5-Hydroxytryptamine-1 receptor activation inhibits endocrine pancreatic secretion in humans

**Coulie, Bernard, J an Tack, Roger Bouillon, Theo Peeters, and J osez J ansSENS.** 5-Hydroxytryptamine-1 receptor activation inhibits endocrine pancreatic secretion in humans. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E317–E320, 1998.—The selective 5-hydroxytryptamine-1 receptor agonist sumatriptan inhibits exocrine pancreatic function in humans. No data are available on the effect of sumatriptan on fasting and postprandial endocrine pancreatic function in humans. To elucidate the influence of 5-hydroxytryptamine-1 receptor activation by sumatriptan on endocrine pancreatic function and blood glucose homeostasis, we determined plasma levels of somatostatin, glucagon, pancreatic polypeptide, insulin, and C-peptide before and after subcutaneous administration of sumatriptan (6 mg) in seven healthy volunteers, and we measured blood glucose and insulin plasma levels during an oral glucose tolerance test after placebo and after subcutaneous administration of sumatriptan (6 mg) in seven healthy volunteers. Sumatriptan significantly decreased the mean plasma levels of somatostatin, glucagon, pancreatic polypeptide, insulin and C-peptide (P < 0.001) and also significantly decreased mean and peak plasma levels of insulin after an oral glucose challenge (P < 0.02 and P = 0.04, respectively) without affecting glucose homeostasis. From our study, we speculate that activation of the 5-hydroxytryptamine-1 receptor inhibits endocrine pancreatic secretion.

enteropancreatic innervation

**MATERIALS AND METHODS**

Fourteen healthy volunteers (11 males and 3 females; mean age 23.9 ± 1.4 yr) participated in this study. None of the subjects had symptoms or a history of gastrointestinal disease, pancreatic insufficiency, or diabetes mellitus, and none was taking any medication. Informed consent was obtained from each participant. The protocol had been previously approved by the Ethics Committee of the University Hospital.

After an overnight fast of 12 h, sumatriptan (6 mg; Glaxo-Welcome, Brussels, Belgium) was administered subcutaneously. This dose of sumatriptan has been shown to be safe and effective in the control of migraine (6). In seven volunteers, blood samples were drawn four times with a 10-min interval before the administration of sumatriptan, twice with a 5-min interval thereafter, and every 10 min during the following 50-min period. Plasma concentrations of somatostatin, pancreatic polypeptide (PP), glucagon, insulin, and C-peptide were measured by radioimmunoassay with methods previously described (10, 18, 20).

In seven volunteers after administration of placebo or sumatriptan, an oral glucose tolerance test was performed on two separate days, with blood samples taken before the ingestion of 75 g of glucose and every 30 min thereafter during 3 h for measurement of blood glucose and plasma insulin levels.

In each subject, mean hormone plasma levels were calculated before and after administration of sumatriptan and compared using a paired Student’s t-test. Mean blood glucose, mean plasma insulin levels, and peak plasma insulin levels during the oral glucose tolerance test after administration of placebo and sumatriptan were calculated over a period of 120 min after ingestion of glucose, because the plasma half-elimination time of sumatriptan is 2 h. Mean blood glucose and mean plasma insulin levels after placebo and after sumatriptan were compared using analysis of variance. Peak plasma insulin levels after placebo and after sumatriptan were compared using the paired Student’s t-test. Differences were considered to be significant at the 5% level. Results are expressed as means ± SE.

**RESULTS**

Mean plasma levels of somatostatin, glucagon, PP, insulin, and C-peptide before and after administration of sumatriptan are shown in Table 1.

Administration of sumatriptan (6 mg sc) resulted in all volunteers in a significant inhibition of the release of somatostatin, glucagon, PP, C-peptide, and insulin (P < 0.001). Inhibition occurred within 5 min after injection of the drug (Fig. 1). The mean percentage decrease in
the release of somatostatin, glucagon, PP, C-peptide, and insulin was, respectively, 44.7 \pm 6.9, 31.4 \pm 1.5, 54.6 \pm 6.2, 31.2 \pm 2.4, and 47.5 \pm 5.3%.

