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Research Articles

Relationship of Antral Motility to Gastrin Activity in Surgically Prepared Dogs

By DONALD D. ABBOTT*, ALFONSO R. GENNARO, and G. VICTOR ROSSI

Chemical secretagogues and insulin-induced vagal stimulation were utilized to evoke gastrin release in dogs prepared with vagally denervated fundic pouches. For comparative purposes a gastrin extract was prepared from hog antral mucosa, using the method of Gillespie and Grossman. Gastrin activity was assessed in terms of the total acid content of periodic samples aspirated from the fundic pouch. Movements of a magnet, affixed surgically to the pyloric antrum, were remotely monitored using a magnetometer. Antral motility was monitored during the stimulation of endogenous gastrin release and the infusion of exogenous gastrin in anesthetized animals. These studies indicated that there is not a direct correlation between endogenous gastrin release and antral motility. The intravenous infusion of exogenous gastrin elicited gastric acid secretion and antral motility; the responses bore a relationship to infusion rate.

RELEASE OF THE hormone, gastrin, from the mucosa of the pyloric antrum is apparently mediated by a mechanism responsive both to chemical secretagogues and mechanical stimulation. The existence of a local neural mechanism, cholinergic in nature, is supported by the observations that topical application of local anesthetic and atropine solutions (1, 2) to the antral mucosa effectively inhibits gastrin release, whereas locally applied acetylcholine (3) evokes release of the hormone.

Several investigators (4–8) have associated vagal activity, a major determinant of gastric motility, with the release of gastrin. On this basis, two mechanisms may be postulated: (*a*) gastrin is released as a direct consequence of vagal nerve activity, and/or (*b*) antral motility, elicited by vagal stimulation, evokes the release of gastrin. Nyhus (9) considered the effect to be primary, based upon studies in which innervated antral mucosa, devoid of musculature, responded to vagal stimulation.

Few studies have been directed toward the relationship of antral motility and gastrin release due, in large measure, to the limitations of available techniques for assessing gastric motility *in vivo*. The most commonly used methods for evaluating gastrointestinal motility, *i.e.*, the balloon and open-end tube procedures, provide only a gross indication of motor activity. In both instances the pressure changes (intraballoon or intraluminal), which are interpreted as reflections of motor activity, are influenced by the presence of the indwelling system which serves as

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a mechanical stimulus to various physiologic reflexes. More recently, the use of surgically implanted endoradiosondes, which transmit intraluminal pressure in terms of FM radio signals, has eliminated the necessity of the indwelling tube. It is generally agreed, however, that the motor activity of the stomach may not necessarily be reflected by pressure changes (10, 11). Using these procedures it is not possible to determine the motility of a specific site or area.

The use of the magnetometer, an instrument capable of remotely detecting changes in a magnetic field resulting from movements of an internally positioned magnet, obviates many of the inherent limitations of the previously cited procedures. This technique has been employed in humans by Wenger *et al.* (12, 13) to study the effect of psychological stimuli on gastric motility. Use of the magnetometric method in animals is unique and, to our knowledge, represents the first time the technique has been employed in conjunction with surgical implantation of the signal magnet at a specific site. Under these conditions the recordings are considered to be representative of the actual motility of the site to which the magnet is affixed.

This study examines, in surgically prepared dogs, the possible relationship between antral motility and gastrin activity in response to chemical secretagogues, insulin-induced vagal stimulation, and the administration of exogenous gastrin.

EXPERIMENTAL

Twenty-four mongrel dogs, of both sexes, were surgically prepared with exteriorized, vagally-denervated (Heidenhain) pouches as a means of assessing gastrin activity without direct interference from neural factors (14). The surgical technique involved the exposure of the stomach along the greater curvature through a midline abdominal incision. The fundic portion of the stomach was transected, through both dorsal and ventral walls, between two points on the greater curvature leaving the gastroepiploic artery intact. For the purpose of monitoring antral motility, a Teflon-covered stirring bar magnet ($^5/_{16} \times 1^1/_8$ in.) was secured to the mucosal surface of the pyloric antrum prior to suturing the main stomach. A blind pouch was formed by suturing together the cut edges of the excised fundic area. The isolated pouch then was fitted with a polyethylene cannula which was exteriorized through the initial abdominal incision. This surgical preparation is illustrated in Fig. 1.

