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Inhibitory and stimulatory effects of secretin on gastric secretion in conscious rats

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Summary

1. The effect of pure secretin on gastrin-induced secretion has been studied in conscious rats with Pavlov or Heidenhain pouches.

2. Rapid intravenous injection of secretin did not inhibit a plateau secretion of acid in the Heidenhain pouch, but infusion of the same amount of secretin over two hours inhibited secretion in both Heidenhain and Pavlov pouches.

3. A rapid intravenous injection of secretin before the onset of gastrin infusion enhanced the acid secretory response to gastrin in both types of pouches.

4. Secretin stimulated pepsin secretion.

Introduction

Following a report by Greenlee, Longhi, Guerrero, Nelsen, El-Bedri & Dragstedt (1957), studies on pure secretin have mainly been concerned with its inhibitory effect on gastric acid secretion. It is now usually accepted that gastrin-induced acid secretion is readily inhibited by secretin, at least in the dog, but that stimulation induced by histamine or cholinergic agents is not inhibited or much less so (for references, see Johnson & Grossman, 1971).

Using rats provided with a gastric fistula, Tumpson & Johnson (1969) reported that secretin completely inhibited pentagastrin-induced acid secretion, but had no effect on histamine-stimulated acid secretion (Johnson & Tumpson, 1970). Since it has been shown that this stomach preparation might be unreliable for quantitative studies of gastric secretion (Svensson, 1970; Borella & Herr, 1971), we have studied the effects of secretin using innervated and denervated stomach pouch preparations in the conscious rat. In this study particular attention has been given to the pattern of administration of secretin.

Pratt (1940) reported that secretin, injected intravenously, increased the concentration of pepsin in histamine-stimulated cat gastric juice and this has been confirmed by Blair (1966) and Magee & Nakajima (1968). These observations have been extended to the rat in the present study.

Methods

Female rats of the Sprague-Dawley strain, fed on a pellet diet, were provided with a Pavlov pouch as described by Svensson (1970) or a Heidenhain pouch by the method of Alphin & Lin (1959). Four weeks were allowed for recovery from surgery before experiments were begun. Before an experiment the rats were fasted

for 16 h and during an experiment they were kept in a restraining cage of the Bollman type. Gastric juice was collected in consecutive 30 min samples by perfusing the pouches, through a two-way plug, with saline at a rate of 3·5 ml/hour. The amount of acid secreted was determined by titration against 0·1 N NaOH with phenol red as an indicator. The pepsin output was measured by a modification of the method of Hunt (1948). The amount of hydrochloric acid is expressed in μequiv/30 min and pepsin output in μg/30 min, referring to the corresponding activity of a commercial crystalline preparation of pepsin (lot 95B-1270, Sigma Chemical Co.) as proposed by Bitsch (1966). Throughout an experiment, a constant infusion of 0·9% NaCl into a catheter inserted in a tail or neck vein was maintained by a motor-driven syringe. First, the interdigestive secretion was collected for two hours. Hog gastrin II (donated by Professor Gregory, Liverpool) was then added to the infusion fluid to provide a dose of 0·08 μg/h with Pavlov pouches and 0·3 μg/h with Heidenhain pouches. These doses have been shown to elicit about 50% of the maximal secretion obtainable with intravenous gastrin (Svensson, 1970). Secretin (donated by Professor Jorpes, Stockholm), in a dose of 75 units/kg, was injected rapidly either 30 min before or two hours after the start of gastrin infusion. In another series of experiments 75 units/kg of secretin was constantly infused during two hours. Experiments with administration of secretin were systematically interspersed with control tests with infusion of gastrin alone.

Results

Effect of a single injection of secretin on gastrin-induced secretion

In six rats with Heidenhain pouches a plateau secretion of acid and pepsin was established by infusing gastrin at a dose of 0·3 μg/hour. As a result, acid secretion increased from 1–2 μequiv/30 min to a plateau level of about 55–60 μequiv/30 minutes. Pepsin secretion, after an initial peak, increased from 70–80 μg/30 min to about 140–150 μg/30 minutes. Secretin, 75 units/kg, injected two hours after the start of gastrin infusion, more than doubled the secretion of pepsin for one hour. The plateau level of acid secretion was not affected. These results are illustrated in Figs. 1a and 1b.

