

## Acid inhibition by intestinal nutrients mediated by CCK-A receptors but not plasma CCK

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**Lloyd, K. C. Kent, Jiafang Wang, and Travis E. Solomon.** Acid inhibition by intestinal nutrients mediated by CCK-A receptors but not plasma CCK. *Am J Physiol Gastrointest Liver Physiol* 281: G924–G930, 2001.—We examined the role of CCK-A receptors in acid inhibition by intestinal nutrients. Gastric acid and plasma CCK and gastrin levels were measured in rats with gastric and duodenal fistulas during intragastric 8% peptone and duodenal perfusion with saline, complete liquid diet (CLD; 20% carbohydrate, 6% fat, and 5% protein), and the individual components of CLD. Acid output was significantly inhibited (50–60%) by CLD, lipid, and dextrose. Plasma CCK was significantly increased by CLD (from  $2.6 \pm 0.3$  to  $4.8 \pm 0.5$  pM) and lipid ( $4.6 \pm 0.5$  pM). CCK levels 50-fold higher ( $218 \pm 33$  pM) were required to achieve similar acid inhibition by exogenous CCK-8 ( $10 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  iv). Intestinal soybean trypsin inhibitor elevated CCK ( $10.9 \pm 2.5$  pM) without inhibiting acid secretion. The CCK-A antagonist MK-329 (1 mg/kg iv) reversed acid inhibition caused by CLD, lipid, and dextrose. Peptone-stimulated gastrin ( $21.7 \pm 1.9$  pM) was significantly inhibited by CLD ( $14.5 \pm 3.6$  pM), lipid ( $12.3 \pm 2.2$  pM), and dextrose ( $11.9 \pm 1.5$  pM). Lipid and carbohydrate inhibit acid secretion by activating CCK-A receptors but not by altering plasma CCK concentrations.

gastric acid secretion; enterogastrone; intestinal phase; cholecystokinin; peptone meal

GASTRIC ACID SECRETION IS regulated by both stimulatory and inhibitory mechanisms that are initiated by the ingestion of food and the presence of nutrients and digestive secretions in the gut lumen. Strong inhibition of acid secretion occurs when certain nutrients enter the small intestine during gastric emptying of a meal. Of the macronutrients comprising a normal mixed meal, carbohydrates (12) and lipids (15) inhibit acid secretion, whereas protein (10, 13) stimulates acid output. Hormonal, paracrine, and neural inhibitory pathways are involved in acid inhibition by luminal nutrients. However, no single regulatory factor (hormone, paracrine agent, or neurotransmitter) has been shown to play a physiological role in inhibition of gastric acid secretion in response to all dietary nutrients.

Dietary lipid has been a carefully defined luminal inhibitor of gastric acid secretion. We have shown that fat in the intestinal lumen of rats causes inhibition of meal-stimulated gastric acid secretion (15). The mechanism of fat-induced inhibition involves a combination of hormonal, paracrine, and neural pathways, including circulating somatostatin (20, 23), somatostatin released from gastric D cells (16, 18), and activation of capsaicin-sensitive vagal afferent nerves (15). The mechanism also appears to depend on CCK, because a CCK-A receptor antagonist blocks inhibition caused by intestinal fat (17). However, whether CCK acts as a hormone, paracrine agent, or neurotransmitter in this mechanism is not clear. Even less is known about the role of CCK in acid inhibition caused by other nutrients.

This study was designed to define the role of CCK-A receptors in mediating inhibition of gastric acid secretion by intestinal nutrients. The contribution and mechanism of CCK-A receptor-mediated inhibition were examined by correlating plasma CCK and gastrin levels and inhibition of acid secretion in response to intestinal nutrients and by quantitating the effect of a specific CCK-A receptor antagonist.