Test animals were allowed to recuperate for not less than 3 weeks prior to investigational use. Sodium chloride, 0.5 Gm., was added daily to the drinking water of each animal in an effort to balance the chloride lost in acid secretions of the pouch.

During each experimental period the animals, having been fasted 18–24 hr., were anesthetized with sodium pentobarbital (35 mg./Kg. i.v.). Except where specifically indicated, 1.0 Gm. of dihydroxyaluminum sodium carbonate (DASC), suspended in 10 ml. of saline, was administered by intubation at the beginning of each experimental period. This treatment served to maintain antral pH at 3 to 4 and thereby prevented the gastrin inhibition which occurs when the pH of the antrum falls below 2 (15).

Gastrin activity was assessed in terms of the total acid content of periodic samples collected from the vagally-denervated pouch. The individual samples, or aliquots thereof, were titrated with 0.1 *N* sodium hydroxide, using a 1% alcohol solution of phenolphthalein as an indicator. The results were calculated in terms of milliequivalents of hydrochloric acid secreted per hour.

Remote monitoring of the movements of the surgically implanted magnet was accomplished by use of a model M-10 Magnetometer (Irwin Laboratories, Los Angeles, Calif.) in conjunction with a Polygraph recorder (Grass Instrument Co., Quincy, Mass.). Figure 2 illustrates a typical recording representative of a control period and the antral motility occurring after vagal stimulation due to insulin hypoglycemia. To elicit the release of endogenous gastrin, chemical secretagogues (ethyl alcohol and liver extract) and insulin-induced vagal stimulation were employed as follows.

Ethyl Alcohol.—Thirty milliliters of a 10% (v/v) aqueous solution was administered by intubation.

Liver Extract.—An aqueous liver extract was prepared by macerating 100 Gm. of calves liver with 500 ml. of water and allowing it to steep for 24 hr. under refrigeration. The total liquid was filtered through cheese cloth and the fluid retained by the solids was expressed by pressure. A 50-ml. volume of the prepared liver extract was administered by intubation.

Insulin-Induced Vagal Stimulation.—Crystalline insulin, 0.2 units/Kg., was administered intravenously.

The effects of exogenous gastrin on pouch acid secretion and antral motility were also investigated.

Gastrin Extract of Hog Pyloric Mucosa.—One milliliter of extract, prepared according to the method of Gillespie and Grossman (16), was equivalent to 10 Gm. of initial wet pyloric gland mucosa. The extract was diluted with physiological saline and administered intravenously at a constant

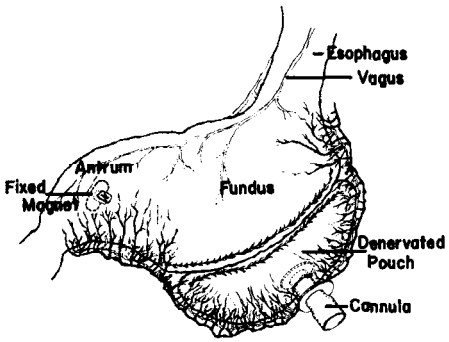

Fig. 1.—Surgical preparation of vagally-denervated pouch with exteriorized cannula and placement of magnet for remotely monitoring antral motility.

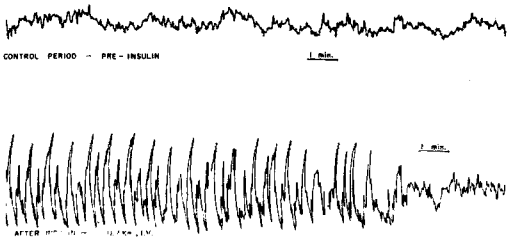

Fig. 2.—Representative magnetometer tracing of antral motility before and after insulin.

infusion rate of 1 ml./min. The following doses of gastrin extract, expressed in terms of initial wet weight of pyloric mucosa, were employed: 2 Gm./hr., 4 Gm./hr., and 8 Gm./hr.