Effect of a constant infusion of secretin on gastrin-induced secretion in Pavlov and Heidenhain pouches

In another series of experiments the effect of a constant infusion of secretin was established in innervated and denervated pouches. In the rat, as in other species studied, the Pavlov pouch is more sensitive to gastrin than the Heidenhain pouch. In order to obtain about the same degree of background stimulation, different doses of gastrin had to be used in the two stomach preparations. In rats with a Pavlov pouch, gastrin II (0·08 μg/h) was infused for 6 hours. A plateau secretion of acid was obtained with a tendency to increase at the final periods of infusion. Pepsin output was not increased on infusing gastrin. Secretin (75 units/kg), infused during 2 h, starting 2 h after the beginning of gastrin infusion, inhibited acid secretion from a plateau level of about 40–45 μequiv/30 min to 25 μequiv/30 minutes. The inhibition was significant for 30 min only (Fig. 2a). Pepsin secretion rose for 1·5 h and appeared after a latency of 30 min (Fig. 2b).

In five Heidenhain pouches investigated, infusion of secretin (75 units/kg) during two hours, inhibited significantly a plateau secretion of acid, maintained by gastrin II (0·3 μg/h), from about 90 μequiv/30 min to about 30 μequiv/30 minutes. In this group of Heidenhain pouches the plateau secretion of acid was higher than in the group referred to above, which may be due to the steep dose-response curve to gastrin in Heidenhain pouches, as described by Svensson (1970). As in the Pavlov pouch, on infusing secretin, pepsin secretion increased for 1·5 h after a latent period of 30 min (Fig. 3a and b).

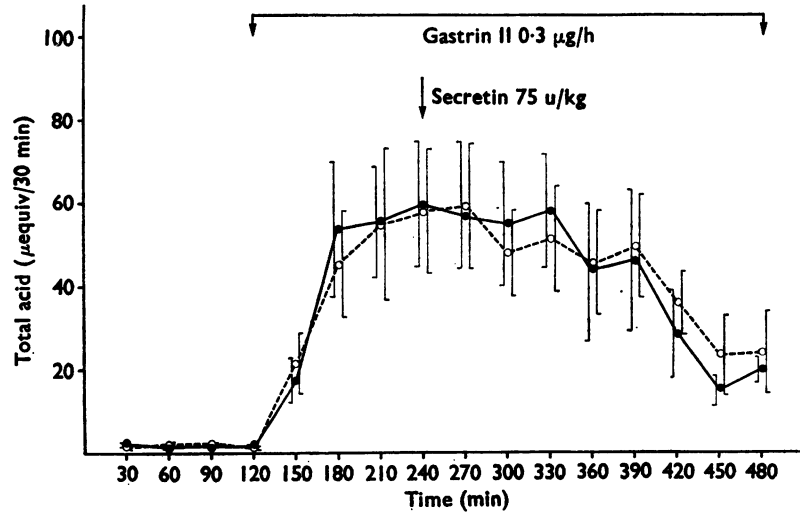

Fig. 1a

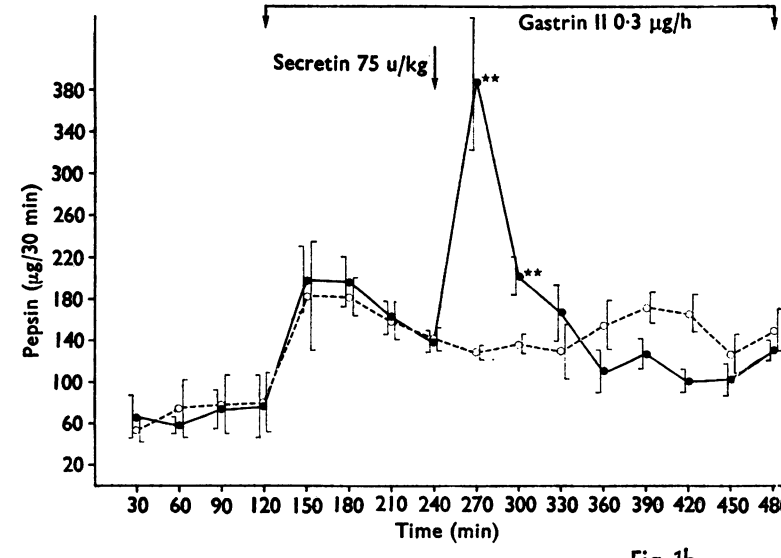

Fig. 1b

FIG. 1a and b. Effects of an intravenous injection of secretin, 75 units/kg, on acid and pepsin secretion maintained by gastrin, 0·3 μg/h intravenously, in six Heidenhain pouches. Each point represents the mean of at least one determination in each rat and the vertical bars represent the S.E. of the mean. The dashed line (○- - -○) indicates control experiments and the continuous line (●——●) experiments with secretin. Asterisks represent the degree of significance of the differences between control experiments and experiments with secretin.

