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Effect of Intravenous Acetylcholine on Serum Gastrin Levels in Dogs[1] (38264)

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Topical application of acetylcholine (Ach) to the gastric antrum is known to stimulate gastric acid secretion and to produce a rise in circulating levels of serum gastrin (5). Whether these effects are due partially to absorption of Ach into the circulation is not clearly understood. Recent *in vitro* experiments have suggested that Ach might act directly upon the acid secreting cells of the stomach (1). Studies *in vivo* in which Ach was given subcutaneously to dogs with denervated pouches (2), intra-arterially or intravenously to anesthetized cats (3) or intra-arterially to vagotomized anesthetized dogs (4) failed to demonstrate a direct action on the parietal cell. The effects of systemically administered acetylcholine upon serum gastrin have not been reported previously.

We have studied the effects of intravenous Ach upon serum gastrin in normal dogs, dogs with gastric fistulas, and dogs with total gastrectomy.

Materials and Methods. Sixteen healthy adult mongrel dogs weighing 15–25 kg were used in these studies. Five dogs had had no previous operation, five had had chronic gastric fistulas placed 6 weeks prior to testing, and six had had total gastrectomy 10 weeks prior to testing.

Following an overnight fast the dogs were placed in Pavlov stands. Catheters were inserted into a foreleg vein for intravenous infusion and into a hindleg vein for blood sampling. An intravenous infusion of 0.9% NaCl was initiated at the rate of 60 ml/hr. After one hour of saline infusion, the dogs received a 5-hr infusion of Ach. The initial dose of Ach was 0.5 mg/kg/hr and this was increased every hr to a maximum of 6 mg/kg during the final hr.

During the studies with the dogs with gastric fistulas, gastric secretions were collected in 30-min aliquots and acid output was measured by titration with 0.1 *N* NaOH (phenol red was used as an indicator). Results were expressed as milliequivalents (mEq) of H^+ per 30-min period.

Blood samples were drawn at the beginning of the experiments and every 30 min thereafter.

Serum gastrin was measured by radioimmunoassay (5). The antigastrin antibody used was developed in New Zealand white rabbits to synthetic human gastrin I (amino acid residues 2–17) conjugated to bovine serum albumin. All samples were assayed in duplicate; reproducibility was within $\pm 10\%$. The average of the duplicates was used as the gastrin concentration, expressed in picograms (pg)/ml.

Results were expressed as arithmetic means and standard errors of the mean. The Student *t* test was used to determine significance of differences between means. Differences with *P* values of less than 0.05 were considered significant.

Results. The results of the studies in the three groups of dogs are shown in Fig. 1. The lower doses of Ach (0.5 mg/kg and 1.0 mg/kg) were well tolerated, but at the doses of 2 mg/kg/hr and above, toxic signs of

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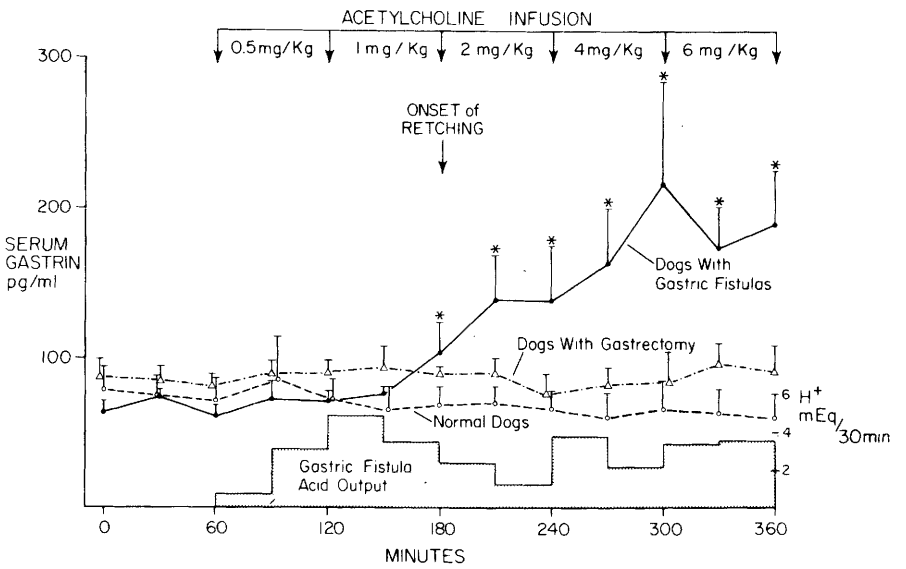

FIG. 1. Effect of intravenous infusion of acetylcholine in graded doses on serum gastrin levels in five normal dogs, five dogs with gastric fistulas, and six dogs with total gastrectomy. Acid output from gastric fistula dogs is shown in the bar graph.

restlessness, excessive salivation, retching and defecation were noted in all dogs.