The prepared gastrin extract was assayed on isolated guinea pig ileum for histamine activity. Ileal strips were suspended in aerated Tyrode's solution at 37.5°, and contractility measured by an E and M A210 Myograph and recorded on an E and M Physiograph Six (E and M Instruments, Houston, Tex.).

RESULTS

Ethyl Alcohol.—In five experiments, in different test animals, acid secretion by the vagally-denervated pouch in response to the intubation of ethyl alcohol was increased 3 to 10 times that of control period levels. Peak acid secretion was manifest between 50 and 70 min. after administration of alcohol; thereafter secretion diminished to approximately the level observed during the control period within 2 to 2.5 hr.

Antral motility was not observed during the control period; however, periods of antral motility were noted, in all experiments, within 2 to 7 min. after the administration of alcohol. Motility occurred sporadically during the ascending phase of acid secretion. Periods of motility lasting 2 to 12 min. were interspersed with quiescent intervals of 3 to 25 min. duration. During the decline of acid secretion, antral motility was not evidenced with the exception of occasional short bursts recorded immediately following the peak acid response.

These findings are presented in Table I, series *A;* the results of a typical experiment are given in Fig. 3.

In a series of three experiments (Table I, series *B*), the intravenous administration of atropine sulfate, 1 mg./Kg., to test animals 30 to 45 min. after the intubation of alcohol, terminated both acid secretion and periodic antral motility. Acid secretion did not decrease precipitously, but returned to approximately control levels within 30–40 min. after the injection of atropine. This latent period suggested that cessation of acid secretion was due to inhibition of gastrin release, rather than a direct action of the acid secreting mechanism. Atropinization prior to the administration of ethyl alcohol completely blocked acid secretion and antral motility.

Liver Extract.—In five experiments on four test animals the intubation of 50 ml. of liver extract resulted in an increase in acid secretion from the vagally-denervated pouch. Initial responses occurred within 10 to 20 min., and peak acid responses, achieved 40 to 70 min. after intubation, ranged from 12 to 16 times that observed during the control periods.

Antral motility was absent during all control periods and during two of the five experimental periods; in the remaining three experimental periods motility was observed for very brief intervals immediately after the administration of the liver extract. These results are presented in Table I series *C;* representative data are graphed in Fig. 4.

Insulin-Induced Vagal Stimulation.—In ten experiments conducted on four test animals insulin (0.2 units/Kg. i.v.) increased acid secretion from 3 to 20 times the levels observed during the control periods. Initial secretory responses were noted in the first 10- to 20-min. period following insulin, while peak acid secretion occurred within 30 to 60 min. Acid secretion returned to approximately control levels about 2 hr. after insulin injection.

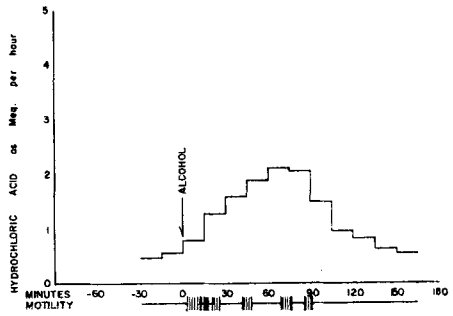

Fig. 3.—Acid secretion and antral motility in response to the intubation of 30 ml. of 10% ethyl alcohol.

TABLE I.—ACID SECRETION BY VAGALLY-DENERVATED FUNDIC POUCH AND ANTRAL MOTILITY IN DOGS

Experiments, No.	Mean Values: Acid Secretion, meq. HCl/hr. Control Period	Acid Secretion, meq. HCl/hr. Peak Response Period	Antral Motility, % of Time Present Control Period	Antral Motility, % of Time Present Peak Acid Response Before	Antral Motility, % of Time Present Peak Acid Response After
Series *A*, intubation of 30 ml. of 10% (v/v) ethyl alcohol					
5	0.72	3.55	0	33.8	6.2
Series B, intubation of 30 ml. of 10% (v/v) ethyl alcohol followed by atropine sulfate (1 mg./Kg. i.v.)					
3	0.25	1.67	0	53	0
Series *C*, intubation of 50 ml. of 20% liver extract					
5	0.18	2.50	0	5.2	1.2
Series *D*, insulin (0.2 units/Kg. i.v.) induced vagal stimulation—antacid pretreatment					
10	0.17	1.92	0	75	67
Series *E*, insulin (0.2 units/Kg. i.v.) induced vagal stimulation—no antacid pretreatment					
3	0.16	0.19	0	68	[a]

[a] No peak acid response was observed.