### METHODS

*Gastric and duodenal cannulation and intravenous catheterization in rats.* Gastric and duodenal cannulas were implanted into adult (180–220 g) male Sprague-Dawley rats by modification of a previously described procedure (15). Rats were fasted (except for water) for 18 h before anesthesia was induced with pentobarbital sodium (50 mg/kg ip). The abdomen was opened, and an incision was made in the nonglandular portion of the stomach. A modified two-part Thomas cannula, assembled from an outer stainless steel sleeve and a lightweight delring insert, was inserted into the gastric corpus and sutured in place. The cannula was exteriorized through a stab incision in the ventrolateral aspect of the body wall left of midline and capped. The duodenal cannula was fashioned from a length of polyethylene (PE)-50 tubing. One end of the tubing was flared by gentle heating with a flame and inserted into the duodenum through an enterotomy

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incision 2 cm distal to the pylorus. The end of the tubing was tunneled subcutaneously to exit between the shoulder blades, where a few centimeters of tubing were exteriorized and secured in place with sutures. The abdomen was sutured closed. The duodenal cannula was flushed daily with saline and plugged with a small amount of petroleum jelly. An intravenous catheter fashioned from PE-50 tubing was secured in a jugular vein through a cervical incision and exited the skin adjacent to the duodenal catheter between the shoulder blades. The catheter was flushed daily with 2 ml saline and plugged with a stainless steel pin.

Rats were returned to their home cages after they had recovered from anesthesia. While recuperating, rats were accustomed to several hours of light restraint in Bollman cages. Rats were used in secretory experiments from 2 to 12 wk after surgery.

**Experimental protocol.** Rats were fasted for 12–18 h from food but not water and then placed in Bollman cages. The stomach was rinsed until clean with 0.15 M saline through the opened cannula. The outer tube of a double-lumen plastic catheter was attached to the external portion of the gastric cannula, and the inner tube was advanced into the stomach. During the basal period, the stomach was rinsed with 10 ml of warm (37°C) saline every 10 min. Acid output ( $\mu\text{mol}/10$  min) was measured in each basal sample by back titration with 0.05 M NaOH (Radiometer, Cincinnati, OH). After 30 min, during which basal acid output stabilized, rats were administered either MK-329 (1 mg/kg iv in 0.5 ml vehicle) or vehicle (25  $\mu\text{l}$  DMSO, 10  $\mu\text{l}$  Tween 80, and 465  $\mu\text{l}$  of 0.15 M saline). After another 30-min period, 5 ml of an 8% solution of peptone (Bacto Peptone, Difco, Detroit, MI) adjusted to pH 5.5 was infused into the stomach and gently mixed by an oscillating pump ( $\sim 20$  rpm). After 10 min, the pump was stopped, and the peptone was allowed to drain through the gastric cannula into a reservoir. The stomach lumen was then gently flushed with 10 ml saline and 5 ml air, and the contents were added to the reservoir containing the peptone. The contents of the reservoir (gastric secretions, 5 ml peptone, and 10 ml saline) were back titrated to pH 5.5 as described above and adjusted each time against a control sample containing 5 ml peptone plus 10 ml saline. From this measurement, acid output was recorded as micromoles per 10 min. This procedure was repeated for the next 2 h. On separate days during the second hour of intragastric peptone perfusion, the following substances were infused into the duodenum (0.05 ml/min): saline as control; complete liquid diet (CLD) (20% dextrose, 5% casein, and 6% lipid; liquid rat diet AIN-76 control, Bio-Serv, Frenchtown, NJ); 20% dextrose (dextrose anhydrous granular powder, Fisher Scientific, Pittsburgh, PA); 5% casein (Sigma Chemical, St. Louis, MO); 6% lipid emulsion (Intralipid, KabiVitrum, Alameda, CA); or 2% soybean trypsin inhibitor (STI; Sigma Chemical). At the end of the hour of duodenal perfusion, blood was drawn from the venous catheter for measurement of CCK and gastrin. To maintain hydration, rats were given a continuous intravenous infusion of saline (0.05 ml/min) throughout the experiment. In a separate experiment, rats received CCK-8 (10 nmol $\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  iv) during the second hour of intragastric peptone. This dose was determined in preliminary studies to produce a similar degree of inhibition of acid secretion as seen with intestinal nutrients (dose response curve not shown). In these rats, blood was drawn from a catheter placed in the aorta to avoid contamination by the exogenously infused CCK-8.

**CCK and gastrin RIA.** Blood samples were placed into tubes containing 100 IU heparin. Plasma was separated by centrifugation and stored at  $-70^\circ\text{C}$ . Extractions and assays

of plasma CCK (3, 27) and gastrin (5, 19) were performed as described previously.

