Changes in Insulin Secretion after Secretin Administration and the Implications in Diabetes Mellitus

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Abstract

Secrepan (Eisai Co. Tokyo, Japan) was administered to 9 healthy volunteers and 36 patients with non-insulin dependent diabetes mellitus (NIDDM) to clarify the effect of secretin on the pancreatic B-cell, by determining the changes in blood of insulin (IRI). Whereas IRI in healthy subjects showed a monophasic change, reaching a peak (ΔIRI=43±7.3 μU/ml, M±SE) 5 min after secretin loading and returning to the basal level in 15 min, NIDDM patients on diet therapy (ΔIRI=40.2±7.6 μU/ml) showed no significant difference from the control group, but NIDDM patients on sulfonylurea (SU) (15.5±2.4 μU/ml) and those on insulin therapy (5.3±1.4 μU/ml), both showed a significant depression in responsiveness. Further, the changes in insulin secretion after atropine administration in healthy subjects and the changes in IRI response to Secrepan in vagotomized patients were also determined. As a result, data which preclude the possibility of association of the vagus nerve and cholinergic nerve with the stimulation of insulin secretion by secretin were obtained, and a direct action of secretin on the cell of islets of Langerhans was suggested.

The maximum IRI response after a secretin load had a significant positive correlation with the IRI response after a 75-gm GTT and the content of C-peptide immunoreactivity in 24-hour urine. Therefore, insulin response to a secretin load can be useful in assessing endogenous insulin secretion and provides a pertinent clinical guide for the selection of an appropriate therapy for diabetes mellitus.

Extensive data are available on insulin secretion promoting factors. These factors are broadly divisible into nutrients, peptide hormones, autonomic nerve, autonomic nerve-related neurotransmitters, and certain drugs.

Secretin is a peptide hormone with a potent stimulatory effect on pancreatic exocrine secretion. It has been reported that physiological doses of secretin lead to a slight increase in blood levels of insulin, while pharmacological doses produce a transient or sustained stimulation of insulin secretion (Unger et al., 1966). The mechanism by which secretin acts on the pancreatic B cell has not been documented, and little work has been done to determine the changes in insulin secretion after secretin administration, in patients with non-insulin dependent diabetes mellitus (NIDDM), using secretin preparation (Secrepan, Eisai Co. Tokyo,
Japan) which is claimed to be of relatively high purity and which does not contain other gastrointestinal hormones. The effects of this secretin preparation were compared with findings with other gastrointestinal hormone preparations, Caerulein, CCK-8 and GIH Secretin, in subjects with normal carbohydrate metabolism. The effects of vagotomy on insulin secretion as well as effects of atropine after secretin administration were also studied.

Materials and Methods

The subjects of the present study were 9 healthy volunteers (averaging in age 45±5 years) without a family history of diabetes mellitus or obesity, 36 NIDDM patients (45±4), and 4 patients (41±6) at 6 to 12 months after vagotomy. Informed consent for the present studies was obtained from all subjects. The secretin load test was performed early in the morning after an overnight fast. Briefly, the subjects rested quietly in bed for at least 30 min and blood samples were taken at -30 and 0 min to obtain control data. At 5, 10, 15, 30, 45, and 60 min after one intravenous administration of secretin (Secrepan, Eisai Co. Tokyo, Japan) 2 U/kg, a blood sample was obtained to determine the levels of IRI. For NIDDM patients, 75-gm oral GTT was performed, and blood levels of IRI were determined before and 30, 60, 90, 120, and 180 min after GTT. Further, the content of C peptide immunoreactivity (CPR) in 24-hour urine was determined, as a general measure of pancreatic insulin secretion.

To determine whether the cholinergic nerve is associated with the stimulation of insulin secretion by secretin, the 2 U/kg secretin load test was performed on 8 healthy subjects following the intravenous administration of atropine, in dose of 500 µg. Healthy subjects were also intravenously administered GIH Secretin (Kabi Diagnostica, Nykoping, Sweden) 2 U/kg, Caerulein (Kyowa Hakko Kogyo Co. Japan) 0.1 µg/kg or CCK-8 (Squibb and Sons, Princeton, NJ) 20 ng/kg, and blood was collected in a similar manner. The blood levels of IRI were determined by the RIA bead method (Yamaguchi et al., 1983), using a Dynabot kit (Tokyo, Japan). The measurement of IRI for the insulin treatment group who have insulin antibody were assayed for free IRI using the polyethylene glycol method (Nakagawa et al., 1972). The urine levels of CPR were determined by the previously described method (Sako et al., 1984). Briefly, the urine was mixed with 0.05% NaN₃ and stored for 24 hours. Following the measurement of the urine volume, part of the sample was diluted 20 times for use in the determination of urine levels of CPR. Measurements were made by the two-antibody method, using a kit from Daiichi Isotope Co. (Tokyo, Japan).