Motility, absent during control periods, was initiated within 2 to 10 min. after the administration of insulin. Thereafter, motility recurred throughout the remainder of each experimental period, both before and after peak acid responses were achieved. Single episodes of motility ranged from as short as 1 min. to as long as 70 min.

The results of these experiments are presented in Table I, series *D;* data from a typical experiment are graphed in Fig. 5.

In three experiments the test animals were not pretreated with DASC prior to the administration of insulin. In these experiments the pattern of antral motility was similar to that observed with animals pretreated with antacid; however, acid secretion did not increase after the administration of insulin. (Table I, series *E.*)

In the absence of the buffering action of DASC, acid secretion in the main stomach inhibited gastrin release, thereby blocking the secretory response of the vagally-denervated pouch.

Gastrin Extract of Hog Mucosa.—When assayed on guinea pig ileum *in vitro,* the gastrin extract manifested spasmogenic activity equivalent to 0.001–0.3 mcg. of histamine base per gram of mucosa. However, succeeding additions of gastrin extract to the *in vitro* test system elicited progressively diminishing contractile responses, whereas the sensitivity of the same isolated intestinal strip to histamine remained constant. This "tachyphylaxis" was taken to indicate that the observed activity of the gastrin extract upon the intestinal strip was not due to histamine.

The intravenous infusion of gastrin extract at rates of 2, 4, and 8 Gm./hr., in three separate experiments, resulted in pouch acid secretions, the magnitudes of which indicated a graded dose response relationship. Variations among the test animals were observed in regard to the rapidity of response and sensitivity to exogeneous gastrin. The peak acid response was obtained between 20 and 110 min. In all instances a precipitous drop in acid secretion occurred after the infusion of the gastrin extract was terminated. Acid secretions returned to preinfusion levels within 30 to 40 min. after the gastrin infusion was discontinued.

Antral motility was not manifested during any of the control periods or those in which gastrin was infused at a rate of 2 Gm./hr. Motility did occur in two of the three experiments at 4 Gm./hr., and in all three experiments at 8 Gm./hr. When motility was observed, it commenced within 10 min. after the start of gastrin infusion and continued unabated until approximately 20 to 30 min. after the infusion was stopped.

The results of these experiments are presented in Table II, and representative results, obtained with a single test animal, are given in Fig. 6.

DISCUSSION

The magnetometric technique obviated many of the limitations inherent in other procedures which have been employed to study gastric motility (10, 17) and, in our estimation, provided an index of the actual motility of the pyloric antrum. However, since this method is dependent upon changes in magnetic field, both in regard to intensity and direction, it was necessary to employ anesthetized

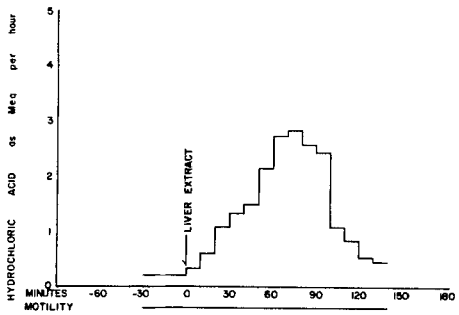

Fig. 4.—Acid secretion and antral motility in response to the intubation of 50 ml. of a 20% aqueous liver extract.

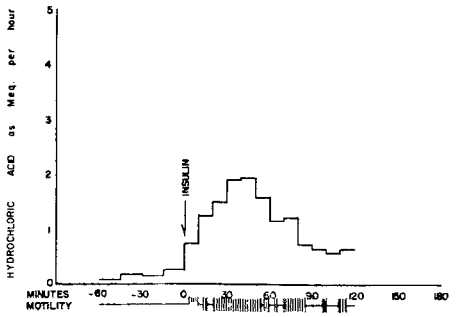

Fig. 5.—Acid secretion and antral motility in response to insulin, 0.2 units/Kg. i.v.

animals so that orientation to the earth's magnetic field remained constant. Although sodium pentobarbital anesthesia eliminated antral motility during the control periods, it did not inhibit responses to chemical secretagogues, insulin-induced vagal stimulation, or exogenous gastrin.