Mean insulin plasma levels during an oral glucose tolerance test were significantly decreased after administration of sumatriptan vs. placebo (P < 0.04; Fig. 2). Administration of sumatriptan also resulted in a significant decrease of the peak insulin plasma level, which occurred 30 min after ingestion of glucose (117.3 \pm 28.4 vs. 61.8 \pm 34.8 \mu U/ml; P < 0.02; Fig. 2). Blood glucose levels were not significantly altered by sumatriptan vs. placebo.

**DISCUSSION**

The present study clearly demonstrates that administration of the 5-HT1 receptor agonist sumatriptan profoundly inhibits fasting and postprandial endocrine pancreatic secretion in humans.

The role of 5-HT in the regulation of endocrine pancreatic secretion is still a matter of debate. In response to 5-HT receptor activation, both decreased and increased insulin levels, respectively with hyperglycemia and hypoglycemia, have been reported in animals (1, 3, 21). Regarding the effect of 5-HT on endocrine pancreatic function in humans, it has been reported that methysergide and cyproheptadine increase hypoglycemia- and arginine-induced glucagon secretion (16). Furthermore, methysergide potentiates glucose-mediated insulin release in rats (1, 3). The inhibitory effect on insulin release is attributed to activation of central 5-HT1A receptors (3), whereas the increase in insulin release observed after administration of 8-OH-DPAT seems to be mediated via activation of oxytocin release (1). Previous clinical studies in humans showed that methysergide, which acts as a partial 5-HT1 receptor agonist and as a 5-HT2C receptor antagonist, potentiates both insulin and glucagon release (15, 16).

From our data, it is apparent that sumatriptan has a strong inhibitory effect on endocrine pancreatic function in humans. The currently available pharmacological tools in humans do not allow us to determine exactly the site of action and the 5-HT receptor subtype involved in this effect. The fact that sumatriptan poorly penetrates the blood-brain barrier makes a central site of action unlikely (6). Although a direct action on

---

**Table 1. Plasma levels of pancreatic hormones before and after administration of 6 mg sc sumatriptan**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Control</th>
<th>Sumatriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>11 \pm 0.9</td>
<td>7.7 \pm 0.8*</td>
</tr>
<tr>
<td>Glucagon</td>
<td>225 \pm 32</td>
<td>151 \pm 19.4*</td>
</tr>
<tr>
<td>PP</td>
<td>102.7 \pm 32</td>
<td>42.6 \pm 13.9*</td>
</tr>
<tr>
<td>C-Peptide</td>
<td>0.56 \pm 0.04</td>
<td>0.39 \pm 0.03*</td>
</tr>
<tr>
<td>Insulin</td>
<td>10.7 \pm 1.4</td>
<td>5.5 \pm 0.9*</td>
</tr>
</tbody>
</table>

Values are means \( \pm SE \). Sumatriptan significantly inhibits release of all pancreatic hormones measured compared with control. Somatostatin, glucagon and pancreatic peptide (PP) plasma levels are given in pg/ml, C-peptide is given in pmol/ml, and insulin is given in \( \mu U/ml \). *P < 0.001 vs. control.

---

**Fig. 1. Plasma levels (means \( \pm SE \)) of 4 hormones measured at each sampling point before and after administration of sumatriptan (6 mg sc) at time 0. PP, pancreatic peptide.**
The therapeutic effect of sumatriptan in the treatment of migraine has been attributed to its action on 5-HT1 receptors on neurons innervating the pancreas. Pancreatic islets receive innervation from both divisions of the autonomic nervous system, and pancreatic endocrine secretion is partly controlled by the autonomic nervous system (8). In addition, intrinsic pancreatic neurons and enteropancreatic neurons also innervate pancreatic islets, pancreatic acini, and pancreatic ducts (11), although their role in the control of endocrine pancreatic secretion has not yet been studied. Presynaptic 5-HT1P receptors on pancreatic cholinergic secretomotor neurons inhibit the exocrine pancreatic secretion via the inhibition of cholinergic outflow (12). In view of the similarities between the innervation of pancreatic acini and pancreatic islets, a similar mechanism may control pancreatic endocrine secretion.

