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The influence of mesenteric denervation on the inhibition of gastric secretion by fat in the intestine

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SUMMARY The inhibitory effect of fat in the upper small intestine was studied in dogs prepared with a Heidenhain pouch, gastric fistula, and jejunal fistula. Gastric secretion was stimulated by a constant intravenous infusion of pentagastrin, and emulsified olive oil was introduced into the jejunum. The small intestine of the dog was denervated by complete transection of the mesentery except for the superior mesenteric vessels. After intestinal denervation inhibition of the vagally innervated stomach was almost abolished while that in the Heidenhain pouch was unchanged. It is concluded that either autonomic innervation is important in the formation of enterogastrone or, more likely, that efferent inhibitory fibres in the vagus to the stomach act synergistically with enterogastrone.

Pavlov (1910) in his classic monograph describes the experiments of Khizhin, Lobasov, and Sokolov, demonstrating that fat introduced into the duodenum reduces gastric secretion. This finding has been confirmed by many workers and has been attributed to a humoral mechanism, 'enterogastrone' (Kosaka and Lim, 1929-30). Subsequent work has indicated that the intestine plays a key role in inhibiting gastric function, both motor and secretory. This regulation is not accomplished by a single mechanism, but by many, including both autonomic nervous and endocrine mechanisms. The inhibitory effect of fat on gastric secretion cannot be fully accounted for by the known polypeptide hormones (Johnson and Grossman, 1969). The present experiment was undertaken to investigate the possibility that the autonomic nervous system might have a significant role in the 'enterogastrone' mechanism by which fat in the intestine inhibits gastric secretion.

Method

Five mongrel dogs weighing 15 to 18 kg were prepared by a one-stage aseptic operative procedure.

A Heidenhain (denervated fundic) pouch was constructed and drained to the exterior by a stainless steel Dragstedt cannula (Dragstedt, Haymond, and Ellis, 1933). A gastric fistula was then created in the remaining stomach by inserting a Thomas cannula in the most dependent portion of the greater curvature (Thomas, 1941). Lastly, an intestinal fistula was instituted by placing a Gregory cannula in the jejunum 6 in. distal to the ligament of Treitz (Gregory, 1950). The animals were permitted a period of four weeks or longer for recuperation before experiments were begun.

Animals were fasted for 18 hours before each experiment, and were not studied on successive days. Each dog was placed in a Pavlov stand and gastric juice collected by gravity from the gastric fistula cannula and the Heidenhain pouch cannula. A venous catheter was placed and gastric secretion stimulated by a continuous intravenous infusion of pentagastrin1 in a dose of 0-5 μg/kg/hour. Pentagastrin was made up by adding 37-5 μg to 100 ml of physiological saline and was infused with a peristaltic pump. A plateau of gastric secretion was established, usually by 90 minutes; the level reached was 30-60% of maximum in all dogs.

When the plateau of gastric secretion was well established in both the gastric fistula and Heidenhain pouch, 15 ml of a 50% olive oil emulsion2 in normal saline was slowly introduced through the Gregory cannula into the proximal jejunum during a period of 15 minutes. The fat infusion into the jejunum very occasionally induced retching or vomiting;

1Gastrin pentapeptide supplied by Project Services Division of Ayerst Laboratories, New York.
22% Colloid magnesium aluminium silicate (Vegum, R.T. Vanderbilt Co, New York) was used as an inorganic emulsifier.

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The influence of mesenteric denervation on the inhibition of gastric secretion by fat in the intestine

whenever this occurred the experiment was terminated. The pentagastrin infusion was maintained at the same rate for an additional two hours while gastric secretion was collected every 15 minutes from both the gastric fistula and the Heidenhain pouch. Acidity of the gastric juice was determined by titrating with 0-1N sodium hydroxide to pH 7-0 using a Beckman model 96 pH meter; gastric secretion was expressed as milli-equivalents of hydrochloric acid per 15 minutes.

Control infusions of pentagastrin were performed for periods of four hours in all animals and in every instance the plateau remained constant. The emulsifier alone was found to have no effect on gastric secretion. Olive oil and corn oil without emulsifier inhibited gastric secretion comparably, but nausea and retching were more frequent.

Twenty-four-hour collections of gastric secretion were obtained for periods of 10 to 20 days in each of the five dogs. Collection bags were attached to the Heidenhain pouch cannulas and the animals were maintained on a diet which was constant both in composition and amount. After electrometric titration gastric secretion was expressed as milliequivalents of HCl per day.

After completion of the above experiments the animals were laparotomized and mesenteric denervation was carried out as follows: the superior mesenteric artery and vein were isolated distal to the inferior pancreaticoduodenal and common colic arteries and veins. The small bowel mesentery was completely transected and the adventitia cleaned off the mesenteric vessels. The jejunum at the ligament of Treitz and the ileum at the ileocolic valve were transected and re-anastomosed. A full-thickness biopsy of the jejunum was taken at this time and the mesentery was repaired (Fig. 1).

Six weeks later gastric secretory studies were resumed and the above protocol was repeated. The jejunum was re-biopsied at the time of sacrifice six to eight months after mesenteric denervation. Statistical analysis was done on gastric secretory data and the significance of the difference between the means of unpaired values was determined using Student's t test (Snedecor and Cochran, 1967).

Results

Sixty-two experiments were performed before and 74 after mesenteric denervation in the five dogs. Fat in the form of an olive oil emulsion significantly inhibited (p < 0-01) the pentagastrin-stimulated secretion of both a vagally innervated gastric fistula (Fig. 2) and a vagally denervated Heidenhain pouch (Fig. 3). This inhibition usually lasted for 90 minutes; the degree of inhibition averaged 69-7% in the gastric fistula and 50% in the Heidenhain pouch (no significant difference statistically).