All data were reported as mean plus or minus standard error (M±SE), and assessed by Student's t-test for the significance of difference. The difference was considered statistically significant at p<0.05.

Results

a) Insulin Response to Secretin Load in Healthy Subjects and Vagotomized Patients

When secretin was administered intravenously to two healthy subjects in doses of 0.5, 1.0, 2.0, and 4.0 U/kg, the blood levels of insulin showed a monophasic response, reaching a peak at 5 min for all the doses and returning to the original value in 15 min. As is clear in Fig. 1, the dose response to secretin was maximal by 2.0 units per kilogram.

When secretin was administered intravenously in a dose 2 U/kg to healthy subjects following the administration of atropine or to vagotomized patients, blood levels of insulin reached a peak in 5 min for all the doses and returning to the original value in 15 min. As is clear in Fig. 1, the dose response to secretin was maximal by 2.0 units per kilogram.

When secretin was administered intravenously in a dose 2 U/kg to healthy subjects following the administration of atropine or to vagotomized patients, blood levels of insulin reached a peak in 5 min, in both groups. When IRI at 5 min after the secretin load was measured, there was no significant change, as is obvious from Fig. 2.

b) Insulin Response to Stimulation by GIH Secretin, Caerulein, and CCK-8 in Healthy Subjects

When GIH Secretin was administered intravenously in a dose of 2 U/kg to healthy subjects, the same increase in blood level
Fig. 1. Mean plasma insulin concentration in response to increasing doses of secretin (n=2).

Fig. 2. Maximum insulin response (JIRI) after secretin injection in 8 controls with and without atropine, and in 4 vagotomized subjects.

Fig. 3. Maximum insulin response (JIRI) after secretin (Eisai 2 u/kg and Kabi GIH 2 cu/kg), CCK-8 20 ng/kg, and Caerulein 0.1 μg/kg in 6 healthy subjects. * significant increment from basal p<0.001.
of insulin as after Secrepan occurred, while a 0.1 µg/kg intravenous Caerulein load or a 20 ng/kg intravenous CCK-8 load failed to elicit any significant insulin response.

e) Insulin Response to 75-gm GTT and Secretin Load in NIDDM Patients

After giving 75-gm GTT, the group of NIDDM patients on diet therapy showed a slight decrease in glucose tolerance and a delayed insulin response, as shown in Fig. 4. This group of NIDDM patients showed a nearly normal pattern of insulin response after a secretin load. To determine the effect of secretin according to type of therapy, these patients were separated into three subgroups, diet therapy, oral SU preparation and insulin (Table 1), and the maximum insulin response (JIRI) to the secretin load was compared among the three groups. All these patients showed the same insulin secretory profile and the maximum insulin response at 5 min after secretin stimulation. The insulin group showed the lowest level of IRI at 5.3 ± 1.4 µU/ml, as shown in Fig. 5, and the oral SU group also showed a depressed level of IRI at 15.5 ± 2.4 µU/ml. The insulin and oral SU groups both had a significantly lower blood level of IRI than did the healthy subjects, and there was a significant difference between the insulin and the oral SU group. The diet therapy group, on the other hand,

Fig. 4. Insulin response after 75-gm GTT and secretin injection in 16 NIDDM patients.

Fig. 5. Maximum insulin response (JIRI) after secretin injection in 9 controls and NIDDM (13 diet group, 13 SU group and 10 Insulin group).

Table 1. Characteristics of NIDDM groups

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of subjects</th>
<th>Age (yr)</th>
<th>Percent of ideal body weight</th>
<th>FBS (mg/dl)</th>
<th>HbAl (%)</th>
<th>Urine CPR (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet group</td>
<td>13</td>
<td>41 ± 10.1</td>
<td>116 ± 9.8</td>
<td>180 ± 24.5</td>
<td>11 ± 2.4</td>
<td>75 ± 17.5</td>
</tr>
<tr>
<td>SU group</td>
<td>13</td>
<td>50 ± 9.5</td>
<td>102 ± 8.1</td>
<td>190 ± 21.3</td>
<td>10 ± 1.5</td>
<td>35 ± 12.5</td>
</tr>
<tr>
<td>Insulin group</td>
<td>10</td>
<td>40 ± 6.2</td>
<td>90 ± 7.6</td>
<td>213 ± 39.2</td>
<td>13 ± 2.3</td>
<td>10 ± 8.2</td>
</tr>
</tbody>
</table>

