Effect of Colectomy on Cholecystokinin and Gastrin Release

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Studies were conducted to determine the effect of resection of the colon on the release of cholecystokinin (CCK) and gastrin. A standard food stimulation test was performed in five dogs. Peripheral blood samples were collected for future measurement of CCK and gastrin by specific radioimmunoassay. Each dog underwent subtotal colectomy with side-to-end ileoproctostomy. The food stimulation test was repeated at approximately weekly intervals for eight weeks after colectomy. Basal plasma CCK levels of 139 ± 21 pg/ml before colectomy did not change after colectomy. Total amount of CCK released after food was increased significantly at both four (5.94 ± 0.78 ng min/ml) and eight (13.00 ± 2.72 ng min/ml) weeks after colectomy in comparison with that observed prior to colectomy (2.94 ± 0.54 ng min/ml). Basal serum gastrin levels of 28 ± 9 pg/ml did not change significantly after colectomy. Total amount of gastrin released after food was increased significantly at both two (8651 ± 2294 pg min/ml) and three (6940 ± 1426 pg min/ml) weeks after operation, but at none of the later weeks. The precolectomy output, used for comparison, was 5608 ± 1346 pg min/ml. It was concluded that resection of the colon leads to an increase in release of CCK and gastrin after food stimulation. This finding provides further evidence that the colon contains a factor that inhibits the release of CCK and gastrin, and that the colon functions as an endocrine organ.

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THE COLON contains an abundance of endocrine cells.[1-3] The physiologic role of the colon as an endocrine organ[4,5] is not clear. In 1930, Kosaka and Lim[6] reported that extracts from colonic and ileal mucosa of dogs, "enterogastrone," contained a potent inhibitor of gastric acid secretion.[7] Harper and colleagues demonstrated that extracts from colonic and ileal mucosa of cats and pigs, which they called "pancreotone," greatly inhibited both pancreatic protein secretion and gallbladder contraction.[8-10] Perfusion of the colon with oleic acid inhibited pancreatic secretion of protein in dogs[11] and cats,[8,9,12] as well as biliary secretion in man.[13] Oleic acid perfusion of the colon also potently inhibited gastric acid secretion in man[14] and dogs.[15] The mechanism by which the colon inhibits pancreatic and gastric secretion and gallbladder contraction is not yet understood.

This study investigates the effect of removal of the colon along with its putative inhibitory factors, on the release of the gastrointestinal hormone chiefly responsible for pancreatic protein secretion and gallbladder contraction (CCK), and for stimulation of gastric acid (gastrin).

Materials and Methods

Five mongrel dogs, weighing from 22 to 35 kg, were used in this study. Food, but not water, was withheld, for 18 hours before each experiment. Blood samples were drawn before a 400-g meat meal, and at 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 140, 160, and 180 minutes afterwards. Plasma was obtained in tubes containing 100 U of Trasylol and 10 U of heparin per ml of blood. The samples were centrifuged immediately at 4 C. Plasma samples and serum samples were stored at −20 C for future measurement of CCK and gastrin, respectively. The next day, near total colectomy with side-to-end ileoproctostomy was performed. The food-stimulation test was repeated at approximately one-week intervals for eight weeks after colectomy.

CCK concentrations in plasma were measured by a specific radioimmunoassay, which was developed in this laboratory.[16] Briefly, it employs CCK antibody UT 132, directed against most of the N-terminal portion of the CCK molecule, and, therefore, it has little or no affinity for gastrin or for the C-terminal octapeptide of CCK. Validation of the CCK radioimmunoassay has been reported previously.[16,17] Serum gastrin concentrations

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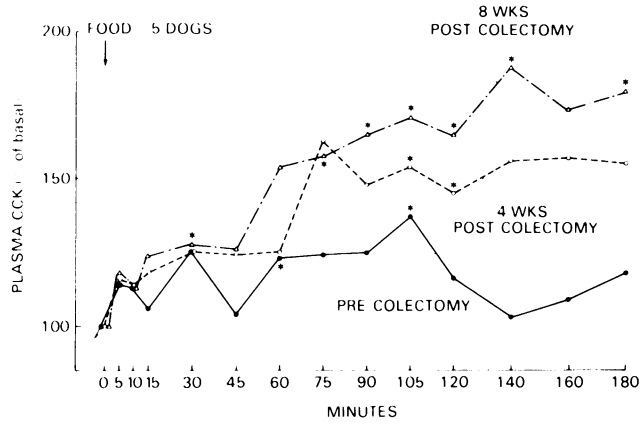

FIG. 1. Comparative CCK responses to food before colectomy and at four and eight weeks afterwards.

were measured by double-antibody radioimmunoassay also developed in this laboratory.[18]

Results are expressed as the mean ± one standard error of the mean. Integrated values for CCK and gastrin were calculated as described previously.[19] The Student's paired t test was used to analyze the data for statistical differences. Differences with a p value of less than 0.05 were considered to be significant.

