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IMPLICATION OF GASTRIC MUCOSAL HISTAMINE IN INHIBITION BY ISOPRENALINE OF PENTAGASTRIN-INDUCED GASTRIC SECRETION

L. LUNDELL & S.E. SVENSSON
Institute of Physiology, University of Lund, Sweden

1 The effect of isoprenaline on pentagastrin-induced gastric secretion was studied in conscious rats with Heidenhain pouches. The influence of isoprenaline on pentagastrin-induced release and formation of gastric mucosal histamine was also examined.

2 Isoprenaline strongly inhibited pentagastrin-induced acid secretion, an inhibition which could not be overcome by increasing the dose of pentagastrin.

3 Propranolol blocked the inhibitory effect of isoprenaline on pentagastrin-induced acid secretion.

4 Isoprenaline enhanced pepsin secretion induced by pentagastrin, an effect which was blocked by propranolol.

5 Isoprenaline reduced the increase in formation and release of gastric mucosal histamine following pentagastrin infusion, an inhibitory influence which was almost completely blocked by propranolol.

6 The inhibition by isoprenaline of pentagastrin-induced acid secretion is tentatively related to alterations in gastric mucosal histamine occurring simultaneously.

Introduction

Injection of gastrin evokes two well-known phenomena: mobilization of gastric mucosal histamine and hydrochloric acid secretion. Similar effects on histamine metabolism occur on vagus excitation in the presence of the antrum. Evidence is accumulating to show that the mobilization of preformed mucosal histamine and accelerated synthesis of the amine are functionally linked to the excitation of the parietal cell (for references, see Kahlson, Rosengren & Svensson, 1973).

Isoprenaline has been found to inhibit the release of histamine from sensitized lung tissue (Assem & Schild, 1969, 1971) and inhibit histamine formation in sensitized human leucocytes (Assem & Feigenbaum, 1972). This β-receptor agonist readily inhibits pentagastrin-induced acid secretion in the dog, whereas that produced by histamine is relatively insensitive to isoprenaline (Curwain & Holton, 1972).

In the present study the effect of isoprenaline on pentagastrin-stimulated gastric secretion has been investigated. The results suggest that the inhibition of acid secretion by isoprenaline is accounted for by a β-receptor mediated reduction of histamine mobilization in the mucosa.

Methods

Determination of gastric secretion

Female rats of the Sprague-Dawley strain, weighing about 250 g, and fed on a standard pellet diet, were used. All operations were done under ether anaesthesia. The rats were provided with Heidenhain pouches, by a slight modification of the method of Alphin & Lin (1959). At least one month was allowed for postoperative recovery. Before the actual experiments the rats were fasted for 16 h and during the experiments the rats were kept unanaesthetized in a restraining cage of the Bollman type. Gastric juice was collected in consecutive 30 min samples by the use of a perfusion technique (Svensson, 1970). 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 μEq/30 min and pepsin output in μg/30 min, with the corresponding activity of a commercial crystalline preparation of pepsin (Lot 95 B-1270, Sigma Chemical Co.) used as a standard as proposed by Bitsch (1966). Throughout an

experiment, a constant infusion of 0.9% w/v NaCl solution (saline), into a catheter inserted in a tail vein, was maintained by a motor-driven syringe. After interdigestive secretion had been collected for 1-2 h, drugs were added to the infusate. The following drugs were used: pentagastrin (Peptavlon, ICI, obtained by the courtesy of ICI–Pharma, Sweden), (±)-isoprenaline sulphate and (±)-propranolol hydrochloride (Inderal, ICI). Doses are expressed in terms of the salt.

Determinations of content and formation of mucosal histamine

Observations were made on intact rats fasted for 16 h and treated with intravenous pentagastrin alone or in combination with isoprenaline and propranolol. The animals were killed by a blow on the head and bled by opening the carotid arteries. The region containing parietal cells was removed by scraping with a scalpel after the stomach had been washed with saline and pinned flat. After mincing, the mucosa from one stomach was divided in two portions, one of which was used for determination of histamine content, the other for formation. Histamine content was determined by a modification of the method of Feldberg & Talesnik (1953), which briefly involved the following steps. About 100 mg of mucosa was homogenized in 2 ml 1 N HCl. The pestle was washed with 1 ml 1 N HCl and 2 ml Tyrode solution. After boiling for 30 min and neutralization, the extract was diluted to a given volume, filtered and assayed for histamine on the guinea-pig atropinized isolated ileum. The specificity of the bioassay was ascertained by use of the antagonist mepyramine maleate. The amount of histamine is expressed in terms of the base.