(Mean ± SE)
with a mean blood insulin level of 40.2 ± 7.6 μU/ml showed no significant difference from the healthy subjects. When the insulin response was compared between the 75-gm GTT and the secretin load, IRI showed a significant positive correlation (r=0.859, p<0.001) between the two tests, as shown in Fig. 6. This result suggests that glucose and secretin produce much the same stimulation of pancreatic B cells.

**Fig. 6.** Relationship between maximum IRI after 75-gm GTT maximum IRI after secretin injection in 17 NIDDM patients.

**Fig. 7.** Relationship between maximum IRI after injection and urine CPR in 36 NIDDM patients.

d) Urine Levels of CPR and Insulin Response to Secretin Load in NIDDM Patients

NIDDM patients showed a significant positive correlation (r=0.823, p<0.001) between CPR content in 24-hour urine and ΔIRI, as shown in Fig. 7.

**Discussion**

There are reports that secretin stimulates insulin secretion without affecting blood levels of glucose and glucagon, in man (Boyns et al., 1967, Pfeiffer et al., 1973). It has been reported that secretin acts on the Pancreatic Polypeptide (PP) cell in stimulating PP secretion by a non-vagal cholinergic mechanism (Glaser et al., 1980), but the mechanism by which it acts on the pancreatic B cell still remains to be clarified. In the present study it was shown that secretin stimulated insulin secretion without the mediation of the vagus nerve and cholinergic nerve. Deckert et al. indicated that secretin-stimulated insulin secretion was not inhibited by adrenaline and that the sympathetic nerve was not involved (Deckert et al., 1970). It is therefore conceivable that rather than act through the mediation of nerves secretin acts directly on the B cell, and the presence of a different receptor from glucoreceptor is suggested in relation to this action. The secretin preparation used in the present study was Secrepan (Eisai Co. Tokyo, Japan). Secrepan and GIH secretin both stimulated IRI secretion similarly. Since one unit of Secrepan corresponds to 1/4 GIH clinical unit (Tachibana et al., 1979), the former can be considered to be a secretin preparation of high purity.

On the other hand, CCK-8 and Caerulein, potent stimulants of pancreatic exocrine secretion, are also known to stimulate pancreatic endocrine secretion. There are reports that these agents strongly stimulate insulin secretion in rats (Ohneda et al., 1978,
Ri et al., 1982). However, as noted in the present study, neither CCK-8 nor Caerulein stimulated insulin secretion, in man at submaximal or maximal exocrine pancreas stimulating dose levels. This suggests that there may exist receptors of differing sensitivity, or that these agents may have certain specificities in different species.

The insulin response to 75-gm GTT along with a significant positive correlation between CPR content in 24-hour urine (Sako et al., 1984, Matsuda et al., 1984), and which is said to clearly reflect the amount of endogenous insulin, and insulin response to a secretin load in NIDDM patients indicates that the insulin response to the secretin load in NIDDM patients can be a reliable measure of insulin secretion, in diabetics. The insulin response was depressed in a stepwise fashion in the order of insulin, oral SU and diet after a secretin load. This suggests that the insulin response to these tests can be used as a useful guide for the determination of an appropriate therapy for patients with diabetes mellitus, and can be used as a simpler test than conventional methods (75-gm GTT and iv GTT).

We also found (data not shown) that the insulin response to a secretin load was not affected by fasting blood levels of glucose and that the secretin load elicited few if any side effects. The secretin load should therefore gain increasing importance as a clinical test.

Conclusions

(1) It is conceivable that secretin may act directly on the pancreatic B cell and stimulate insulin secretion.

(2) Secretin-stimulated insulin secretion in NIDDM patients shows a high correlation with the insulin response to the 75-gm GTT and urine levels of CPR.

(3) The insulin response to a secretin load was decreased in step fashion in the order of healthy subjects (ΔIRI = 43 ± 7.5 μU/ml), dietotherapy group (40.2 ± 7.6 μU/ml), SU preparation group (15.5 ± 2.4 μU/ml), and insulin group (5.3 ± 1.4 μU/ml). The insulin response to the secretin load provides a useful clue to appropriate therapy for clinical diabetes mellitus.

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References


