Gastrin Injected into the Lateral Hypothalamus Stimulates Secretion of Gastric Acid in Rats

Abstract. *Intrahypothalamic injections of 100 picomoles of pentagastrin or natural gastrin promptly increased secretion of gastric acid in conscious rats. The response was blocked by atropine and by vagotomy. The same doses, injected intravenously or into other forebrain sites, did not increase secretion, nor did intrahypothalamic injections of other peptides common to the gut and brain.*

Gastrin is an important peptide hormone in the physiological regulation of gastric acid secretion. Its main source is the antrum of the stomach. Recently, Rehfeld (*1*) and Rehfeld *et al.* (*2*), using radioimmunoassay techniques, found a peptide very similar if not identical to gastrin in the hypothalamus, medulla, and pituitary of several mammals. Thus gastrin can be added to the growing list of peptides common to the gut and brain. Although it is evident that, in the gut, these peptides act as endocrines or paracrines to control gastrointestinal function, their physiological role in the brain is unknown. The presence of gastrin in the hypothalamus is of particular interest since a number of studies have demonstrated the importance of this brain region in controlling the digestive tract (*3*). To investigate whether gastrin might also participate at the hypothalamic level in the control of gastrointestinal function, we examined the effects of direct intracranial injections of gastrin on gastric acid secretion in conscious rats.

Male Wistar rats (250 to 350 g) were anesthetized with pentobarbital, and one or more stainless steel guide cannulas (inner diameter, 0.3 mm; outer diameter, 0.6 mm) were implanted stereotaxically into the lateral hypothalamus, lateral ventricle, or striatum. During the same operation, a stainless steel gastric cannula (*4*) was implanted into the most dependent part of the nonglandular portion of the stomach. Experiments were begun 1 week later.

The rats were deprived of food overnight before each experiment. They were tested in plexiglass restraining cages with an opening in the bottom through which the gastric cannula projected and an opening at the top for access to the brain cannulas. The gastric juice was collected continuously by gravity drainage. The volume secreted was measured at 15-minute intervals, and the acidity was determined by electrometric titration with an autoburette and *p*H meter (Radiometer, Copenhagen). Injections were begun when the basal rate of secretion had stabilized. Intracranial injections were made by inserting a stainless steel injector cannula (inner diameter, 0.15 mm; outer diameter, 0.30 mm), connected by polyethylene tubing to a microliter syringe, into one of the guide cannulas. The substances were dissolved in 0.9 percent saline and were injected in a volume of 1 μl. In most experiments, we used the gastrin analog pentagastrin (Peptavlon; Ayerst), which contains the active amino acid sequence of gastrin at the COOH terminus. Normally, several injections were made in each experiment to ascertain the reproducibility of a response, to test other substances, or to test another brain site in animals with more than one cannula. We waited at least 1/2 hour between injections, and in every experiment we gave at least one injection of the vehicle itself as a control. At the end of the experiments, the rats were killed and their brains were removed for histological verification of the cannula placements.

Injection of 100 pmole of pentagastrin into the lateral hypothalamus consistently caused gastric acid secretion to double or triple in the first 15 minutes after the injection ($P < .05$, Student's t-test) (Fig. 1). In some cases, the total amount of acid secreted during this period increased to over 100 μEq. An increase in the volume of secretion was often evident within minutes. Normally the rate of secretion returned to basal levels during the second 15-minute collection period, but similar responses could be elicited repeatedly in the same animal by further injections of pentagastrin on the same or subsequent test days. When pentagastrin was infused into the lateral hypothalamus at rates of 3 to 30 pmole per 0.5 μl per minute for up to 1 hour, gastric acid secretion remained elevated throughout the infusion. In contrast, nei-