The lack of suitable pharmacological tools precludes identification of the 5-HT receptor subtype involved. The therapeutic effect of sumatriptan in the treatment of migraine has been attributed to its action on 5-HT1D receptors (6). Although the presence of this 5-HT receptor subtype has never been demonstrated in the gastrointestinal tract, there is some pharmacological evidence that sumatriptan stimulates the peristaltic reflex in the guinea pig ileum and enhances contractile activity of the longitudinal smooth muscle in the chicken ileum (2, 17). Furthermore, we recently demonstrated that sumatriptan decreases gastric emptying of solids and liquids in humans (4). In vitro studies in the rat demonstrated that activation of presynaptic 5-HT1P receptors on cholinergic neurons inhibits exocrine pancreatic secretion (12). Recently, we observed that sumatriptan acts as an agonist at 5-HT1P receptors on enteric neurons (19). Therefore, one of the possible mechanisms by which sumatriptan inhibits endocrine pancreatic secretion in humans is via activation of presynaptic 5-HT1P receptors on cholinergic neurons innervating the pancreas. Nonetheless, a recent in vitro study in the rat bowel and pancreas using radioautography demonstrated that both 5-HT1A and 5-HT1P receptors are coexpressed by many nerve cells and processes (13). Because sumatriptan is an agonist with intermediate potency at 5-HT1A receptors (9), activation of presynaptic 5-HT1A receptors on cholinergic neurons innervating the pancreas cannot be discarded as a potential mechanism by which sumatriptan inhibits endocrine pancreatic secretion. On the other hand, in the guinea pig antrum sumatriptan does not mimic the 5-HT1A receptor-mediated slow hyperpolarization in those myenteric neurons that do display a slow hyperpolarization to 5-HT (19). In agreement with the fact that activation of presynaptic 5-HT1P rather than 5-HT1A receptors is responsible for inhibition of endocrine pancreatic secretion is the potentiating effect of methysergide on insulin and glucagon secretion in humans (15, 16). Methysergide has agonistic activity at 5-HT1A receptors but has also been demonstrated to be an antagonist at 5-HT1P receptors (7).

Although administration of sumatriptan strongly inhibits fasting and postprandial insulin secretion, postprandial blood glucose levels are unaffected by sumatriptan in healthy subjects. This is probably because the residual insulin secretion after sumatriptan in healthy subjects is still sufficient for adequate metabolism of the postprandial rise of blood glucose. Nevertheless, it cannot be excluded from our data that sumatriptan resets peripheral insulin sensitivity at muscle, liver, or adipose tissue. Further studies using insulin- and glucose-clamp techniques are warranted to clarify this issue. Also, the effect of sumatriptan on postprandial insulin secretion and blood glucose homoeostasis in patients with decreased insulin secretion remains to be studied.

We conclude that administration of sumatriptan inhibits fasting and postprandial endocrine pancreatic secretion in humans, probably via activation of a presynaptic 5-HT1A receptor. Thus our data suggest that neural 5-HT1A receptors are involved in the control of endocrine pancreatic function. However, at this point, the physiological significance of these observations regarding the potential role of 5-HT1A receptors in the regulation of endocrine pancreatic secretion is not fully clarified. To address this issue and to elucidate the 5-HT1A receptor subtype involved and its exact location, further studies using selective antagonists that can be safely used in vivo are warranted.

Present address of B. Coullie: GI Research Unit, Mayo Foundation, 200 First St. SW, Rochester, MN 55905.

Address for reprint requests: J. Tack, Assoc. Prof. of Medicine, Div. of Gastroenterology, Univ. Hospital Gasthuisberg, Katholieke Universiteit Leuven, Herestraat 49, B-3000 Leuven, Belgium.

Received 16 April 1997; accepted in final form 24 October 1997.

REFERENCES