Results

Basal plasma CCK concentrations of 139 ± 21 pg/ml before colectomy did not change significantly at two, three, four, six, or eight weeks after colectomy (Fig. 1). The postprandial CCK response before colectomy, and at four and eight weeks afterwards, are shown in Figure 1. The peak postprandial concentrations of CCK before colectomy were 137 ± 10% of basal (at 105 minutes); four weeks after colectomy were 163 ± 27% of basal (at 75 minutes); and eight weeks after were 188 ± 15% of basal (at 140 minutes). The total amount of CCK released after food stimulation (integrated CCK response) before colectomy, 2.94 ± 0.54 ng min/ml, was increased significantly at four weeks (5.94 ± 0.78 ng min/ml), at six weeks (11.13 ± 1.63 ng min/ml) and at eight weeks (13.00 ± 2.72 ng min/ml) after colectomy (Fig. 2).

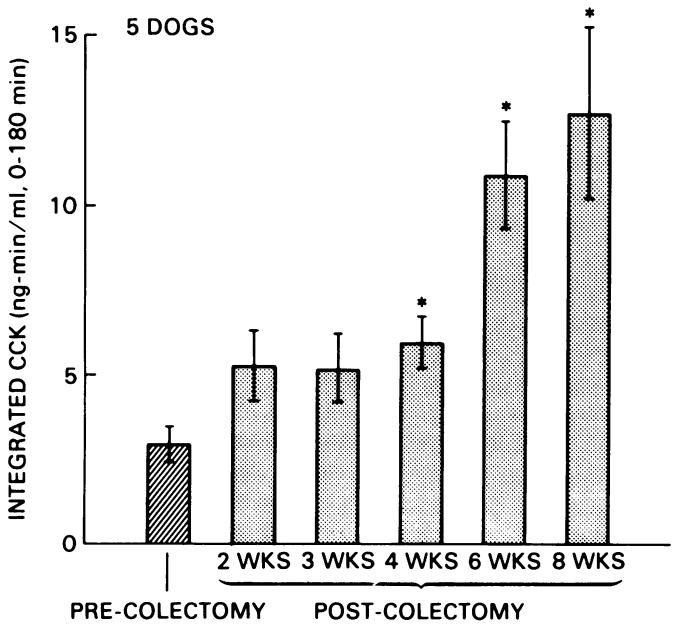

FIG. 2. Integrated CCK response to food before and after colectomy. * = significant difference between before and after colectomy.

The basal serum gastrin concentrations of 28 ± 9 pg/ml after colectomy were the same as before colectomy. The comparative responses of gastrin to food before colectomy, and at three and six weeks afterwards are shown in Figure 3. The peak postprandial concentrations of gastrin before colectomy were 321 ± 57% of basal (at 160 minutes); three weeks after colectomy were 387 ± 130% of basal (at 180 minutes); and six weeks after were 207 ± 19% of basal (at 90 minutes). The total amount of gastrin released after food stimulation (integrated gastrin response) was 5.61 ± 1.35 ng min/ml before colectomy, and it was significantly increased to 8.66 ± 2.29 ng min/ml at two weeks and to 6.94 ± 1.43 ng min/ml at three weeks after colectomy (Fig. 4). This increase was transient, however, and by four weeks after colectomy, the integrated response to food was unchanged from that seen before colectomy.

By one week after colectomy, all of the dogs had developed severe diarrhea as a reaction to food stimulation, and it persisted the entire eight weeks. The mean body weight before operation (26.5 ± 2.2 kg) had not changed significantly at four weeks (24.8 ± 2.5 kg), at six weeks (25.0 ± 2.3 kg), or at eight weeks (25.9 ± 2.2 kg) after colectomy.

Discussion

In conscious dogs, perfusion of the colon, but not of the ileum, with oleic acid caused inhibition of all measurements of stimulated pancreatic secretion, especially protein output (56% inhibition).[11] Harper and colleagues[8,9,12] confirmed the inhibitory effect on pancreatic secretion of infusion of oleic acid into the colon and ileum of the cat. Section of the vagal and splanchnic nerves did not alter the inhibitory effect, which suggested that the inhibition was mediated humorally.

The occurrence of a delayed inhibition of pancreatic protein secretion in conscious rats after intraduodenal injection of oleic acid has been confirmed.[20-22] This delayed inhibition was suggested to be a consequence of oleic acid-stimulated release of a hormonal factor ("anticholecystokinin factor") from the distal small bowel which inhibited pancreatic secretion.[23] The instillation

of oleic acid into either the colon[13] or ileum[24] in man has been reported to exert an inhibitory effect on pancreatic exocrine secretion. Voirol and colleagues[24] speculated that the agent was a hormone that inhibits release of CCK. Previous studies have shown similar colonic inhibitory effects on gallbladder contraction in man[23,25] and dogs.[23] Intracolonic instillations of oleic acid and other materials caused a pronounced inhibition of bilirubin output in man.[13]

Harper and colleagues[8-10] demonstrated that "pancreotone," a polypeptide material extracted from the colonic and ileal mucosa of cats and pigs, caused a pronounced inhibition of both pancreatic enzyme secretion and gallbladder contraction in cats. They observed that the actions of pancreotone resemble the inhibitory effects of intracolonic and intraileal infusions of oleic acid (and other substances) in cats, and they speculated that pancreotone may be the humoral mediator of these inhibitory effects.[12]

The mechanism by which the colon causes inhibition of both pancreatic protein secretion and gallbladder contraction is not known. In addition to affecting the release of gastrointestinal hormones, and the colonic inhibitory factor may alter the responsiveness of the target organ to CCK. Harper and colleagues[8-10] demonstrated inhibition of the usual response of the target organ (gallbladder and pancreas) to exogenous CCK or caerulein when pancreotone was infused intravenously.