**Chemicals.** Peptone was prepared as an 8% (isotonic, 295 mosM) solution in water, adjusted to pH 5.5 with 6 M HCl, and warmed to 37°C before intragastric instillation. CLD was made by blending 1,029 g of the powdered diet in 3,360 ml of cold ( $<10^\circ\text{C}$ ) water for 20–30 s at low speed. A 20% solution of dextrose was made by dissolving 20 g dextrose in 100 ml saline. A 5% solution of casein was made by dissolving 5 g casein in 100 ml of 0.15 M saline. Lipid emulsion was diluted from 20% to 6% with saline to maintain an isotonic solution and pH between 6 and 7. MK-329 (a gift from R. Freidinger, Merck Sharp and Dohme Research Laboratories, West Point, PA) was dissolved in 25  $\mu\text{l}$  DMSO, sonicated briefly after the addition of 10  $\mu\text{l}$  Tween 80, and brought to a total volume of 500  $\mu\text{l}$  with saline before slow intravenous injection.

**Data analysis.** Acid secretion data is presented as acid output vs. time (in  $\mu\text{mol}/10$  min). For statistical analyses,  $n$  was the number of rats in each treatment group (if more than 1 identical experiment was performed with an animal, data were averaged). The average percent inhibition of peptone-stimulated acid output was calculated by dividing stable acid output values during intragastric peptone plus intestinal nutrient perfusion (the last 30 min of *hour 2*) by stable acid output values during intragastric peptone alone (the last 30 min of *hour 1*), subtracting the quotient from 1, and multiplying the difference by 100. Plasma gastrin and CCK concentrations are presented as picomoles vs. treatment. The significance of treatment effects ( $P < 0.05$ ) was assessed by Student's *t*-test or ANOVA; nonparametric methods were used if preliminary testing for normality of the data failed. Appropriate corrections were made for multiple comparisons.

## RESULTS

**Peptone-stimulated acid output.** In vehicle-treated rats (Fig. 1B), intragastric peptone markedly increased acid output to a stable plateau about fourfold higher than basal values. Acid output during the 30- to 60-min period of intragastric peptone ( $83 \pm 8 \mu\text{mol}/10$  min,  $n = 12$ ) was similar to that in response to a maximal intravenous dose (20  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) of pentagastrin ( $87 \pm 6 \mu\text{mol}/10$  min,  $n = 5$ ; Fig. 1A). Acid output fell slightly ( $8 \pm 8\%$ ) and insignificantly to  $73 \pm 7 \mu\text{mol}/10$  min during the 90- to 120-min period of intragastric peptone. Figure 1B also shows that administration of MK-329 significantly increased the acid response to intragastric peptone by 17% ( $P < 0.05$ ). The volumes of meal recovered from the stomach before and after MK-329 treatment did not differ significantly (Table 1). Basal acid output in 63 rats was  $21 \pm 1 \mu\text{mol}/10$  min and was not affected by administration of the vehicle used for MK-329 ( $20 \pm 1 \mu\text{mol}/10$  min). In a separate group of 39 rats analyzed for any effects of MK-329 on basal acid output, 1 mg/kg iv MK-329 also had no statistically significant effect on unstimulated acid output ( $21 \pm 2$  vs.  $23 \pm 2 \mu\text{mol}/10$  min).

**Effect of dietary nutrients alone or with MK-329 on peptone-stimulated acid output.** Intraduodenal administration of saline (3 ml/h) had no significant effect on peptone-stimulated acid secretion when values were compared before and during saline (Fig. 1B) or in separate groups of rats without saline perfusion (data not shown). In contrast, intraduodenal administration