The rate of histamine formation, i.e. histidine decarboxylase activity, was determined by a method originally introduced by Schayer, Davis & Smiley (1955). The *in vitro* method, as employed in the present work, has been described in detail by Kahlson, Rosengren & Thunberg (1963). This involved incubation of minced mucosal tissue for 3 h at 37° C under nitrogen in beakers containing about 100 mg of tissue, 40 μg of 2-ring-^{14}C-labelled L-histidine (base), 10^{-4} M aminoguanidine sulphate, 10^{-1} M sodium phosphate buffer, pH 7.4 and 0.2% glucose, all made up to a final volume of 3.0 ml. At the end of incubation, carrier histamine and perchloric acid were added. After filtration, radioactive histidine was separated from radioactive histamine on an ion exchange resin, and after conversion of the histamine to pipsyl histamine the radioactivity of formed histamine was determined at infinite thickness in a flow counter. With the [^{14}C]-histidine and measuring equipment used, 1 μg [^{14}C]-histamine formed corresponded to 5,000 ct/minute. Values are expressed as μg of [^{14}C]-histamine formed per g tissue in 3 hours.

Results

The effect of isoprenaline on pentagastrin-induced secretion

In 6 rats with Heidenhain pouches the effect of isoprenaline (20 $\mu g\ kg^{-1}\ h^{-1}$) on pentagastrin-induced (0.25 μg/h) acid and pepsin secretion was studied. Pentagastrin infusion was followed by a substantial increase in acid secretion attaining about 20 μEq/30 min after 2 h of infusion. Isoprenaline infusion given 30 min before and maintained during pentagastrin infusion, inhibited acid secretion by about 60% maximally (Figure 1a). In contrast the stimulatory effect of pentagastrin on the pepsin secreting cells was augmented by isoprenaline infusion (Figure 1b).

When the dose of pentagastrin was increased to 16 μg/h an acid secretory response was induced with a peak at 1 h of 88.1 ± 8.53 (s.e. mean) μEq/30 min after which the secretory response faded. Isoprenaline (40 $\mu g\ kg^{-1}\ h^{-1}$) reduced the secretory response to this high dose of pentagastrin (Figure 2), much less than to the lower dose (Figure 1a). The inhibition was significant during the last two 30 min periods ($P < 0.01$).

Observations during β-receptor blockade with propranolol

The mode of action of isoprenaline on pentagastrin-induced secretion could involve a β-receptor if the effect was blocked by an appropriate antagonist, e.g. propranolol. Isoprenaline and pentagastrin were given as described above. Injections of propranolol (2 mg/kg) 10 min before and 50 min after the start of isoprenaline infusion (Fig. 3a), partially reversed the inhibitory effect of isoprenaline (20 $\mu g\ kg^{-1}\ h^{-1}$) on pentagastrin (0.25 μg/h)-induced acid secretion as described above in Figure 1a. During the last 30 min period acid secretion fell, a fact which might be due to inadequate β-receptor blockade. Propranolol injected 10 min before and 50 min after the start of pentagastrin infusion augmented the acid secretion ensuing on infusion of pentagastrin alone (Figure 3a). The inhibition by isoprenaline (40 $\mu g\ kg^{-1}\ h^{-1}$) of pentagastrin (16 μg/h)-induced acid secretion was completely blocked by propranolol on injecting the β-receptor