Effect of secretin when injected before the onset of gastrin infusion in Pavlov and Heidenhain pouches

In a third series of experiments, secretin (75 units/kg) was injected 30 min before the onset of gastrin infusion. The ensuing alterations in acid and pepsin secretory responses were measured in Pavlov and Heidenhain pouches. In both types of pouch higher rates of acid secretion were noted, especially during the first period of gastrin infusion. Pepsin secretion was also greater in both types of

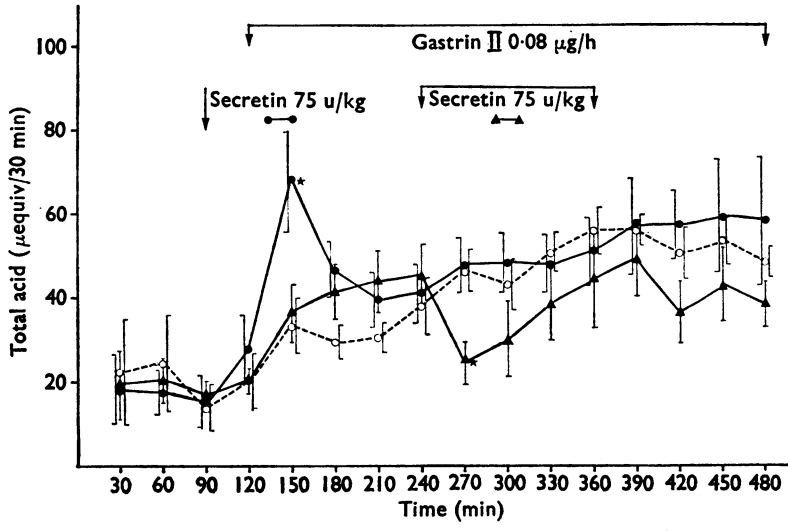

Fig. 2a

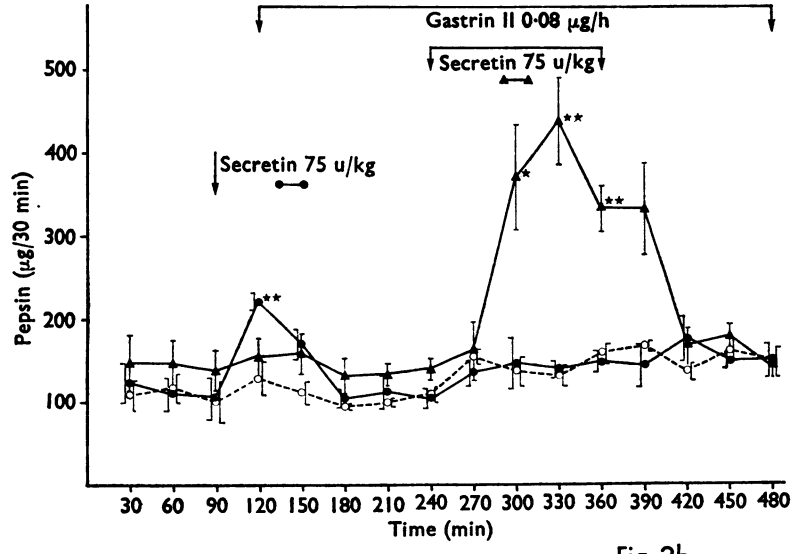

Fig. 2b

FIG. 2a and b. Effects of an intravenous injection of secretin, 75 units/kg (●——●), or an intravenous infusion of secretin, 75 units/kg for two hours (▲——▲), on acid and pepsin secretion maintained by gastrin 0·08 µg/h in four Pavlov pouches. Each point represents the mean of four to nine determinations. The dashed line (○- - -○) indicates control experiments. Asterisks as in Fig. 1.

pouch following pre-treatment with secretin. In the denervated pouch the increase in pepsin output was larger than in the innervated pouch (Figs. 2a and b, 3a and b).

