Stimulatory Effect of Secretin on Pancreatic Polypeptide in diabetic Patients

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Abstract

In diabetic patients plasma levels of pancreatic polypeptide (PP) increased four fold after intramuscular injection of secretin (50 CHRU, Eisai Co.) in spite of the lack of response of plasma insulin, plasma glucagon and blood glucose levels. In control subjects, PP levels did not change significantly after secretin injection. Since pancreatic polypeptide has is known to have an inhibitory effect on the exocrine pancreas, the present study suggests the possibility that disturbed function of the exocrine pancreas in diabetic patients could be related to the remarkable response of PP to secretin-stimulation.

Secretin has been isolated as an intestinal polypeptide with 27 amino acid residues (Mutt and Jorpes, 1965). The fact that insulin secretion is enhanced by the injection of secretin (Duprè, 1964; Deckert, 1968; Duprè et al., Lerner and Porte 1972; Shima and Tarui, 1974) has promoted investigation of the interaction between intestinal hormones and pancreatic islet cells. The present study was undertaken to determine whether in diabetic patients secretin stimulates the release of pancreatic polypeptide (pp), a newly recognized hormone with a 36 amino acid sequence (Lin et al., 1977).

Subjects and Methods

Ten diabetic patients aged from 28 to 73 years (mean 48.8) including two patients with juvenile onset diabetes and ten healthy subjects aged from 26 to 43 years (mean 35.5) were studied. Obese persons over 120% of ideal body weight were excluded in this series. Two diabetic patients were treated with insulin, two were treated with sulfonylurea and six were managed with diet therapy. Poorly controlled patients were excluded.

After an overnight fast, they received an intramuscular injection of 2 ml of secretin (Secrepan, Eisai Co., 50 CHRU). Venous blood samples were obtained at 0, 5, 10, 20, 30, 45 and 60 min. Plasma was separated with a centrifuge as soon as possible, after which 0.1 ml of whole blood was put into a test tube for determination of glucose concentration. Two, ml of plasma with 0.1 ml of aprotinin (Trasylol, Bayer Co.) was frozen at -20°C until analyses. Blood glucose was measured by the glucose oxidase method. Insulin and glucagon were measured by dextran-coated charcoal separation using anti-bovine insulin serum and anti-glucagon serum (30 K, Hoechst Co.), respectively.

Pancreatic polypeptide (PP) was measured by the double antibody method of radioimmunoassay (Chance, 1978). Anti-human PP serum of rabbit, human PP and bovine PP were kindly given by Dr. Chance. Bovine PP was labeled with 125I-Na according to the method with chloramine-T. A mixture of 0.1 ml plasma sample or human PP as a standard, 0.1 ml of anti-human PP serum (diluted to 96 x 105), 0.1 ml of 0.5% normal rabbit serum and 0.4 ml of 0.05 mol veronal buffer (pH 8.2) containing 0.5% bovine albumin and aprotinin (250 units) was incubated at 4°C for 24 hr. After that, 0.1 ml of 125I-bovine PP (ca. 2000 cpm) was added and incu-
bated at 4°C for 48 hr. Finally, 0.1 ml of 0.1 mol EDTA were added and incubated at 4°C for 24 hr. The radioactivity in the precipitates after separation with a centrifuge was determined with an automatic well-type scintillation counter.

Results

In diabetes patients, the fasting value of plasma PP was 260 ± 109 pg/ml (mean ± S.E.) and the level of plasma PP increased significantly after intramuscular injection of secretin, reaching a peak of 1012 ± 403 pg/ml at 5 min (0.02 < p < 0.05). The increase in PP provoked by the secretin injection was unrelated to types of diabetes mellitus and their treatment. On the other hand, in healthy subjects the PP concentration did not change after the injection of secretin. Blood glucose, plasma insulin and plasma glucagon were not changed by secretin in either diabetic patients or healthy subjects. The results are summarized in Table 1.

Discussion

Although secretin stimulates or potentiates insulin release in pharmacologic experiments (Duprè, 1964; Deckert, 1968; Duprè et al., 1969; Lerner and Parte, 1972), a physiological role of secretin in insulin secretion has not been recognized (Boyns et al., 1967; Buchanan et al., 1968). The present study shows that secretin has no acute effect on the release of insulin and glucagon. Recently, Adrian et al. (1978) reported that secretin (1 mol/l) clearly enhances insulin levels in dogs at the 8.3 mol/l glucose concentration. The effect was not recognized at lower glucose concentration. The intravenous injection of ten units of secretin during glucose infusion has also been found to cause a rise in plasma insulin in humans (Shima and Tarui 1974). These results mean that secretin potentiates insulin secretion.