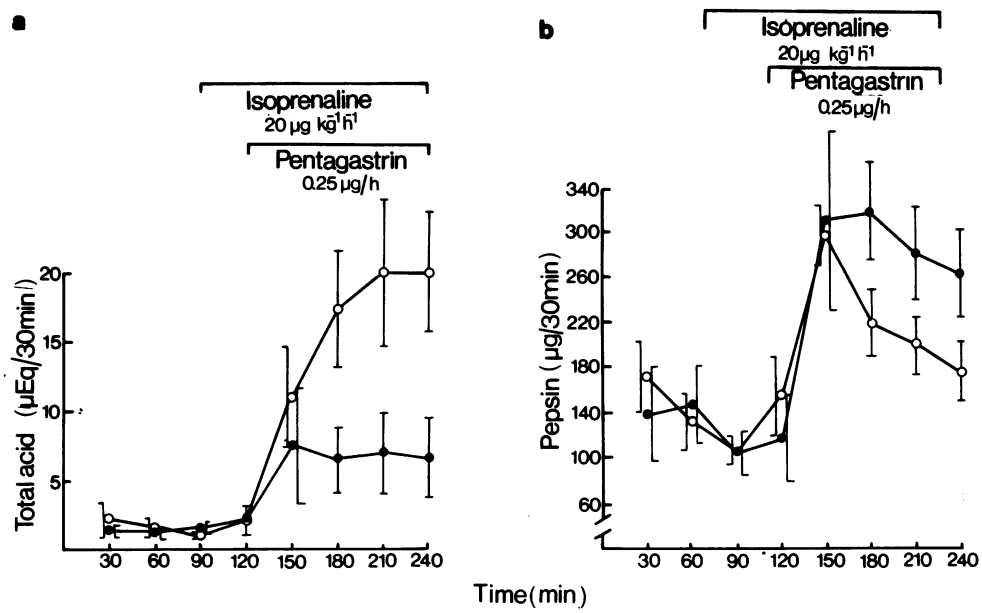
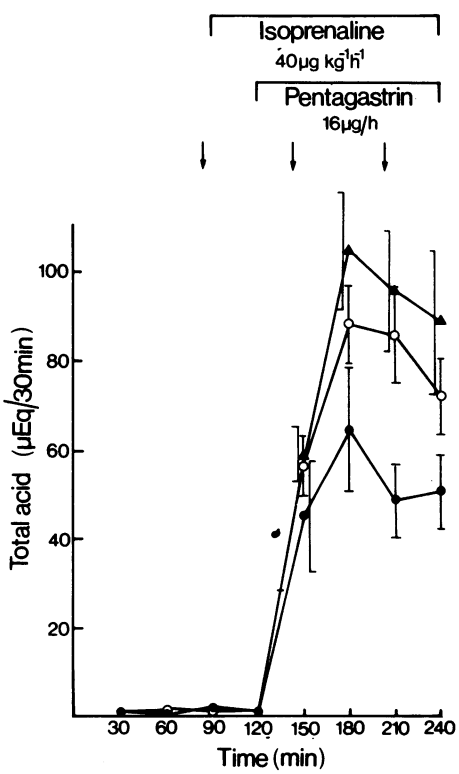


Fig. 1 Effects on (a) acid and (b) pepsin secretion produced by i.v. infusion of (○) pentagastrin (0.25 μg/h); and of (●) pentagastrin plus isoprenaline (20 μg/kg^{-1} h^{-1}). Each point represents the mean of one determination in each of six rats. The vertical bars represent the s.e. mean.



antagonist three times at hourly intervals (Figure 2).

The stimulatory effect of isoprenaline on pepsin secretion (20 μg kg^{-1} h^{-1}) was inhibited by propranolol. Propranolol itself slightly reduced stimulation of pepsin secretion induced by pentagastrin (0.25 μg/h) (Figure 3b).

Inhibition of the mobilization of mucosal histamine by isoprenaline

The marked inhibition of pentagastrin-induced acid secretion by isoprenaline may be due to reduced mobilization of gastric mucosal histamine. Isoprenaline (40 μg kg^{-1} h^{-1}) was infused starting 30 min before and maintained during pentagastrin infusion (0.25 μg/h) after which the gastric mucosa was assayed for histamine formation and content 1, 2.5 and 5 h after the start of

Fig. 2 Effects on acid secretion produced by i.v. administration of (○) pentagastrin (16 μg/h); (●) pentagastrin plus isoprenaline (40 μg kg^{-1} h^{-1}); and (▲) pentagastrin plus isoprenaline and propranolol. Propranolol (2 mg/kg) was given i.v. as indicated by the arrows. Each point represents the mean of one determination in each of seven rats. The vertical bars represent the s.e. mean.