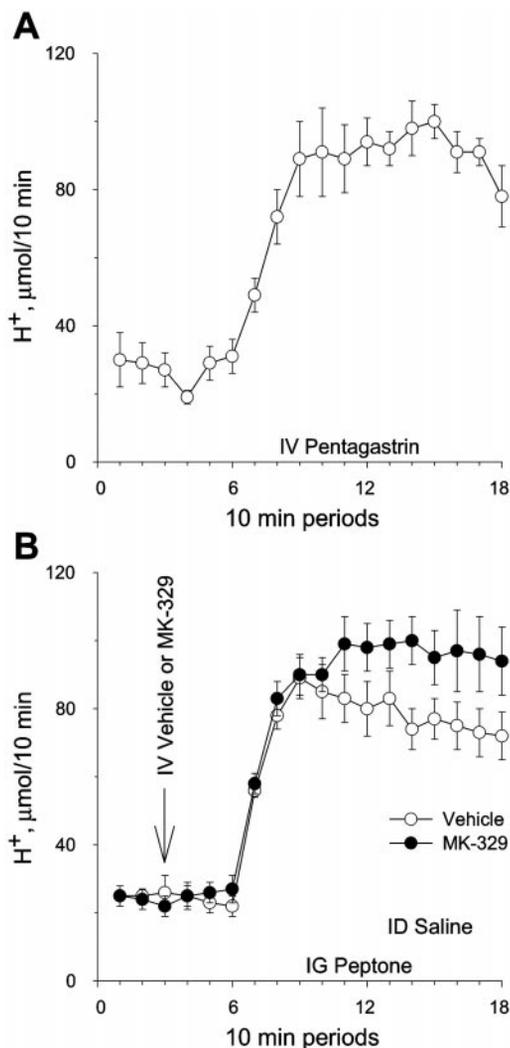


Fig. 1. Time course of gastric acid secretion (means  $\pm$  SE,  $\mu\text{mol}/10$  min) during a 60-min basal period followed by 120 min of intravenous (IV) pentagastrin ( $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) in 1 group of rats (A) or intragastric (IG) peptone (8%, wt/vol) in 2 groups of rats given either the vehicle for IV administration of MK-329 ( $n = 12$ ) or 1 mg/kg MK-329 ( $n = 12$ ) (B). As shown, neither IV agent changed basal acid secretion, but MK-329 significantly (17%,  $P < 0.05$ ) increased the acid response to peptone. Addition of intraduodenal (ID) perfusion with saline at 3 ml/h did not alter peptone-stimulated acid output in either group of animals.

of CLD resulted in a marked decrease in peptone-induced acid output (Fig. 2), with acid secretion declining  $60 \pm 7\%$  from the initial plateau. This effect was completely reversed by prior treatment with the CCK-A receptor antagonist MK-329 (Fig. 2). The effects of the individual nutrient components of CLD on acid secretion are shown in Fig. 3. Intestinal perfusion with 6% Intralipid and 20% dextrose elicited acid inhibition similar to that caused by CLD (Fig. 3); MK-329 also completely reversed the inhibitory effects of both nutrients. However, intraduodenal administration of 5% casein did not affect peptone-induced acid output, either alone or with prior MK-329 (Fig. 3). A summary and statistical analysis of these data are shown in Fig. 4. Intestinal perfusion with CLD or its lipid or carbo-

Table 1. Residual volume of 8% peptone meal recovered from stomach before and after dietary nutrient infusion and treatment with MK-329

Treatment	Residual Volume
Before dietary nutrient infusion	$5 \pm 0.2$
MK-329	$5.1 \pm 0.1$
Saline	$4.9 \pm 0.3$
CLD	$5.2 \pm 0.1$
Dextrose	$5.1 \pm 0.1$
Lipid	$5.1 \pm 0.1$
Casein	$5.1 \pm 0.2$

Values are means  $\pm$  SE (in  $\text{ml}\cdot 10 \text{ min}^{-1}\cdot 60 \text{ min}^{-1}$ ). Residual volume of the 5 ml of 8% peptone meal recovered from the stomach 10 min after intragastric administration before intraduodenal (ID) dietary nutrient infusion and after intraperitoneal treatment with MK-329 (1 mg/kg) and ID infusion of 0.9% saline, complete liquid diet (CLD), 20% dextrose, 6% lipid, or 5% casein.

hydrate components strongly (50–60%) and significantly ( $P < 0.05$  and 0.01) reduced acid secretion stimulated by intragastric peptone.

