RELATIONSHIP BETWEEN GASTRIC SECRETION AND SERUM GASTRIN LEVELS IN DOGS ANESTHETIZED WITH MORPHINE AND URETHANE

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Abstract—The serum levels of immunoreactive gastrin (IRG) and secretion of gastric juice were simultaneously determined in dogs anesthetized with morphine and urethane. There was a significant positive linear correlation between secretion and serum IRG level in these dogs. Serum IRG level and gastric secretion were reduced by bilateral vagotomy at the neck. The amount of gastric juice was reduced dose-dependently by an intravenous injection of atropine (0.001-0.016 mg/kg), hexamethonium (0.064-1 mg/kg) and secretin (2-8 U/kg). The reduction of gastric secretion paralleled that of the serum IRG level. However, the reduction of gastric secretion did not parallel that of serum IRG level under the influence of prostaglandin E1 (0.002-0.008 mg/kg i.v.) and duodenal acidification. Prostaglandin E1 and duodenal acidification reduced gastric secretion without the reducing serum IRG level. These findings were discussed in relation to the mechanism of gastric juice stimulation by morphine, and it is suggested that endogenous gastrin release through the vagal and non-vagal pathways participates in morphine-induced gastric secretion. The difference in inhibitory effect between duodenal acidification and secretin suggests the possibility that substances other than secretin may participate in the regulation of gastric secretion in dogs.

Yamaguchi reported that the inhibitory activity of atropine and hexamethonium on morphine-induced gastric secretion was approximately the same as that on food-induced gastric secretion in Heidenhain pouch dogs (1). Cholinergic nerve fibers were identified histochemically in the antro-pyloric mucosa, and particularly those in close contact with endocrine-like cells which seemed to be identical with gastrin cells (2). Thus it should be considered that morphine may stimulate gastric secretion by endogenous gastrin release through an activation of the cholinergic nerves.

The present study deals with the relationship between the serum immunoreactive gastrin (IRG) level and gastric secretion in dogs anesthetized with morphine and urethane and given secretory inhibitors.

MATERIALS AND METHODS

Experiments were performed on 19 Beagle dogs of either sex weighing about 10 kg. They were deprived of solid food for 24 hours before experiment, permitted free access to water, and anesthetized with 10 mg/kg of morphine and 1.5 g/kg of urethane given s.c. on the day of the experiment. The subsequent surgical procedures were as reported previously (1). The animals with an acute gastric fistula in the body of the stomach and two ligatures
Duodenal acidification

A duodenal sac was made by ligating the pylorus and the jejunum at 20 cm proximal to the pylorus. Two polyethylene tubes were inserted into the duodenal lumen, one from the pylorus and the other from the jejunum, with their open tips reaching almost completely the opposite ends of the duodenal sac. The duodenal sac was perfused with physiological saline or with canine gastric juice which had been collected beforehand from morphine-urethane anesthetized dogs. The H⁺ concentration of the gastric juice was 153 mEq/l. The perfusion fluids were maintained at 37°C and infused at a rate of 1.5 ml/min.

Determination of gastrin

Blood samples were taken from the leg vein once in the control period and 5, 15, 30, 60 and 90 min after drug administration and bilateral vagotomy. In the case of duodenal acidification, blood samples were taken every 15 min. The serum concentrations of IRG were determined by radioimmunoassay as described by Yalow and Berson (3). Antisera to gastrin were produced in rabbits by immunization with synthetic human gastrin I (SHG: 1-17) conjugated to bovine serum albumin. ¹²⁵I-SHG (specific activity; approx. 600 mCi/mg) was obtained from Dainabott Radioisotope Lab., Japan. Separation of the antibody-bound ¹²⁵I-SHG was achieved using activated Amberlite IRG-58 (100 to 400 mesh; Organo, Japan). SHG was used as the standard gastrin. Procedures of this radioimmunoassay system were as reported previously (4).

Drugs

The following drugs were injected intravenously. Atropine sulfate (Merck), hexamethonium bromide (Methobromin, Yamanouchi) and secretin (Eisai). Prostaglandin E₁ was a gift from Upjohn Research Laboratories, U.S.A. Prostaglandin E₁ was dissolved in a minute volume of ethanol and diluted with 0.9% saline to the appropriate concentration. The other drugs were dissolved in 0.9% saline.

RESULTS

Relationship between serum gastrin level and gastric secretion

The dogs anesthetized with morphine and urethane secreted a considerable amount of gastric juice, and the secretion rate was rather constant throughout the experiment. Blood samples were obtained from each of the 19 dogs during the control observation period (at least 2 hours after operation) to determine serum IRG concentrations. Gastric juice was collected for 15 min after blood sampling.

The serum IRG level was plotted against the corresponding gastric secretion in each dog (Fig. 1). There was a significant linear correlation between the gastric secretion and serum IRG level (r=0.603).
Effect of drugs, vagotomy and duodenal acidification on serum gastrin level and gastric secretion

(i) Drugs

Atropine in intravenous doses of 1 to 16 μg/kg reduced both the serum IRG level and gastric secretion. The serum IRG level decreased to approx. 50% of the control 5 min after injection of 16 μg/kg of atropine, and gradually returned to approx. 74% of the control 2 hours after injection (Fig. 2). The secretion decreased to about 30% of the control in the 15-30 min period, and returned to about 77% of control in the subsequent 90 min.

