Suppression of somatostatin release by duodenogastic reflux in dogs

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SUMMARY The effect of duodenogastic reflux on systemic and portal venous blood concentrations of somatostatin has been studied in the dog. Duodenogastic reflux suppressed somatostatin concentrations in both systemic and portal venous blood, but this did not occur when bile alone was diverted into the stomach. The suppression was also much less marked when truncal vagotomy accompanied the reflux. These findings suggest that altered somatostatin activity may play a part in the production of the pathophysiological changes occurring in clinical conditions such as peptic ulceration, in which there is an increase in duodenogastic reflux.

Dogs with surgically produced duodenogastic reflux hypersecrete gastric acid in response to pentagastrin but not to histamine. This selective hypersecretory response is accompanied by normal fasting serum gastrin concentrations but hypergastrinaemia in response to a standard meal and is associated with antral gland hyperplasia. These changes do not occur with bile diversion alone into the stomach and can be abolished by the addition of truncal vagotomy. One possible explanation of these functional changes would be that duodenogastic reflux suppresses a naturally occurring inhibitory substance produced by the antrum, that normally suppresses gastrin release from the G cells and also inhibits the acid response to pentagastrin, but not to histamine. Somatostatin fulfils these criteria and indeed a low dose infusion of 0.25 μg/kg/h has been found to restore the functional changes seen with duodenogastic reflux down to control levels. The effects of such reflux have therefore been studied on the systemic and portal venous concentrations of somatostatin.

Methods

ANIMALS
Adult litter mate beagles were randomly allocated into four groups each of five animals.

1. A control group.
2. A group with bile diversion, achieved by ligating and dividing the common bile duct and fashioning a cholecystogastrostomy high on the lesser curvature of the stomach (Fig. 1). A group with duodenogastic reflux, achieved by dividing the duodenum distal to the entry of the common bile duct and pancreatic ducts, and anastomosing the proximal end to the upper lesser curvature of the stomach. Intestinal continuity was restored by a posterior gastro-duodenostomy (Fig. 1). A group with duodenal reflux as above, with the addition of truncal vagotomy.

All animals were kept in the same environmental surroundings and fed on a standard diet. All animals were kept for six months postoperatively during which time secretion experiments were performed as previously described. After six months all dogs were killed, but before this, samples of portal and systemic venous blood were collected by direct puncture. All samples were assayed for somatostatin concentrations using a radioimmunoassay technique.

Blood samples were withdrawn into iced heparinised tubes, centrifuged at 4°C and the plasma extracted by alcohol, the extracts blown dry in a jet of air and then stored at 4°C pending assay. The samples were reconstituted before assay in 0.04 M phosphate buffer pH 7.4. The standard was synthetic cyclic somatostatin. The antibody (OB 5(1)) was raised in rabbits to cyclic somatostatin and was used at a 1:15 000 final dilution in the assay tube. No crossreactivity with any other gut or islet peptide was found. The antibody was C-terminally directed although reaction with fragments was low,

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Table  Secretory data and serum gastrin concentrations

<table>
<thead>
<tr>
<th>Group</th>
<th>Fasting serum gastrin concentrations (pg/ml)</th>
<th>Maximal acid output to pentagastrin 8 µg/kg/h (mmol/30 min)</th>
<th>Maximal acid output to histamine 80 µg/kg/h (mmol/30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>57</td>
<td>9-1</td>
<td>14-4</td>
</tr>
<tr>
<td>Bile diversion</td>
<td>60</td>
<td>6-6</td>
<td>11-9</td>
</tr>
<tr>
<td>Duodenal reflux</td>
<td>60</td>
<td>15-3</td>
<td>14-5</td>
</tr>
<tr>
<td>Duodenal reflux with vagotomy</td>
<td>60</td>
<td>4-0</td>
<td>10-9</td>
</tr>
</tbody>
</table>