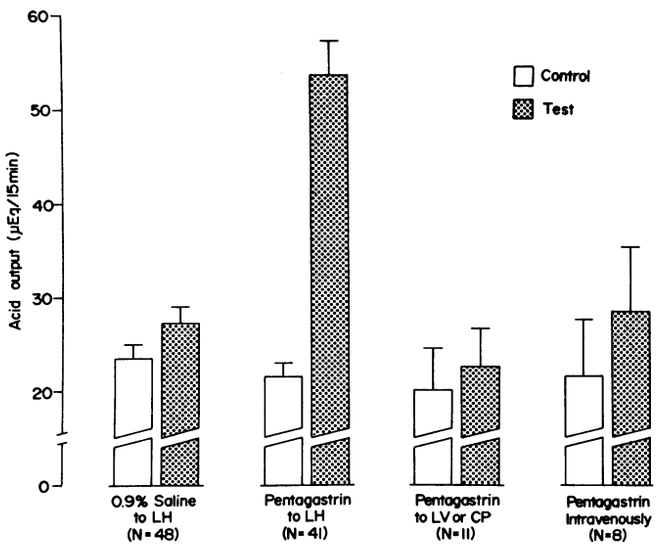

Fig. 1. Mean gastric acid output (± standard error) during 15-minute periods immediately before (open bars) and immediately after (shaded bars) injections of 0.9 percent saline or 100 pmole of pentagastrin into the lateral hypothalamus (*LH*), lateral cerebral ventricles (*LV*), or caudate-putamen area (*CP*), or intravenously through a jugular catheter (N = number of observations in 6 to 11 rats).

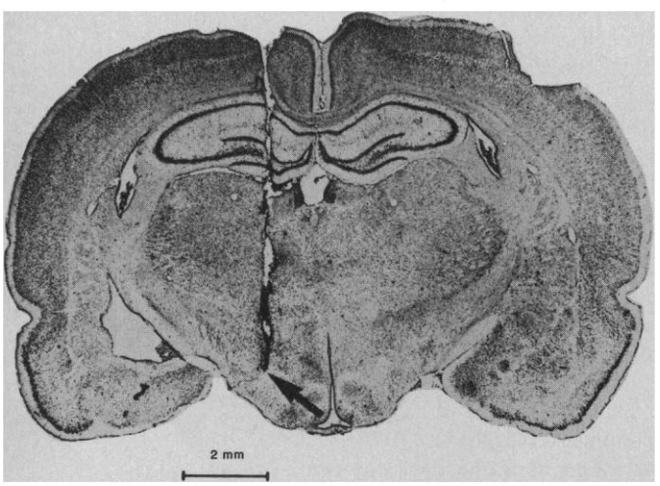

Fig. 2. Coronal section of brain, stained with thionine, showing the site of termination (arrow) of a cannula in the lateral hypothalamus where injections of pentagastrin stimulated gastric acid secretion.

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ther intracranial injections nor infusions of the saline vehicle significantly altered gastric acid output (Fig. 1). The stimulation of acid secretion caused by intracranial injections of pentagastrin was abolished by subdiaphragmatic vagotomy (two rats) and by atropine sulfate (0.3 mg/kg, subcutaneously; two rats), suggesting that the response was mediated by vagal parasympathetic fibers to the stomach.

Since pentagastrin is a potent secretagogue when injected systemically in the rat (*5*) and since vagal blockade also reduces the secretory response to systemic injections of gastrin (*6*), we were concerned that the stimulation of acid secretion in our experiments might have been caused by peptide leaking from the brain into the bloodstream. To test this directly, we implanted catheters in the jugulars of rats that had shown a consistent secretory response to intracranial injections. A dose of 100 pmole of pentagastrin, which potently stimulated acid output when injected intrahypothalamically in these animals, had no significant effect when injected intravenously (Fig. 1). Only intravenous injections of doses 10 to 100 times larger caused effects similar to those caused by 100 pmole injected intracranially.

Figure 2 shows an example of a hypothalamic cannula placement where injection of pentagastrin stimulated acid output. Injections of the same dose into other brain sites, including the lateral cerebral ventricles and caudate-putamen area, failed to increase gastric acid secretion. These results are consistent with those of Manaker *et al.* (*7*), who found that even higher doses of pentagastrin injected into the ventricular system did not increase acid output. Furthermore, in two of our rats in which the intracranial cannulas barely missed the lateral hypothalamus (one about 2 mm anterior and one about 1 mm medial), injections of pentagastrin also failed to increase gastric acid secretion. Similarly, no such increases were observed in two rats in which the hypothalamic cannulas were too ventral, puncturing the base of the brain so that injected pentagastrin entered the subarachnoid space. These results suggest that the lateral hypothalamus may be uniquely sensitive to this action of pentagastrin in the forebrain.