These results demonstrate that colectomy augments CCK release in response to food, possibly by removing a humoral inhibitory agent. Colonic inhibition of pancreatic and cholecystic function may occur through inhibition of CCK release by a colonic hormone.

The severe diarrhea in response to food stimulation after colectomy may be a consequence partially of the stimulatory effect of CCK on the motor activity of the small bowel,[26,27] and thus may be caused by the increased release of CCK.

A similar inhibitory influence of the colon on gastric acid secretion has been demonstrated by Seal and Debas in the dog[15] and by Soon and colleagues in man.[14] The mechanism of this inhibition may be mediated through inhibition of gastrin release or through alteration of the sensitivity of the parietal cell to stimulants.

Massive small-bowel resection is followed by gastric acid hypersecretion[28] and hypergastrinemia in man,[29] dogs,[30] and rats.[31,32] These data show that colectomy results in a significant but transient increase in output of gastrin after a meal. By four weeks after colectomy, gastrin release in response to food is unchanged from that seen before colectomy. Perfusion studies[14,15] and pancreotone infusion studies[10] demonstrate that the colonic inhibitory factor inhibits the sensitivity of the parietal cell to pentagastrin. Landor and colleagues[33] observed that even two months after colectomy, dogs exhibited gastric hypersecretion. This may be related to the altered responsiveness of the parietal cell rather than to increased release of gastrin. Kitagawa and colleagues[34] reported that both basal gastrin concentrations and gastrin responses to intravenous L-arginine infusion under pentobarbital anesthesia were increased one month after colectomy, but the duration of the phenomenon was not reported. The concentration of gastrin, which is elevated initially after colectomy, may be partially responsible.

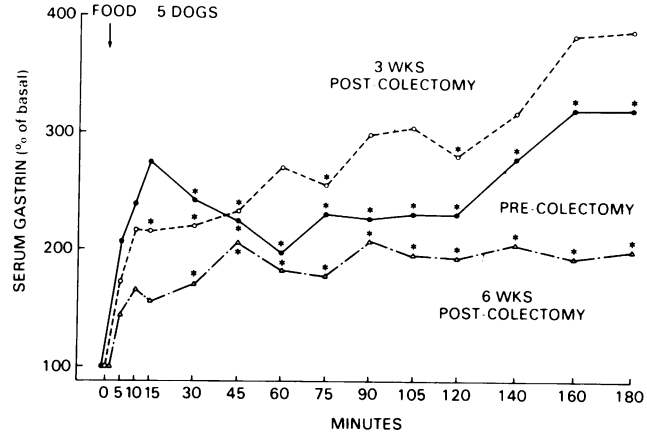

FIG. 3. Comparative gastrin response to food before colectomy and at three and six weeks afterwards.

The mechanism by which the colon inhibits gastric secretion is not clear. Since division of the vagal and splanchnic nerves did not affect colonic inhibition of pancreatic secretion,[12] a humoral agent appears likely. The colonic inhibition of gastric acid secretion[15] may be mediated in part by humoral inhibition of gastrin release.

In summary, this study demonstrates that resection

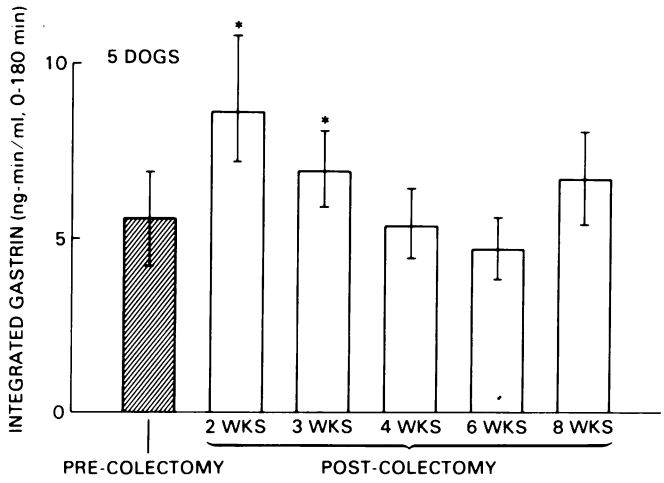

FIG. 4. Integrated gastrin response to food before and after colectomy. * = significant difference between before and after colectomy.

of the colon leads to an increase in the response of CCK and gastrin after food stimulation, which provides further evidence that the colon contains a factor that inhibits release of CCK and gastrin.

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