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The Inhibition of Gastric Acid Secretion by Caerulein (41348)

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Abstract. In conscious beagle dogs, with gastric fistulae and Thomas pancreatic fistulae, gastrin-stimulated acid secretion from the gastric fistula declined significantly in the course of an hour with the Thomas fistula closed, but did not when pancreatic juice was diverted to the exterior. In the latter case added caerulein produced a significant decrease in acid secretion, but not in the former with the pancreatic fistula closed. The conclusion is that the presence of pancreatic juice modifies both the acid response to gastrin and the competitive action of caerulein.

Recently doubt has been cast on the view that pure CCK is a physiological antagonist of gastrin-stimulated gastric secretion (1). Magee and Dutt (2) found that pure CCK in doses of 0.5, 1, and 1.5 units/min significantly inhibited gastrin-stimulated fistula acid and Heidenhain pouch acid and pepsin, but augmented methacholine-stimulated secretion. The major difference between the two sets of experiments is that in those of Magee and Dutt (2) there was no exteriorly draining pancreatic fistula while in those of Corazziari *et al.* (1) pancreatic juice was diverted in the human and most of the dog experiments. Only in the six dogs without pancreatic fistulae did CCK produce a decline in acid secretion. Since Abita *et al.* (3) have noted that the enzymatically inactive peptide which results from the activation of trypsinogen inhibits gastrin-stimulated gastric acid secretion it is possible that the extent of inhibition is proportional to the amount of trypsinogen entering the duodenum. In some of the experiments of Corazziari *et al.* (1) this was zero. We have investigated this possibility using caerulein which acts precisely like CCK.

Materials and Methods. Six beagle dogs were used. Each had a large, 2-cm-diameter gastric fistula and a Thomas pancreatic fistula. The dogs were fasted overnight before experiments. Synthetic human gastrin[4] was started by intravenous infusion (3 μg/kg/hr) after three basal collection periods. After a further hour caerulein[5] (25 ng/kg/hr) was added to the infusion for a further six collection periods and its effects on gastric acid secretion compared with the Thomas pancreatic fistula closed (juice entering the duodenum) and open (juice diverted to the exterior). These doses in these animals were approximately half-maximal stimulants for gastric acid and pancreatic protein secretion, respectively. Additional saline was given intravenously throughout to match the total volume of fluid secreted. Gastric juice and pancreatic juice, where relevant, were collected by simple drainage and tubes changed at 10-min intervals. Acid was titrated to pH 7 with N/20 NaOH. The protein in pancreatic juice was determined by absorption at 280 mμ in a Gilson spectrophotometer.

For statistical comparison the differences between the means of the last two samples before caerulein (samples 5 and 6) were compared with the last two with added caerulein or controls without (samples 11 and 12, Figs. 2 and 3). The individual means of samples 5 and 6 and 11 and 12 were compared with and without caerulein and with open and closed fistulae for each experi-

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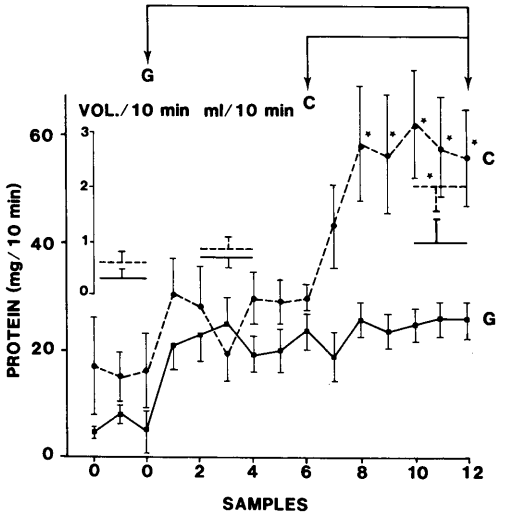

FIG. 1. The effect (mean effect ± SE) of gastrin (G) (●), 3 μg/kg/hr, and gastrin + caerulein (C) (■), 25 ng/kg/hr, on the protein content and volume of pancreatic juice. n = six dogs. ★Point significantly different from gastrin-only control, $P < 0.05$. Samples here, and subsequently, are at 10-min intervals.

ment (Fig. 4). Thus change with time (control) was always pair compared with change following experimental procedure, i.e., paired difference between paired differences were analyzed. Paired t was used in each comparison.

Results. Gastrin produced a significant increase in pancreatic protein and gastric acid secretion but not in the volume of pancreatic juice. Caerulein produced a further increase in pancreatic juice protein secretion (Fig. 1) and now also in volume, from 0.8 ± 0.2 to 2.1 ± 0.4 ml/10 min in the animals with open Thomas fistulae. In the course of an hour in control experiments gastric acid secretion declined significantly when the pancreatic fistula was closed (Figs. 2 and 3). This decline was significantly greater than with the Thomas fistula open (Fig. 4). Addition of caerulein produced a decline in gastric acid which was significant only when pancreatic juice was drained to the exterior (Figs. 2–4). This decline was significantly greater than with the fistula closed (Fig. 4).

