucose was found in JD. The highest and the lowest value of CPR/BS, above described, was observed in NS (4.65 ± 0.60 x 10^{-2}) and in JD (0.34 ± 0.11 x 10^{-2}). The value in CP treated with diet and/or oral hypoglycemic agents was significantly lower than that in AD (p<0.05). The value of CPR/BS in CP treated with insulin was low, but was significantly higher than that in JD (p<0.05) (Table 1).

Comparison of serum CPR response during O-GTT were performed in two groups of patients with chronic pancreatitis on the degree of abnormality in PS.
Fig. 3 CPR response during 50g O-GTT and abnormalities in PS test in patients with chronic pancreatitis

Discussion

According to Peters\textsuperscript{14}, the patients with chronic pancreatitis showed an inadequate production of insulin. A similar result, also that insulin production was defective in most of their patients with chronic pancreatitis, appeared in a report by Anderson et al.\textsuperscript{15} On the other hand, the determination of human C-peptide can be the most useful for the evaluation of the B-cell secretion in insulin-requiring diabetic patients\textsuperscript{5,6,9,10,11}.

In our series, six patients with chronic pancreatitis are insulin-requiring diabetic patients and IRI could not be determined. In them, concentrations of fasting plasma CPR are low as compared with those never treated with insulin. This fact probably indicates that the B-cell is largely deteriorated especially in patients with insulin-requiring chronic pancreatitis.

Concerning the CPR response to glucose ingestion, no significant peak was observed in patients with chronic pancreatitis as a whole, and the CPR response is smaller than that of adult type diabetics in spite of the fact that glucose change was the same. This may be due to the difference in sensitivity of B-cell to glucose stimulation or the difference in severity of the lesion of islet cells. Namely, in adult type diabetics, sensitivity of B-cell may be maintained or the lesion may be little as compared with that of chronic pancreatitis.

Another possible explanation of this phenomenon is that the insulin sensitivity of the peripheral tissue, that is, insulin sensitivity may be maintained better in the patients with chronic pancreatitis.

Moreover, in order to numerize the B-cell response against glucose stimulation, we used the $\Sigma$CPR/$\Sigma$B3 formula\textsuperscript{16}, and this formula is thought well express the residual B-cell function. In patients with chronic pancreatitis, those who had been treated by diet showed a higher score than those who had been treated by insulin. From this, it is suggested that the residual B-cell function is maintained better in the former. But, even in insulin treated patients with chronic pancreatitis, the score are still higher than those of juvenile type diabetics. Namely, the residual B-cell function may be less defective than in juvenile type diabetics.

Peters\textsuperscript{14} et al. reported that there was no close correlation between disturbance of exocrine and endocrine function in patients with chronic pancreatitis. But
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Ohlsen referred to, found that there was good correlation between various indices of endocrine pancreatic function and of amylase output in patients with chronic pancreatitis. We tried to find the correlation between disturbance of endocrine and exocrine function in patients with chronic pancreatitis using CPR concentrations in 50g O-GTT and pancreozymin-secretin test. In the group with normal or low values in one factor in pancreozymin-secretin test, CPR in plasma peaked at 120 minutes (4.2 ± 0.8 ng/ml). These changes of plasma CPR resemble those of adult type diabetics. In contrast with this, very small CPR responses, like those of juvenile type diabetics, were shown in the group with low values in two or three factors in pancreozymin-secretin test. From this, two possibilities are suggested. One is that in patients whose B-cell function is deteriorated, exocrine function may have also deteriorated as a result of little insulin secretion. Another is that in patients whose exocrine function of the pancreas is deteriorated largely, residual B-cell function may have also deteriorated as a result.

In conclusion, these results indicate that in chronic pancreatitis, plasma CPR responses tend to be reduced. Moreover, in patients treated with insulin, or those with low values in two or three factors in pancreozymin-secretin test, change of plasma CPR are very small. From this data, it is possible to say that the residual B-cell function in the patients with chronic pancreatitis who have impaired glucose tolerance are obviously disturbed when compared with that of adult type diabetics. But, even in insulin treated chronic pancreatitis, B-cell function is thought to be not completely impaired as compared with that of juvenile type diabetics.

References

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