Normal dogs. During the control period in which saline was infused intravenously, basal serum gastrin levels averaged 73 ± 16 pg/ml. There was no significant alteration from this level during the entire dose range of the acetylcholine infusion.

Dogs with gastric fistulas. There was an immediate increase in gastric acid output in response to acetylcholine, 0.5 mg/kg/hr. Maximal gastric acid secretion, 4.9 ± 1.4 mEq/30 min, was achieved with Ach, 1 mg/kg/hr. Mean basal levels of gastrin were 66 ± 7 pg/ml, and there was no significant change during infusion of Ach at either 0.5 mg/kg/hr (72 ± 10 pg/ml) or 1 mg/kg/hr (75 ± 8 pg/ml).

After initiation of Ach at the dose of 2 mg/kg, gastric acid secretion fell to 1.3 ± 0.4 mEq/30 min, but serum gastrin levels rose significantly to 137 ± 35 pg/ml. During infusion of Ach at doses of 4 and 6 mg/kg/hr, serum gastrin rose to a peak of 216 ± 70 pg/ml and gastric acid output increased to a maximum of 3.8 ± 1.1 mEq/30 min. Some gastric secretory collections showed slight bile staining; there was no greater incidence of this staining after the onset of nausea.

Dogs with total gastrectomy. The average serum gastrin value was 84 ± 5 pg/ml during the control period and did not significantly change throughout the period of Ach infusion. The gastrin values in these dogs were slightly but not significantly higher than those of normal dogs. This probably reflects interassay variation in gastrin measurements, since gastrin values are diminished in gastrectomized dogs (6).

Discussion. These results demonstrate that intravenous acetylcholine caused an early increase in gastric acid secretion in dogs with gastric fistulas draining the innervated stomach. This increase occurred before either significant alteration in circulating levels of serum gastrin or the onset of toxic signs from the Ach. The mechanism of production of increased gastric acid secretion is unknown. It could be due to activation of cholinergic receptors on the parietal cell or to synergistic augmentation of the stimulatory action of basal levels of gastrin.

It has been suggested (2) that absorption into the circulation of Ach applied topically to the gastrointestinal mucosa may stimulate

gastric acid secretion. Previously reported studies, however, failed to demonstrate increased gastric acid secretion from denervated fundic pouches in dogs when Ach was applied topically to different regions of the gastrointestinal tract (2). The fundic mucosa in the present studies was innervated and therefore more sensitive. Parietal cell insensitivity may also partly account for the failure of Ach to stimulate gastric acid even when injected directly into the short gastric arteries supplying the vagotomized stomach of the cat (3) or dog (4). Gastric acid secretion is known to be diminished during anesthesia (7) and this, together with vagal denervation, may account for the failure in previously reported studies (3, 4) to demonstrate stimulation of gastric acid secretion in response to systemic Ach.

Studies with gastric fistula dogs show that intravenous Ach releases gastrin if acid inhibition of the antrum is averted by removing gastric acid. Increases in serum gastrin did not occur until after maximal gastric secretory rates had been achieved and after signs of acetylcholine toxicity had appeared. Gastrin release cannot therefore account for the increased gastric acid secretion. Increases in serum gastrin were not seen in normal dogs. This is probably due to acid inhibition of gastrin release. The origin of the released gastrin is not clear but is probably from the antrum since no gastrin release could be demonstrated in the dogs with total gastrectomy. Extragastric gastrin is known to exist in the mucosa of the proximal small bowel (8) and is probably the source of normal basal gastrin levels in gastrectomized dogs. It is clearly not released in detectable quantities by increased circulating levels of acetylcholine even when given to the point of toxicity. We have also been unable to demonstrate release of extragastric gastrin in dogs by Ach applied topically to the duodenal mucosa or by feeding (unpublished observation).

Summary. The effect of intravenous acetylcholine upon serum gastrin in normal dogs, dogs with gastric fistulas and dogs with total gastrectomy has been studied. No alteration in serum gastrin was seen in normal dogs or dogs with total gastrectomy. In dogs with gastric fistulas significant increases in serum gastrin were seen with supratoxic doses of acetylcholine. Acid secretion from gastric fistulas occurred before the onset of toxic signs and before the increases in serum gastrin. It is concluded that: (a) intravenous acetylcholine can stimulate gastric secretion without increasing serum gastrin, (b) supratoxic doses of intravenous acetylcholine stimulate release of gastrin but only if gastric acid is removed, and (c) gastrin which is released came from the gastric antrum.

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