**Effects of dietary nutrients on plasma CCK and gastrin levels.** Intragastric peptone did not alter plasma CCK concentrations compared with values in fasting rats ( $2.6 \pm 0.3$  vs.  $2.8 \pm 0.2$  pM,  $n = 12$ ). Significant ( $P < 0.05$ ) increases in CCK occurred during intestinal perfusion with CLD ( $4.8 \pm 0.9$  pM,  $n = 9$ ) and lipid ( $4.6 \pm 1.0$  pM,  $n = 7$ ) but not with casein ( $4.2 \pm 1.0$  pM,  $n = 7$ ) or dextrose ( $2.2 \pm 0.6$  pM,  $n = 7$ ). Intragastric peptone significantly ( $P < 0.05$ ) increased circulating levels of gastrin ( $21.7 \pm 1.9$  pM,  $n = 12$ ) compared with values in fasting rats ( $4.1 \pm 2.1$  pM,  $n = 12$ ). Gastrin levels were significantly lower during intestinal perfusion with CLD ( $14.5 \pm 3.6$  pM,  $n = 9$ ), lipid ( $12.3 \pm 2.2$  pM,  $n = 7$ ), and dextrose ( $11.9 \pm 1.5$  pM,  $n = 7$ ).

**Effects of CCK-8 and intestinal perfusion with STI.** Two other conditions were examined to further define

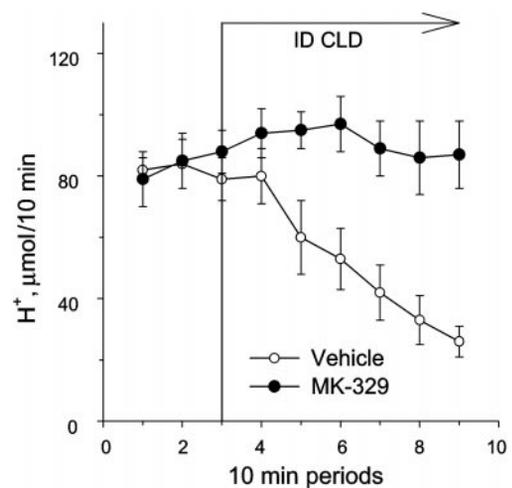


Fig. 2. Effects of intestinal perfusion with mixed nutrient complete liquid diet (CLD) on peptone-stimulated gastric acid secretion in rats treated IV with vehicle ( $n = 9$ ) or 1 mg/kg MK-329 ( $n = 8$ ). The design of this experiment was identical to that in Fig. 1 except that CLD was substituted for saline as the intestinal perfusate. Acid secretory values (means  $\pm$  SE) are shown for the 40- to 120-min period of intragastric peptone.