Hexamethonium in intravenous doses of 0.064 to 1 mg/kg also reduced the serum IRG level and gastric secretion. Though the reduction of the serum IRG level slightly preceded that of gastric secretion, both reductions were quite parallel after the dose of 1 mg/kg of hexamethonium.

Secretin (2-8 U/kg i.v.) reduced gastric secretion dose-dependently and was similar to the reduction in serum IRG level. After an injection of 4 U/kg of secretin, gastric secretion dropped to approximately 20% of the control in the 15-30 min period and recovered to approx. 80% of the control 90 min after dosing (Fig. 3). The reductions in gastric secretion and serum IRG level were roughly in parallel. The serum IRG level decreased to approx. 40% of the control 15 min after injection of 4 U/kg of secretin, and recovered to approx. 90% of the control in the subsequent 45 min.

Prostaglandin E₁ (2-8 μg/kg i.v.) reduced gastric secretion in a dose-dependent manner.
without any reduction in serum IRG level. After a dose of 8 \( \mu g/kg \) of the drug, gastric secretion fell sharply and recovered gradually, whereas the serum IRG level was little affected in the first 45 min and increased with the recovery of gastric secretion.

(ii) Vagotomy

The serum IRG level was reduced to approx. 50% of the control 15 min after bilateral vagotomy at the neck and remained at this level (Fig. 4). Gastric secretion was reduced

![Graph showing the effect of bilateral vagotomy on serum gastrin level and gastric secretion in dogs anesthetized with morphine and urethane.](image)

**Fig. 3.** Effect of secretin and prostaglandin E\(_1\) on serum gastrin level and gastric secretion in dogs anesthetized with morphine and urethane.

![Graph showing the effect of bilateral vagotomy on serum gastrin level and gastric secretion in dogs anesthetized with morphine and urethane. The arrow indicates the time of bilateral vagotomy at the neck.](image)

**Fig. 4.** Effect of bilateral vagotomy on serum gastrin level and gastric secretion in dogs anesthetized with morphine and urethane. The arrow indicates the time of bilateral vagotomy at the neck.
FIG. 5. Effect of duodenal acidification on serum gastrin level and gastric secretion in dogs anesthetized with morphine and urethane. The duodenum was perfused with saline for the first three 15-min periods, with canine gastric juice for the subsequent four 15-min periods, and with saline for the last four 15-min periods.

(iii) Duodenal acidification

Gastric secretion was reduced to approx. 30% of the control during the perfusion of the duodenum with canine gastric juice, but reverted to the control level when the gastric juice was replaced with saline (Fig. 5). As in the case of prostaglandin E1 injection, the serum IRG level was minimally changed when gastric secretion was maximally reduced, and increased with the recovery of gastric secretion.

DISCUSSION

It has been shown that unanesthetized dogs, unlike rats, secrete minimum basal acid, and dogs anesthetized with chloralose and urethane do not secrete measurable amounts of gastric juice (1). In the present study, dogs anesthetized with morphine and urethane continuously secreted large amounts of gastric juice. The amount of gastric juice positively correlated with serum IRG level. In addition, the almost equal inhibitory effect of vagotomy on gastric secretion and serum IRG level suggests that vagally released gastrin is important for the secretagogue effect of morphine. This suggestion is supported by the parallel reduction of the secretion volume and serum IRG level after dosing with hexamethonium and atropine. Vagal gastrin release has been well elucidated (5, 6).

The residual secretion and serum IRG level even after vagotomy in the present study suggest a non-vagal gastrin release. Non-vagal gastrin release after peptone meal has been demonstrated by Konturek et al. (7). Furthermore, Lanciault et al. (8) demonstrated a clear correlation between serum gastrin levels and gastric secretion in vagotomized dogs under morphine-chloralose anesthesia. Both the vagal and non-vagal gastrin releases may participate in the morphine-induced secretion.
Duodenal acidification reduced morphine-induced secretion without reducing serum IRG levels. Secretin reduced serum IRG level as well as gastric secretion, and such is in agreement with observations in humans (9) and in Heidenhain pouch dogs (4). These results favor the view that substances other than secretin may participate in the feed-back inhibition of gastric secretion by duodenal acidification. There is in fact evidence which suggests release of an unidentified substance after duodenal acidification (10).

On the other hand, prostaglandin $E_1$ inhibited gastric secretion without reducing serum IRG levels. Prostaglandins are known to be distributed in the gastric mucosa (11). Furthermore, a supramaximal dose of pentagastrin increased the concentration of prostaglandins in the gastric juice, but reduced gastric secretion (12). These results suggest the possibility that prostaglandins may participate in the inhibition of gastric secretion by acting directly on the parietal cells.

REFERENCES