Like the pentapeptide fragment, intrahypothalamic injections of 95 percent pure porcine gastrin also increased gastric acid secretion. In eight animals in nine experiments, the acid output after injection of 100 pmole of porcine gastrin was 44.6 ± 5.3 μEq per 15 minutes compared to 20.6 ± 3.4 μEq per 15 minutes when the same rats were injected with the saline vehicle ($P < .05$). On the other hand, intrahypothalamic injections of the same dose of other peptides common to the gut and brain, including neurotensin, substance P, and vasoactive intestinal polypeptide, failed to alter gastric acid secretion. In fact, bombesin, the amphibian peptide recently found in mammalian gut and brain and known to stimulate acid secretion when injected systemically (*8*), actually reduced gastric acid output from 24.7 ± 3.4 to 4.2 ± 1.3 μEq per 15 minutes ($N = 6$, $P < .05$) when injected into the lateral hypothalamus. Therefore the stimulation of gastric acid secretion by peptides in the hypothalamus appears to be specific to gastrin-like substances.

These observations demonstrate that gastrin can increase gastric acid secretion by acting on the hypothalamus as well as on the stomach. It is uncertain whether circulating gastrin could stimulate the brain sites implicated in our experiments, since it is controversial whether such peptides can cross the blood-brain barrier (*9*). Preliminary findings, however, suggest that intracarotid infusions of pentagastrin in sheep are more potent than intravenous infusions at inhibiting motility of the reticulum of the stomach (*10*). Alternatively, our results also support the idea that gastrin endogenous to the hypothalamus, perhaps acting as a neurotransmitter or neurohormone, participates in the neural control of gastrointestinal function. Since gastrin has been identified in the medulla and in fibers and terminals of the vagus nerve (*2*), it is conceivable that a gastrinergic pathway connecting the hypothalamus and the vagal nuclei and projecting to the gut could be an important component of the neural mechanisms controlling digestion.

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11. Supported by the Medical Research Council of Canada. We thank E. Potter and B. Soper for technical assistance, M. I. Grossman for his gift of porcine gastrin (G-17-1), and V. Mutt for his gift of vasoactive intestinal polypeptide (the synthetic peptides neurotensin, substance P, and bombesin were purchased from Peninsula Laboratories). A preliminary version of this report was presented at the 80th Annual Meeting of the American Gastroenterological Association, New Orleans, May 1979.

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Holographic Assessment of Microwave Hearing

Human beings with normal audiograms can "hear" pulsed microwaves; they perceive a clicking or popping sound each time a suprathreshold, 1- to 30-μsec pulse is incident on the head (*1*). While the quantity of energy absorbed per pulse at the threshold of hearing is small (~ 20 μJ/g), as is the resulting increment of average temperature, ~ 5×10^{-6} °C (*2*), most investigators of this phenomenon believe that the hearing is due to thermoelastic expansion (*3*); that is, one hears because a minuscule wave of pressure is set up within the head when the absorbed microwave pulse is converted to thermal energy (*4*). Frey and Coren (*5*) challenge the thesis that thermoelastic expansion of the skull or soft tissues of the head is critical to microwave hearing. Using a time-averaged laser-holographic procedure during pulsed irradiation of dead rats and guinea pigs, they failed to find evidence of thermoelastic displacement in serially exposed scalp, skull, and brain. They then argue (i) that thermoelastic events in these structures are not responsible for microwave hearing and (ii) that thermoelastic events within the cochlea probably are. We show that methodological and conceptual errors reduce both of these arguments to non sequiturs.

Frey and Coren (*5*) claim that their holographic technique is sensitive to vibratory displacements on the order of 6×10^{-8} m. They do not indicate (i) that this level of sensitivity is achieved only in measurement of a continuous, undamped vibration (*6*); (ii) that the putative sonic wave launched in the head by a microwave pulse is a rapidly damped transient that persists for less than 300 μsec (*7*), which would reduce the sensitivity of their technique well below the level claimed (*8*); or (iii) that the energy

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