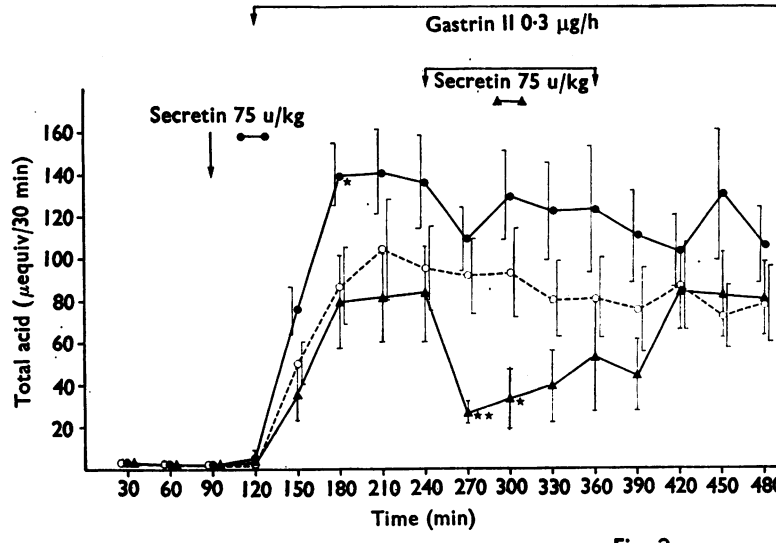

Fig. 3a

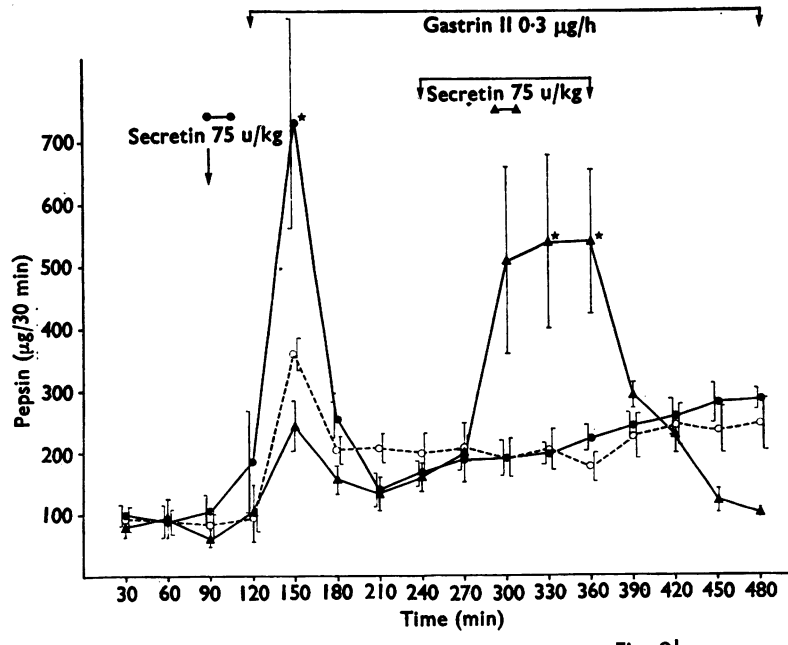

Fig. 3b

FIG. 3a and b. Effects of an intravenous injection of secretin, 75 units/kg (●——●), or an intravenous infusion of secretin, 75 units/kg for two hours (▲——▲), on acid and pepsin secretion maintained by gastrin, 0·3 µg/h, in five Heidenhain pouches. Each point represents the mean of five determinations. The dashed line (○- - -○) indicates control experiments. Asterisks as in Fig. 1.

Discussion

In this laboratory it has been shown that rats, provided with Pavlov or Heidenhain pouches, are extremely useful for studies on stimulation and inhibition of gastric secretion (Svensson, 1970; Johansson, Lundell & Svensson, 1971).

Little is known of natural inhibitory influences on gastric secretion in rats. Diminished release of antral gastrin has been revealed as an inhibitory factor when the stomach was perfused with dilute hydrochloric acid (Rosengren & Svensson, 1969), but the inhibitory effect of acid in the duodenum has still to be established (Brodie, 1966; Lee & Thompson, 1967).

In the present study secretin, under certain circumstances, inhibited gastrin-induced secretion. When secretin was infused during continuous gastrin administration, acid secretion was inhibited in both innervated and denervated pouches. By contrast, a rapid injection of secretin failed to inhibit submaximal gastrin-stimulated secretion of acid, whereas that of pepsin was stimulated. The reason for this is obscure but the action of secretin on acid secretion is perhaps dual in nature inhibitory and stimulatory, depending on circumstances.

The complexity of the action of secretin is shown by our observation that secretin, when administrated before the onset of gastrin infusion, enhanced the secretory effect of gastrin.

Alterations in pepsin secretion produced by secretin are more uniform in pattern. Secretin, injected or infused, at every stage of the tests and with the doses employed, stimulated pepsin secretion. Whether this effect would also be obtained with endogenously-released amounts of secretin is not yet known. It is interesting to note, however, that no increase in pepsin secretion was observed in the Pavlov pouch on infusing gastrin, as would be expected if the duodenum was sufficiently acidified by acid secretion from the main stomach.

The differences between our findings using rats with stomach pouches and those reported by others (Tumpson & Johnson, 1969; Chey, Sivasomboon, Hendricks & Lorber, 1970) using rats with stomach fistulae emphasizes the importance of methodology in gastroenterological studies.

We are indebted to Professor R. A. Gregory and Professor Erik Jorpes for generous gifts of gastrin II and secretin and to Professor Georg Kahlson for his stimulating interest in this work, which was supported by grants from the Medical faculty of the University of Lund and from Albert Pålsson's Foundation.

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