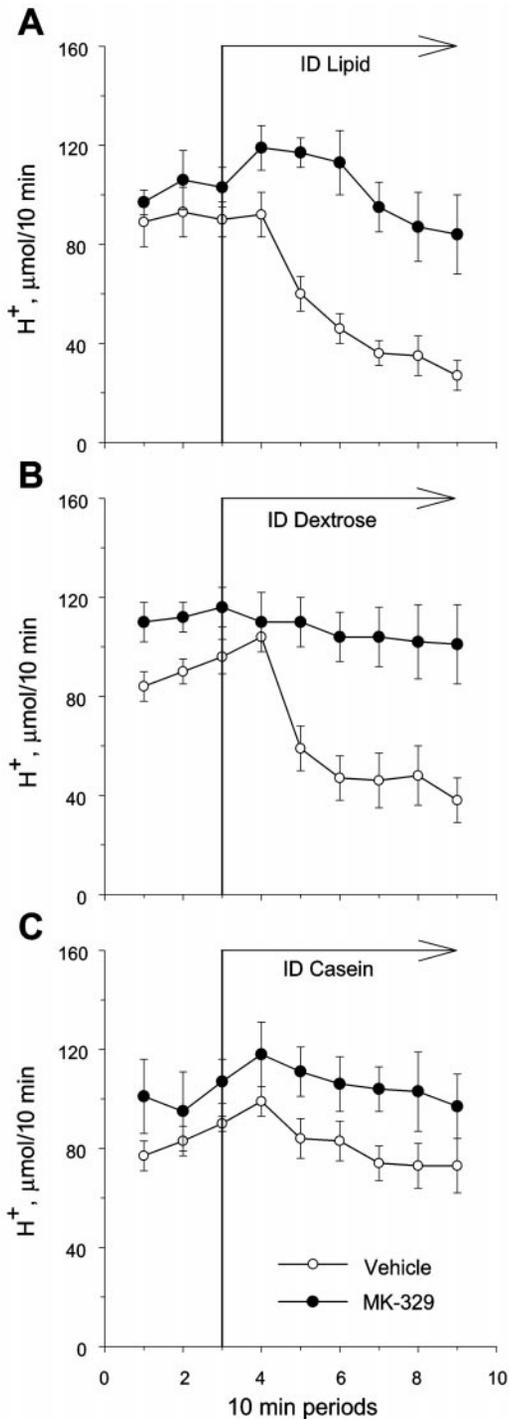


Fig. 3. Effects of intestinal perfusion with individual nutrient components of CLD on peptone-stimulated gastric acid secretion in rats treated IV with vehicle (6% Intralipid,  $n = 10$ ; 20% dextrose,  $n = 11$ ; and 5% casein,  $n = 9$ ) or 1 mg/kg MK-329 ( $n = 7, 6,$  and 4 for Intralipid, dextrose, and casein, respectively). Experimental design and presentation are the same as in Fig. 2.

the relationship between circulating CCK levels and inhibition of peptone-induced acid secretion. Intravenous administration of CCK-8 at  $10 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  inhibited peptone-induced acid secretion to a similar degree as CLD, lipid, and dextrose (Fig. 5). Prior treatment with MK-329 reversed this effect (Fig. 5). CCK-8

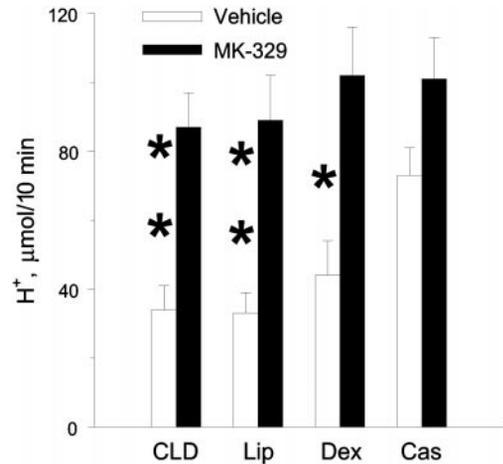


Fig. 4. Summary of data from Figs. 2 and 3. Average acid output (means  $\pm$  SE, in  $\mu\text{mol}/10 \text{ min}$ ) is given for the last 30 min of intragastric peptone + intestinal CLD or individual nutrient components. In the groups treated with IV vehicle, there was marked inhibition of acid secretion by CLD, Intralipid (Lip), and dextrose (Dex); treatment with MK-329 prevented inhibition of acid secretion. Cas, casein. \* $P < 0.05$ ; \*\* $P < 0.01$ .

at  $10 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  increased plasma CCK to  $218 \pm 33 \text{ pM}$  ( $n = 5$ ). Intestinal perfusion with STI markedly increased plasma CCK ( $10.9 \pm 2.9 \text{ pM}$ ,  $n = 9$ ) but had no effect on acid secretion (Fig. 6).

The specificity of MK-329 was characterized by measuring its effects on inhibition of peptone-induced acid secretion caused by somatostatin-14, the selective somatostatin-2 receptor subtype agonist DC(32–87), and secretin. MK-329 did not block the inhibitory effects of any of these agents (data not shown).

DISCUSSION

In awake rats, duodenal perfusion with CLD mimicking the daily diet of the laboratory rat (22, 33)