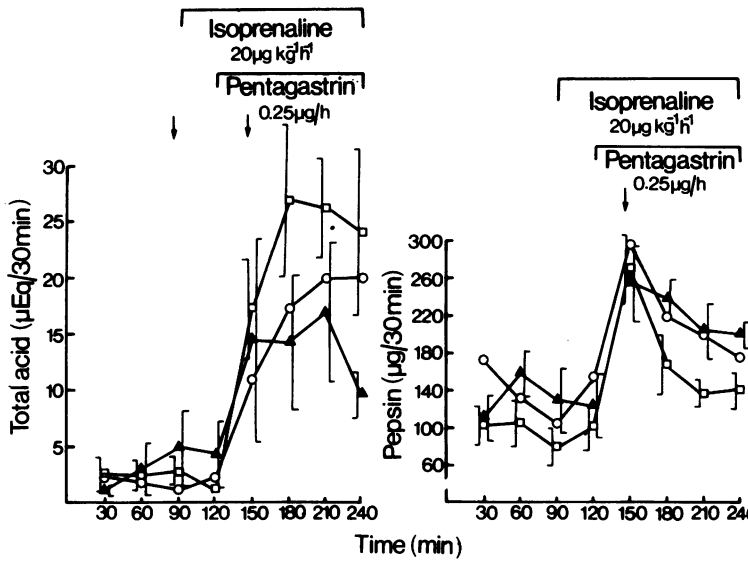


Fig. 3 Secretion of (a) acid and (b) pepsin in response to i.v. administration of (○) pentagastrin (0.25 μg/h); (▲) pentagastrin plus isoprenaline (20 μg kg^{-1} h^{-1}) and propranolol; and (□) pentagastrin plus propranolol. Propranolol (2 mg/kg) was given i.v. as indicated by the arrows. Each point represents the mean of one determination in each of six rats. The vertical bars represent the s.e. mean.

pentagastrin infusion. Isoprenaline reduced the rate of histamine formation at all time intervals (Figure 4a). The inhibition diminished in the course of combined infusion of pentagastrin and isoprenaline.

The mucosal histamine content as determined at 1 and 2.5 h was not significantly different in rats treated with pentagastrin alone or in combination with isoprenaline. At 5 h, however, the gastric mucosal histamine content was significantly higher in the rats receiving isoprenaline ($P < 0.05$) (Figure 4b).

Histamine formation and content during β-receptor blockade

In these experiments two dose levels of pentagastrin were used, 0.25 μg/h and 16 μg/hour. The smaller dose of pentagastrin increased the rate