suggesting that the whole molecule was required for full crossreactivity. N-tyrosylated somatostatin was iodinated by the chloramine-T technique and the iodinated peptide purified on a cation exchanger, Whatman CM52 using 0·05 M and 0·25 M acetate buffer. Horse serum was filtered through charcoal to remove endogenous peptides and extracted in an identical manner to the plasma samples, and added to the calibration samples to equilibrate conditions between standards and unknowns. Separation of free from antibody bound peptide was achieved by dextran coated charcoal. The assay could detect 3 ng/l (pg/ml) with 95% confidence. When three samples measuring mean values of 8 ng/l, 42 ng/l and 193 ng/l were repeatedly assayed eight times in different batches, the coefficient of variance was 10·6%, 5·5%, and 4·4% respectively.

Results

Throughout the study, all dogs remained well, put on weight, and there was no evidence of problems with gastric emptying. The median control systemic venous somatostatin level of 20 pg/ml (range 10–45) was depressed by duodenogastric reflux down to 10·0 pg/ml (range 5–25) (p<0·05). This depression appeared less marked in dogs with reflux and truncal vagotomy (range 5–65 pg/ml) and did not occur when bile alone was diverted into the stomach (range 10–50 pg/ml) (Fig. 2). Portal venous somatostatin concentrations were higher than in systemic venous blood (Fig. 3). Duodenogastric reflux depressed the median control level from 55·0 pg/ml (range 40–120) down to 20·0 pg/ml (range 10–40) (p<0·05), however, and again

Fig. 1 (a) Bile diversion preparation. (b) Duodenal reflux preparation.
this appeared less marked with the addition of truncal vagotomy (range 30–100 pg/ml) and did not occur with bile diversion alone (range 30–140 pg/ml). Statistical analysis used the non-parametric Wilcoxon’s rank sum test.

**Discussion**

The physiological role of somatostatin in the control of acid secretion remains uncertain. It is a strong inhibitor of acid secretion and gastrin release, however, and portal venous blood concentrations appear to respond to a change in gastric pH. Gustavsson and Lundqvist showed that somatostatin levels in antral and portal venous blood of the pig fell after irrigation of the antrum with alkali, while conversely intragastric 0.1 M HCl caused degranulation of the D cells in the canine pyloric antrum. Such intragastric acid also caused a marked rise in the somatostatin concentration in antral venous blood, and this is reflected by a later smaller rise in somatostatin activity in the systemic venous circulation.

Suppression of somatostatin by duodenogastric reflux could therefore explain the hypersecretory state seen in these dogs. The nature of this suppression is unclear, however, and it does not occur with bile diversion alone and therefore appears to be a function of the addition of pancreatic juice. It therefore may not be simply a matter of alkaline reflux, but possibly an enzymic reaction or the effects of some compound formed by the combination of bile and pancreatic juice such as lysolecithin.

It is vital to exercise caution in the extrapolation of experimental findings in dogs to the clinical situation in man although the clinical relevance of these findings may be important. Increased duodenogastric reflux occurs in a wide variety of clinical conditions, but particularly in patients with gastric ulcers and to a lesser degree in those with duodenal ulcers. It has been suggested that such reflux, leading to altered somatostatin activity, is responsible for the pathophysiological changes observed in these conditions. The involvement of somatostatin is supported by the finding that infusions of this hormone can restore the functional changes to normal concentrations and also prevent the development of duodenal ulcers in cats. The normal ratio of G to D cells is 7:1 and this ratio can alter in some cases of duodenal ulcer, with ratios reaching 90:1 in G cell hyperplasia. Other workers report this ratio is unaltered in duodenal ulcer patients, however, although it does appear that antral pH governs the ratio of G and D cells. In spite of conflicting reports concerning these ratios, many workers have found lower antral somatostatin concentrations in patients with peptic ulcer while the D cell count may also fall in the duodenum itself.

It thus appears that altered somatostatin activity may play an important part in the functional changes...
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observed in patients with peptic ulcers, and the findings of this present study suggest that this altered somatostatin activity may well be secondary to duodenogastric reflux.

References


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