Lacking a direct procedure for the determination of circulating gastrin, release of this hormone must be estimated in terms of its effect on acid secretion by the parietal cells of the fundic mucosa (14). The vagally-denervated (Heidenhain) pouch has been used as a basic preparation to assess the effect of humoral or chemical agents without direct interference by neural factors.

In this study, gastrin inhibition by low antral pH, as shown by Woodward (15), was prevented by the administration of dihydroxyaluminum sodium carbonate (DASC), which maintained the pH of the main stomach at approximately 3–4.

The administration of ethyl alcohol, by intubation, elicited both gastrin release and antral motility. Episodic antral motility generally occurred only during the time that gastrin activity was increasing. On this basis it would appear that a positive relationship exists between gastrin release and antral motility. However, the mechanism of the gastric secretory response to ethyl alcohol is complex and may include histamine release (18), gastrin release (19), central vagal stimulation (20), and direct stimulation of the parietal cells (19). The acid secretion elicited from the vagally-denervated pouch, following the intubation of ethyl alcohol into the main stomach may therefore have involved any one or a combination of the factors cited. The associated antral motility may have been due

TABLE II.—ACID SECRETION[a] (meq. HCl/hr.) BY VAGALLY-DENERVATED FUNDIC POUCH IN RESPONSE TO EXOGENOUS GASTRIN

Dog	Saline Control	Gastrin Infusion Rate 2 Gm./hr.	4 Gm./hr.	8 Gm./hr.
1	0.11	0.39	1.15	2.65
2	0.07	0.41	1.73	2.68
3	0.15	1.31	2.18	3.17
Mean values	0.11	0.70	1.69	2.83

[a] Based upon peak plateau levels obtained from the infusion of gastrin extract.

to direct local reflex stimulation and/or central vagal stimulation. The profuse salivation noted in some of the test animals tends to support participation of the latter mechanism.

The intravenous administration of atropine sulfate (1 mg./Kg.) before, concurrent with, and after the administration of ethyl alcohol, prevented or suppressed acid secretion and antral motility. Inhibition by atropine supports the involvement of neural factors, local or central, with gastrin release. Gregory and Tracy (21) reported that the intravenous injection of either gastrin I or II caused a strong initial gastric contraction followed by rhythmical activity of the stomach musculature, and that the latter contractions were abolished by atropine.

Aqueous liver extract intubated into the main stomach resulted in acid secretion from the vagally-denervated pouch. This evidence of gastrin release was obtained without significant concomitant antral motility. The absence of antral motility or minimal motility during the period of gastrin release following administration of liver extract

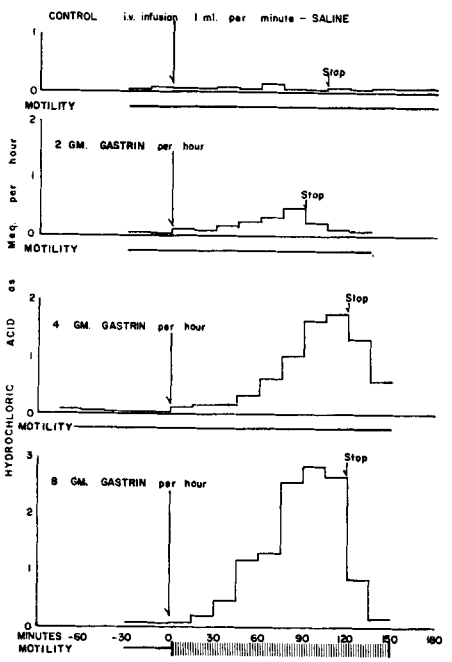

Fig. 6.—Acid secretion and antral motility by a single test animal in response to the intravenous infusion of exogeneous gastrin.

is interpreted as evidence that these two physiologic functions can operate independently of each other. Therefore, it may be assumed that a chemical secretagogue, in this instance a component of liver extract, elicits gastrin release by direct action on the antral mucosa. This concept is supported by the studies of Woodward (15), in which vagally-denervated, isolated antral pouches were employed; however, motility of the pouches was not recorded.