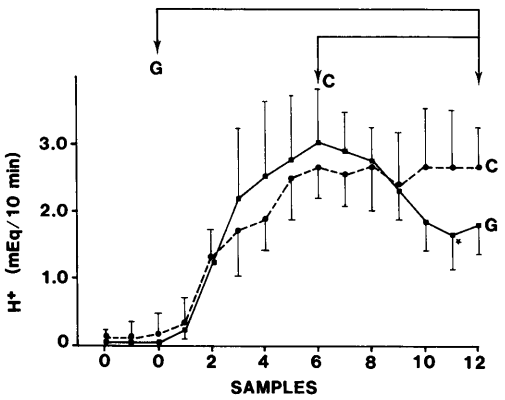

FIG. 2. The effect (mean effect ± SE) of gastrin (G), 3 μg/kg/hr, and gastrin + caerulein (C), 25 ng/kg/hr, on gastric fistula acid secretion when pancreatic secretion was entering the duodenum. n = six dogs. ★Significantly different from corresponding control (G), $P < 0.05$.

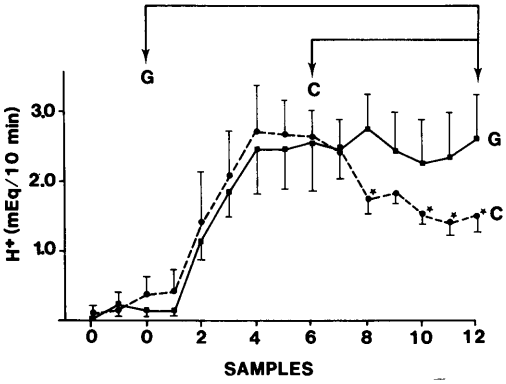

FIG. 3. The effect (mean effect ± SE) of gastrin (G), 3 μg/kg/hr, and of gastrin + caerulein (C), 25 ng/kg/hr, on gastric fistula acid secretion when pancreatic juice is diverted exteriorly. n = six dogs. ★Significantly different from corresponding control (G). $P < 0.05$.

Discussion. The results show that caerulein depressed gastric secretion when the Thomas fistula was open and pancreatic juice diverted to the exterior but, on the other hand, increased gastric secretion when the Thomas fistula was closed. Thus unless caerulein and CCK act differently from each other on the parietal cells, for which there is no evidence, our explanation for the failure of Corazziari *et al.* (1) to see CCK antagonism of gastrin-stimulated acid secretion is incorrect. In fact in contrast to their study with CCK, we realized good inhibition of gastric secretion with caerulein when the duodenal fistula was open. This inhibition, therefore, could not depend on the activation peptide of trypsin (3).

Our results are complicated by the time-

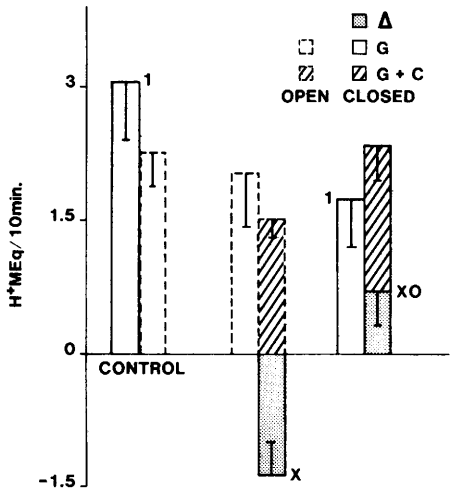

FIG. 4. Comparison of the effect of time and intravenous caerulein on gastrin-stimulated acid secretion from a simple gastric fistula when a Thomas pancreatic fistula is open or closed. Control: Mean secretion of two collections immediately before caerulein or its saline control, i.e., 50- and 60-min collection. Other bars represent means of acid secretion with gastrin or gastrin plus caerulein after a further 50 and 60 min again with the Thomas fistula open or closed. Δ, Difference between gastrin and gastrin plus caerulein; X, difference from corresponding gastrin; O, difference between Δ's; difference between 1 and 1, i.e., between 50- and 60-min control and 110- and 120-min control ($P < 0.05$, paired t test).

dependent decrease in gastric secretion which unexpectedly was significantly greater with the fistula closed than when open (-1.089 ± 0.280 and -0.384 ± 0.170 meq H^+/10 min, respectively) and was itself indeed significant only with the fistula closed.

This may be a manifestation of "fade" or gastrin tachyphylaxis (6). Inspection of the data of Stening *et al.* (7) seems, although unclaimed, to indicate absence of tachyphylaxis in dogs with draining Thomas duodenal fistulae. If this is the case then perhaps the explanation for the reversal of the caerulein effect when the Thomas fistula is opened is that caerulein no longer acts its usual part as a gastrin antagonist, but as an agonist when gastrin tachyphylaxis supervenes, i.e., when the Thomas fistula is closed. Caerulein is well known to be capable of both actions (4, 5). The trypsin activation peptide of Abita *et al.* (3) could explain the onset of gastrin tachyphylaxis when the Thomas pancreatic fistula is closed since addition of it to the duodenum has been shown to depress gastrin-stimulated acid secretion, but cannot explain the action of caerulein under these same circumstances.

We do not believe acid leakage from stomach to duodenum and the absence of neutralization when pancreatic juice is exteriorized to be a factor since an acid reaction in the duodenal effluent, though methodically tested for with pH indicator paper, was never observed and the volume of pancreatic juice secreted in response to gastrin was not different from basal. The significant increase in pancreatic juice volume produced by added caerulein is itself of interest, but that this should have occurred while gastric acid was falling and also that the marked decline in gastrin-stimulated acid secretion was seen when the Thomas fistula was closed and not when the neutralizing bicarbonate of pancreatic juice was diverted are against the acid leakage idea.

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