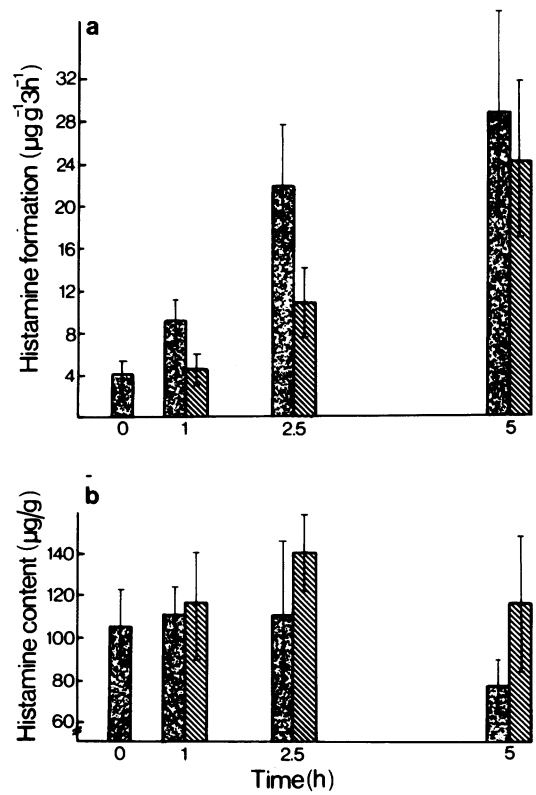


Fig. 4 (a) Histamine formation (μg g^{-1} 3 h^{-1}) and (b) content (μg/g) of the gastric mucosa at different times after the start of pentagastrin infusion alone (0.25 μg/h, stippled columns) or in combination with isoprenaline (40 μg kg^{-1} h^{-1}, hatched columns). Nil indicates interdigestive state. Each column represents the mean of determinations from at least six rats. The s.d. is also given.

Table 1 Histamine formation ($\mu g\ g^{-1}\ 3\ h^{-1}$) and content ($\mu g/g$) after 2 h of i.v. infusion of pentagastrin alone and in combination with isoprenaline, isoprenaline plus propranolol or propranolol.

	PG (0.25 μg/h)	*PG + ISO*	*PG + ISO + PROP*	*PG + PROP*
Histamine formation	15.7 ± 3.81 (10)	9.7 ± 2.38 (10)	12.4 ± 3.82 (5)	15.5 ± 5.76 (6)
Histamine content	88.1 ± 19.58 (10)	114.8 ± 22.33 (10)	100.3 ± 17.02 (5)	83.4 ± 21.01 (6)
	PG (16 μg/h)			
Histamine formation	23.5 ± 3.28 (6)	16.2 ± 3.41 (6)	25.5 ± 3.97 (6)	–
Histamine content	26.2 ± 7.22 (6)	61.8 ± 12.07 (6)	35.8 ± 4.01 (6)	–

Isoprenaline infusion started 30 min before addition of pentagastrin to the infusate. Propranolol was injected 10 min before the start of isoprenaline or pentagastrin infusion and the injection was subsequently repeated at hourly intervals. In each group the mean and s.d. are given, (*n*) indicates number of rats in each group. PG, pentagastrin; ISO, isoprenaline (40 $\mu g\ kg^{-1}\ h^{-1}$); PROP, propranolol (2 mg/kg).

of histamine formation, while the larger dose also mobilized preformed histamine to a large extent. With both doses of pentagastrin, the reduction produced by isoprenaline of pentagastrin-induced changes in the rate of mucosal histamine formation was blocked by propranolol. Propranolol itself did not augment the enzymatic response to pentagastrin (0.25 μg/h) alone (Table 1), a fact that is not helpful in explaining the observation that pentagastrin and propranolol combined are more active than pentagastrin alone.

The lower dose of pentagastrin in combination with isoprenaline and/or propranolol did not markedly alter mucosal histamine content in comparison with the effect of pentagastrin alone. The larger dose of pentagastrin (16 μg/h) lowered gastric mucosal histamine content to 26.2 ± 7.22 (s.d.) μg/gram. Isoprenaline lessened the reduction in histamine content caused by pentagastrin, resulting in a histamine content of 61.8 ± 12.07 (s.d.) μg/gram. This effect of isoprenaline was almost completely blocked by propranolol. During β-receptor blockade, isoprenaline did not affect the increase in the rate of histamine formation in response to this dose of pentagastrin. These results are summarized in Table 1.

Discussion

The present observations concern the problem of inhibiting the mobilization of gastric mucosal histamine as a possible way of inhibiting gastric secretion. Kahlson, Rosengren, Svahn & Thunberg (1964) inhibited histidine decarboxylase actity by subjecting rats to semicarbazide superimposed on a pyridoxine-deficient diet without being able to demonstrate any inhibition of gastric secretion. These experiments have been repeated by other workers using other inhibitors of histidine decarboxylase (Levine, 1965; Thayer & Martin, 1967; Lloyd Fletcher, Pitts, Everett & Griffith, 1969) or inhibitors of protein synthesis (Yeh & Shils, 1969; Henman, 1972) since it is known that gastrin-induced increase in histidine decarboxylase activity depends on intact protein synthesis (Snyder & Epps, 1968). Experiments so far with enzyme inhibition have not elucidated this problem.