Table 1. Effects of secretin on blood glucose, insulin, glucagon and pancreatic polypeptide after intramuscular injection of secretin in diabetic patients

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>45</th>
<th>60 min</th>
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<tr>
<td><strong>Diabetic patients (N=10)</strong></td>
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<tr>
<td>Blood glucose (mg/100 ml)</td>
<td>118±12</td>
<td>112±12</td>
<td>113±12</td>
<td>107±12</td>
<td>108±11</td>
<td>108±12</td>
<td>103±11</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>6.4±1.3</td>
<td>8.6±1.6</td>
<td>8.3±1.6</td>
<td>6.3±1.4</td>
<td>6.3±1.4</td>
<td>7.3±1.8</td>
<td>9.0±0.8</td>
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<tr>
<td>Glucagon** (pg/ml)</td>
<td>145±36</td>
<td>185±41</td>
<td>130±22</td>
<td>200±44</td>
<td>215±22</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PP*** (pg/ml)</td>
<td>260±109</td>
<td>1012±403</td>
<td>686±179</td>
<td>250±65</td>
<td>163±40</td>
<td>275±91</td>
<td>490±205</td>
</tr>
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</table>

| **Healthy persons (N=10)** |        |        |        |        |        |        |        |
| Blood glucose (mg/100 ml) | 91±2.9 | 89±1.9 | 88±1.6 | 87±1.9 | 87±2.2 | 85±1.8 | 83±1.5 |
| Insulin (μU/ml)          | 6.5±1.2| 6.8±1.2| 7.7±1.3| 7.3±0.9| 9.7±0.7| 7.4±0.7| 7.0±0.9|
| Glucagon (pg/ml)         | 207±49 | 179±51 | 208±61 | 156±48 | 146±44 | —      | —      |
| PP*** (pg/ml)            | 110±17 | 98±18  | 110±15 | 115±23 | 79±12  | 165±18 | 118±26 |

* 0.02 < P < 0.05 by paired t-test.
** Glucagon value is a mean of four patients.
*** PP, pancreatic polypeptide.
It is surprising that the amount of pancreatic polypeptide increased remarkably after an injection of secretin in diabetic patients. Gut hormones, especially gastrin, GIP, VIP stimulate release of pancreatic polypeptide (Adrian et al., 1978), but an acute stimulatory effect of secretin has never been found. It could not be ruled out completely that the secretin-preparation used in the present study might be contaminated with GIP, VIP and other peptides. However, as trace amounts of these gut hormones (less than 0.01%) seldom, if any, increased the release of insulin and glucagon, the stimulation of PP secretion in diabetic patients is probably mediated by secretin itself. From the viewpoint on the enteroinsular axis, it is important that there is an interaction of secretin with pancreatic polypeptide in diabetic patients. Because pancreatic polypeptide inhibits the output of bicarbonate and amylase into pancreatic juice (Taylor et al., 1979), the remarkable response of pancreatic polypeptide to secretin possibly disturbs the function of the exocrine pancreas in diabetic patients.

Pancreatic polypeptide is released from the pancreatic islet cells which have paracrine effects (Weir et al., 1979). However, pancreatic polypeptide itself has no acute effect on the A, B and D cells (Ipp et al., 1978). In the postprandial period, the pancreatic polypeptide is continuously released to sustain high blood levels (Floyd et al., 1978; Taylor et al., 1979). In adult onset diabetes, postprandial levels of pancreatic polypeptide were significantly higher than normal controls (Ishida et al., 1979). Therefore, it is possible that in diabetic patients the response of pancreatic polypeptide to gut hormones including secretin, gastrin, GIP and VIP is remarkably increased. Since it is unknown why and how pancreatic polypeptide is increased after intramuscular injection of secretin in diabetic patients, further study is necessary to obtain an understanding of the modulation of pancreatic polypeptide secretion by gut hormones in diabetic patients.

Acknowledgement

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References

Chance, R. E. In personal communication