Vagal stimulation resulting from insulin-induced hypoglycemia evoked both acid secretion and concurrent antral motility. These findings are in agreement with investigations where motility (22, 23) and acid secretion (24–27) in response to intravenously or subcutaneously administered insulin were evaluated separately.

In the present study a relatively small dose of insulin was used to avoid the untoward effects of severe hypoglycemia. Antral motility was observed both before and after the maximal secretory response. On this basis, the relationship between gastrin release and antral motility resulting from insulin-induced hypoglycemia could be considered as both positive and negative, *i.e.*, there was an initial positive correlation during the ascending phase of acid secretion and a negative correlation during the descending phase since motility continued unabated.

Gastrin extracts, prepared by the method of Gillespie and Grossman (16), from hog antral mucosa, elicited acid secretion from the vagally-denervated pouch and initiated antral motility. Doses of 2, 4, and 8 Gm./hr. (in terms of wet weight of hog pyloric mucosa) were infused intravenously at a constant rate in saline solution. The magnitude of acid secretion, in response to exogenous gastrin, was proportional to dosage. Saline infused at the same rate as the diluted gastrin had no effect upon either antral motility or acid secretion. Antral motility was observed only with the doses of 4 and 8 Gm./hr.

The extent of acid secretion and the magnitude and type of motility obtained with the infusion of exogenous gastrin were comparable to those observed in response to alcohol, liver extract, and insulin-induced hypoglycemia. In all instances acid secretion diminished immediately upon termination of the gastrin infusion. Antral motility, when present, continued for varying periods after the infusion of gastrin extract was stopped. These findings, relative to acid secretion in response to exogenous gastrin, corroborate those of other investigators (16, 21, 28, 29). However, in the investigations cited, no correlative studies of acid secretion and antral motility, in response to exogenous gastrin, were performed.

The doses and rate of infusion of the gastrin extract used in this study were less than those which Gillespie and Grossman (16) found to be capable of causing inhibition of acid secretion. When the gastrin extract used in this study was evaluated for possible histamine content on the isolated guinea pig ileum, an inhibitory phenomenon was encountered. The phenomenon observed could be described as a tachyphylaxis, since the contractile response to histamine remained constant. Sensitivity to gastrin was regained after a period of time elapsed during which the intestinal strip was

not challenged with gastrin. It remains to be established whether the mechanism of inhibition observed with this isolated tissue is related to the previously reported (16) inhibition of acid secretion in the intact preparation.

The fact that the gastrin extract elicited contractions of the isolated intestinal strip would appear to support the occurrence of antral motility following the infusion of gastrin into the vagally-denervated pouch animals. It is not possible, however, to ascribe either the *in vitro* or *in vivo* motility responses to a direct effect of gastrin inasmuch as the gastrin was not a purified entity.

SUMMARY

Correlative studies were conducted in which antral motility was monitored during the stimulation of endogenous gastrin release and the infusion of exogenous gastrin. Gastrin activity was assessed in terms of total acid secretion from the vagally-denervated (Heidenhain) pouch in anesthetized dogs. Motility of the pyloric antrum was monitored by means of a magnetometric technique.

Chemical secretagogues (ethyl alcohol and liver extract) and insulin-induced vagal stimulation were used to evoke gastrin release. Assuming the acid secretion from the vagally-denervated pouch to be a valid indication of gastrin activity, the over-all correlation of antral motility and gastrin release was positive with ethyl alcohol, negative with liver extract, and negative with insulin-induced vagal stimulation. The response to alcohol is considered to have been complicated by central vagal activation and direct stimulation of parietal cells.

The intravenous infusion of gastrin extract, prepared from hog pyloric antral mucosa, elicited both acid secretion and antral motility. These actions of exogenous gastrin bore a relationship to infusion rate.

On the basis of studies performed with chemical secretagogues and insulin-induced vagal stimulation, in surgically prepared dogs, it is concluded that a direct causal relationship does not exist between gastrin release and antral motility

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