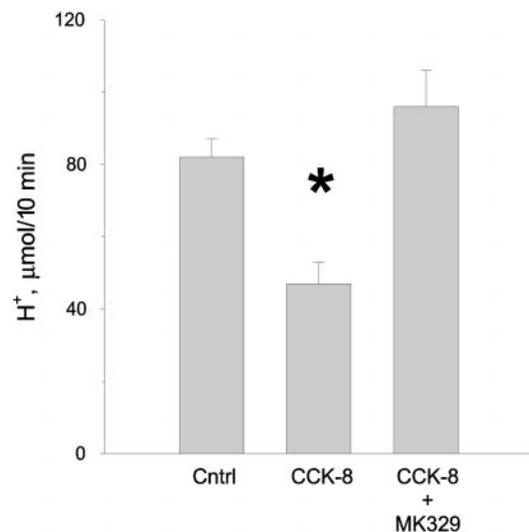


Fig. 5. Average acid output (means  $\pm$  SE, in  $\mu\text{mol}/10 \text{ min}$ ) during the last 30 min of intragastric peptone + intestinal saline (control, Cntrl;  $n = 12$ ), IV CCK-8 ( $10 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) in rats given IV vehicle ( $n = 5$ ), and IV CCK-8 in rats given 1 mg/kg MK-329 ( $n = 5$ ). CCK-8 inhibited acid secretion by  $46 \pm 10\%$ ; this effect was blocked by MK-329. \* $P < 0.05$  compared with control.

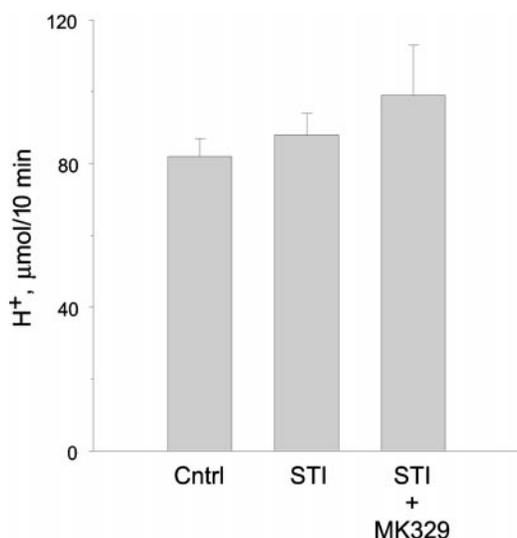


Fig. 6. Average acid output (means  $\pm$  SE, in  $\mu\text{mol}/10$  min) during the last 30 min of intragastric peptone + intestinal saline (Cntrl;  $n = 12$ ), intestinal soybean trypsin inhibitor (STI; 2% wt/vol;  $n = 9$ ) in rats given IV vehicle, and STI in rats given 1 mg/kg MK-329 ( $n = 5$ ). Intestinal STI did not alter acid output under either treatment condition.

significantly inhibited by approximately one-half the gastric acid response to a peptone meal instilled intragastrically. The acid inhibition was slow in onset, reaching maximum inhibition by 30–40 min after the start of intestinal perfusion. In addition, when nutrient components in concentrations (20% carbohydrate, 6% fat, and 5% protein) similar to those in CLD were administered individually into the duodenum, acid output was variably inhibited compared with CLD. Of the nutrient components tested, lipid and dextrose were the most effective and inhibited acid output by 61% and 51%, respectively. In comparison, casein had no significant effect. Plasma gastrin levels showed the same patterns of response to peptone and intestinal nutrients. Therefore, the acid inhibition by a natural diet depends on the characteristics of individual components. Furthermore, because the inhibitory effects are not additive, these results suggest that the mechanisms mediating acid inhibition share a common pathway.

One such pathway could be mediated by CCK acting as a hormone, paracrine agent, or neurotransmitter. To address this question, we first studied the regulation of gastric acid secretion induced by a meal. Intragastric peptone is a well-characterized stimulant of gastric acid secretion. The stimulatory effects of peptone are primarily mediated through gastrin/CCK-B receptors (2, 28, 29) and neural (21, 25) pathways. However, we now find that there is also an inhibitory component of a peptone meal on gastric acid secretion. We observed that MK-329 enhances peptone-stimulated acid output, consistent with similar studies in dogs (14). Even though experiments were conducted in rats in which the pylorus was patent and not ligated, the effect of MK-329 was not due to emptying of a portion of the peptone meal into the duodenum. Measurement of the

residual volume of the peptone meal remaining in the stomach 10 min after intragastric administration indicated that nearly all of the peptone meal was recovered, and there was no significant difference between treatment groups. An important additional finding was that plasma CCK was not increased over basal levels by intragastric peptone in our study. Taken together, these observations enabled us to hypothesize that endogenous CCK acts as a paracrine agent or neurotransmitter, rather than as a hormone, to inhibit peptone-induced acid secretion.