After mesenteric denervation the gastric fistula secretion was inhibited by only 23-5% (Fig. 4). This change from the studies before denervation proved to be statistically significant (p < 0-01). The Heidenhain pouch secretion after mesenteric denervation was inhibited by 40% (Fig. 5); this proved to be not significantly different from the inhibition observed in the studies before denervation.

Twenty-four-hour collections of gastric juice from the Heidenhain pouch demonstrated a significant increase after mesenteric denervation in four of the five dogs (Table 1). This change was noted immediately, and was present as late as eight months after mesenteric denervation (Fig. 6). Study of the jejunal biopsies indicated no change in the microscopic appearance six to eight months after mesenteric denervation.

Discussion

There are many reports demonstrating that fat in the intestine inhibits the gastric secretory response to both endogenous and exogenous gastrin (Sircus, 1958; Gregory and Tracy, 1959; Konturek and Grossman, 1965; Bibler, Harkins, and Nyhus, 1966; Swan, Konturek, Jacobson, and Grossman, 1966; Debas, Bedi, Gillespie, and Gillespie, 1969; Windsor,
Cockel, and Lee, 1969). In the present study a continuous infusion of pentagastrin was used and emulsified olive oil was administered into the proximal jejunum. Denervation of the small intestine by transection of the entire small bowel mesentery appeared clearly to affect the 'enterogastrone' mechanism. In the vagally innervated main stomach the inhibitory effect of fat in the intestine was almost completely abolished at these dose levels of gastrin and fat. There was no significant change in the

<table>
<thead>
<tr>
<th>Dog</th>
<th>No. of Collections</th>
<th>Before Denervation (m-equiv HCl ± SEM)</th>
<th>After Denervation (m-equiv HCl ± SEM)</th>
<th>Percentage Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>13</td>
<td>38.21 ± 3.38</td>
<td>60.03 ± 2.83</td>
<td>+57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>52.20 ± 2.98</td>
<td>74.24 ± 4.38</td>
<td>+42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C</td>
<td>14</td>
<td>9.46 ± 0.55</td>
<td>28.15 ± 2.20</td>
<td>+197</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>20.54 ± 1.61</td>
<td>43.27 ± 2.32</td>
<td>+110</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>E</td>
<td>17</td>
<td>40.08 ± 3.06</td>
<td>37.00 ± 2.34</td>
<td>-8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table I Numerical values of 24-hour gastric secretion from the Heidenhain pouches of five dogs before and after mesenteric denervation

FIG. 2. Inhibitory effect of intrajejunal instillation of 15 ml of emulsified olive oil on the pentagastrin-stimulated gastric fistula secretion before mesenteric denervation. Mean of 13 control (broken line) and 25 oil experiments (solid line) in five dogs. Vertical bars indicate standard error of the mean.

FIG. 3. Inhibitory effect of intrajejunal instillation of 15 ml of emulsified olive oil on the pentagastrin-stimulated Heidenhain pouch secretion before mesenteric denervation. Mean of nine control (broken line) and 15 oil experiments (solid line) in five dogs.
The influence of mesenteric denervation on the inhibition of gastric secretion by fat in the intestine

FIG. 4. Inhibitory effect of intrajejunal instillation of 15 ml of emulsified olive oil on the pentagastrin-stimulated gastric fistula secretion after mesenteric denervation. Mean of 19 control (broken line) and 29 oil experiments (solid line).

FIG. 5. Inhibitory effect of intrajejunal instillation of 15 ml of emulsified olive oil on the pentagastrin-stimulated Heidenhain pouch secretion after mesenteric denervation. Mean of 14 control (broken line) and 22 oil experiments (solid line).

Table II Percentage maximal inhibitory effect of emulsified olive oil on pentagastrin-stimulated gastric fistula and Heidenhain pouch secretion before (control) and after mesenteric denervation
inhibition of Heidenhain pouch secretion. Post-operative changes in the intestine seem an unlikely explanation in view of the normal gross and microscopic appearance of the intestinal wall including the mucosa. There was no evidence of vascular insufficiency or lymphatic obstruction. Also, such an effect on the intestine would be expected to reflect equally in the inhibition of gastric fistula and Heidenhain pouch.

Another possible explanation would be that the autonomic nervous system is important in the formation or release of the hormone enterogastrone. This would be supported by our finding that the Heidenhain pouch secretion over a period of 24 hours on the standard dietary intake increased after intestinal denervation. Other investigators also have reported an increase in gastric secretion following extra-gastric vagotomy or posterior selective vagotomy (Landor, 1964; Kelly, Nyhus, and Harkins, 1964; Middleton, Kelly, Nyhus, and Harkins, 1965). A reduction in enterogastrone, however, would be expected to reduce the inhibition of both the gastric fistula and the Heidenhain pouch secretion. In fact, the vagally denervated pouch might be expected to be less responsive to an inhibitory influence than the vagally innervated stomach. Gastric secretory inhibition due to acid in the duodenum is more effective in a vagally innervated pouch (Code and Watkinson, 1955). Halvorson, Middleton, Bibler, Harkins, and Nyhus (1966) found that vagal innervation of the intestine did not influence the inhibition produced by fat in the intestine. However, they used histamine as a gastric secretory stimulant and also gave a much larger volume of fat.

The remaining explanation is that efferent fibres in the vagus nerves to the stomach are important in the enterogastrone mechanism. It seems unlikely that this humoral agent acts centrally and we would suggest instead that there is an inhibitory bonus in some vagus efferent fibres which acts synergistically with the humoral agent we call enterogastrone.

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