Agonists of β-receptors have been reported to inhibit histamine release from sensitized lung tissue (Assem & Schild, 1969, 1971) and reduce the rate of histamine formation in sensitized human leucocytes (Assem & Feigenbaum, 1972).

In the present study, we have shown that the β-receptor agonist isoprenaline did reduce the increase in histidine decarboxylase activity following pentagastrin infusion. With pentagastrin (0.25 μg/h) the inhibition declined from about 50% at 1 and 2.5 h to virtually zero at 5 h; the decline may be accounted for by an increased endogenous plasma gastrin concentration due to inhibited acid secretion and from direct stimulation of gastrin secretion by the β-receptor agonist (compare Hayes, Ardill, Kennedy, Shanks & Buchanan, 1972 and Stadil & Rehfeld, 1973). Nevertheless, isoprenaline strongly inhibited the rise in enzyme activity induced by infusion of pentagastrin, 16 μ/hour. It has been proposed that the mucosal histidine decarboxylase activity is controlled by a feed-back mechanism working in both directions, since lowering of histamine content on gastrin injection precedes the increase in enzyme activity and injection of histamine restrains the enzymatic response to gastrin (Kahlson *et al.*, 1964; Johansson, Lundell, Rosengren & Svensson, 1972). With pentagastrin (0.25 μg/h) small changes in histamine content take place. In combination with isoprenaline higher values of histamine content were noted. Pentagastrin, 16 μg/h lowered the gastric mucosal histamine content, an effect which is partly

prevented by isoprenaline. At present it is uncertain whether the primary effect of isoprenaline is on histamine content or on enzyme activity.

The effect of adrenoceptor stimulation on gastric secretion is complex because of circulatory side-effects which might be adverse to gastric secretory responses. This topic has recently been reviewed by Holton (1973). Isoprenaline in the doses employed in the present study did not affect arterial blood pressure (unpublished observations of this laboratory) and probably increased mucosal blood flow as has been described in dogs (Jacobson, Linford & Grossman, 1966; Curwain & Holton, 1972). We have shown that isoprenaline inhibited acid secretion in response to an infusion of pentagastrin which is in accord with results obtained by Bass & Patterson (1967) in the pylorus-ligated rat stomach preparation and the reduction of interdigestive secretion, demonstrated by Misher, Pendleton & Staples (1969) in rats with gastric fistulae. It would appear that a β-receptor is involved since the inhibitory action of isoprenaline was blocked by propranolol. This finding differs from the results obtained by Curwain & Holton (1972) who recorded a potent inhibitory action of isoprenaline on pentagastrin-induced acid secretion in dogs subjected to effective cardiac β-receptor blockade. In the present study it was necessary to administer propranolol repeatedly in order to maintain effective β-receptor blockade probably due to the reported short half-life of propranolol in rats (Faulkner, Hopkins, Boerth, Young, Jellett, Nies, Bender & Shand, 1973). Propranolol alone enhanced the acid secretory effect of pentagastrin in rats as in dogs (Evans & Lin, 1970; Lin & Evans, 1973; Curwain, Holton & Spencer, 1973) and man (Konturek & Oleksy, 1969). The augmentation of acid secretion by propranolol itself invalidates the suggestion that the inhibitory effect of isoprenaline may be mediated by β-receptor activation. However, the effect of propranolol alone might possibly be explained by its counteraction of the effects of circulating catecholamines.

As to pepsin secretion we have earlier shown that denervation of the peptic cells renders them more sensitive to stimulation by gastrin or histamine (Svensson, 1970; Johansson *et al.*, 1972). Isoprenaline enhanced stimulation of pepsin secretion by pentagastrin in the Heidenhain pouch, which seemed to be mediated by β-receptor stimulation, since it was blocked by propranolol, an effect also reported to occur in dogs (Grechishkin, 1970).

It seems tempting to connect the reduction caused by isoprenaline in gastric mucosal histamine mobilization with the diminished acid secretion in response to pentagastrin. The β-receptor agonists and antagonists would thus appear to provide new approaches to the study of the relationship between gastric mucosal histamine and the excitation of the parietal cell.

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