To further test this hypothesis, we used the following two approaches: examining the patterns of acid inhibition by intestinal nutrients and the effects of MK-329 and measuring plasma CCK and gastrin levels in response to the same intestinal nutrients. In earlier studies in dogs (17) and rats (15), we determined that CCK-A receptors are important in mediating lipid-induced inhibition of meal-stimulated acid secretion. In this study, we found that CCK-A receptors play an even broader role in intestinal phase regulation of acid secretion. Acid inhibition caused by CLD was reversed by MK-329. Furthermore, MK-329 reversed acid inhibition caused by individual intraduodenal infusions of lipid and dextrose. This effect was not due to changes in gastric emptying. Therefore, CCK-A receptors play an important physiological role during intestinal phase regulation of gastric acid secretion. Our conclusion is supported by experiments (26) performed in Otsuka Long-Evans Tokushima fatty rats, which do not express CCK-A receptors; in these rats, intestinal perfusion with lipid fails to inhibit gastric acid secretion.

The second aspect of our study was to examine the pathway (hormonal, paracrine, or neural) involved in acid inhibition by CCK. We found no relationship between plasma CCK levels and the degree of acid inhibition caused by intestinal nutrients. Additionally, acid inhibition was not produced by supraphysiological levels of endogenous CCK (in response to intestinal STI) but only by pharmacological levels of exogenously administered CCK. These data provide strong evidence against either a hormonal or paracrine inhibitory pathway for CCK. A peripheral afferent neural pathway is also unlikely to mediate acid inhibition by CCK. In earlier findings in rats (18), capsaicin treatment had no effect on acid inhibition caused by exogenous infusion of CCK but significantly reduced the acid inhibition by intestinal lipid. This line of reasoning suggests that MK-329 blocked the acid inhibitory effects of nutrients by acting on CCK-A receptors in the central nervous system.

Studies (30, 33) have shown that intestinal nutrients, including lipid and dextrose, activate central nervous system neurons, as evidenced by brain stem c-FOS expression. This effect is reversed by MK-329 administration (30). The fact that MK-329 is freely permeable across the blood-brain barrier supports acid inhibition by centrally acting CCK-A receptors (31). Although peripherally administered CCK can also activate brain stem c-FOS expression (6, 7, 34), the doses required to produce this action are likely supraphysi-

ological in terms of acid inhibition. They do not elicit acid inhibition themselves and yet they achieve circulating levels substantially greater than those after intestinal perfusion with lipid or dextrose, which markedly inhibit meal-stimulated acid secretion.

Several other substances, including secretin (23), peptide YY (1, 11), neurotensin (4, 8), and somatostatin (20), can inhibit acid output. However, specific blockade of each of these factors does not reverse the inhibitory effect of intestinal fat on a physiological (i.e., meal stimulation) level of acid secretion as effectively as does blockade of CCK-A receptors. Furthermore, the inhibitory effects of these substances are not blocked by MK-329. Therefore, although CCK is not the sole mediator of acid inhibition induced by intestinal nutrients, it appears to be one of the most important.

In summary, intestinal lipid and dextrose strongly inhibit peptone-stimulated gastric acid secretion. CCK-A receptor antagonism reverses these inhibitory effects of lipid and dextrose. Plasma CCK is not correlated with the degree of acid inhibition. These results suggest that intestinal nutrients inhibit gastric acid secretion through centrally located CCK-A receptors.

*Perspectives.* Final definition of the location of the CCK-A receptors mediating intestinal nutrient-induced inhibition of gastric acid secretion will require the use of permeant and nonpermeant receptor antagonists, as has been done for regulation of food intake (31). The efferent pathways responsible for inhibition of acid secretion by postulated central CCK-A receptors have not been identified. One possible pathway may involve gastric somatostatin. In an earlier study (18), acid inhibition by exogenous CCK was completely reversed by immunoneutralization of somatostatin. Furthermore, acid inhibition caused by activation of CCK-A receptors depends on somatostatin in rats (18), dogs (9), sheep (32), and humans (24).

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