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The inhibitory action of 5-hydroxytryptamine on gastric secretory function in rats

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1 The inhibitory action of 5-hydroxytryptamine (5-HT) on gastric function was studied in vagotomized rats.

2 5-HT (0.6, 1 or 5 mg kg^{-1}, s.c.) dose-dependently reduced gastric acid secretion evoked by histamine, pentagastrin or methacholine. Pepsin secretion induced by pentagastrin or methacholine was also depressed by 5-HT.

3 Basal secretion of both acid and pepsin was not significantly affected by any of the three 5-HT doses.

4 Indomethacin pretreatment, which significantly decreased gastric mucosal prostaglandin E_2 content, did not modify the inhibitory effects of 5-HT on histamine-induced acid secretion, nor did phentolamine or propranolol.

5 This study suggests that 5-HT inhibits gastric secretory function through mechanisms other than by sympathetic influence or increased prostaglandin synthesis. The inhibitory action appears not to be vagus-dependent. Other mechanisms of action are discussed.

Introduction

Endogenous 5-hydroxytryptamine (5-HT), located largely in the proximal part of duodenum, has been reported to play a physiological role in the control of gastric acid secretion in dogs (Jaffe *et al.*, 1977); the inhibitory action which the amine exerts is thought to be partly mediated via the vagus. Black *et al.* (1958) have further demonstrated that 5-HT is a strong inhibitor of histamine-induced gastric acid secretion. In studies on man, Resnick *et al.* (1962) found that 5-HT antagonists enhanced both basal and histamine-evoked gastric acid secretion, whereas a 5-HT precursor antagonized the stimulant effects of histamine. However, little is known about the mechanism of the inhibitory action of 5-HT, including its influence on acid and pepsin secretion in the stomach.

The present study employs an *ex vivo* stomach chamber preparation to study the pharmacological actions of 5-HT on gastric secretory function in rats.

Methods

General

Male Sprague-Dawley rats weighing 300–350 g were used. They were fed normal pellet chow (Ralston Purina Company) and given tap water to drink. Each experimental group comprised at least 6 randomly allocated rats. Animals were fasted for 24 h before use, but were allowed tap water *ad libitum*. They were anaesthetized with sodium pentobarbitone (40 mg kg^{-1}, i.p.) just before experimentation.

Preparation of ex vivo *stomach chamber for gastric secretion studies*

A plexiglass chamber was used for collecting gastric secretion from a stomach placed *ex vivo* in the apparatus (Himal *et al.*, 1975). This chamber consisted of a plexiglass ring 0.4 cm thick (inner diameter 3 cm and outer diameter 4 cm) placed on a plexiglass platform with an oval central aperture 2 cm long and 1 cm wide. The stomach was exposed through a ventral midline abdominal incision. The pylorus and the cardiac end of the oesophagus were ligated, following which the oesophagus was severed proximal to the ligation. The vagotomized stomach was then drawn up through the aperture in the platform placed immediately above the animal, opened along the greater curvature and the stomach wall spread out, radiating from the centre of the platform, with the mucosal surface uppermost. A plexiglass ring was placed over the periphery of the opened stomach, after ensuring that the platform aperture was in its centre;

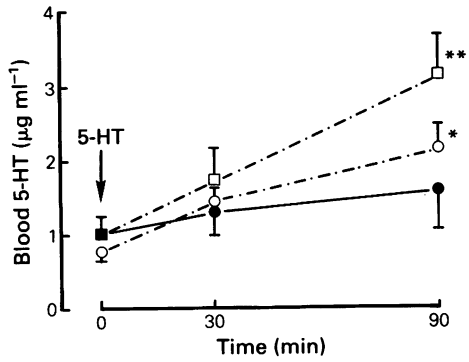

Figure 1 Effects of s.c. injection of 5-hydroxytryptamine (5-HT, ● = 0.6, ○ = 1 and □ = 5 mg kg^{-1}) on arterial blood 5-HT levels. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P < 0.05$, **$P < 0.01$ when compared with its own basal blood level at 0 min.

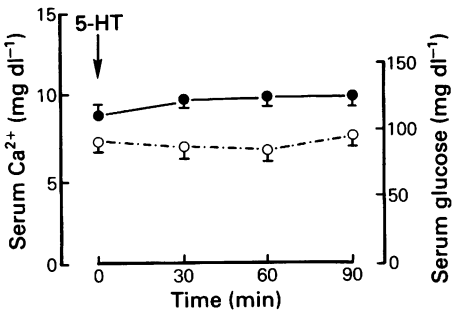

Figure 2 Effects of 5-hydroxytryptamine (5-HT, 5 mg kg^{-1}, s.c.) on serum calcium (●) and glucose (○) level changes. Each symbol indicates the mean of 7 rats; vertical lines represent s.e.mean.

the ring was then secured to the platform by 3 winged nuts. The exposed area of gastric mucosa, bounded by the inner wall of the plexiglass ring, was 9.4 cm^2; this chamber was filled with 1.5 ml distilled water which was removed (gastric collection), and immediately replaced with a similar volume of distilled water, at 15 min intervals. On completion of the *ex vivo* stomach preparation, the first group of experiments was begun by injecting 5-HT 0.6, 1 or 5 mg kg^{-1}, s.c. at − 15 min. After two 15 min gastric collections (at 15 min), histamine 10 mg kg^{-1}, pentagastrin 50 μg kg^{-1} or methacholine 1 mg kg^{-1} was injected s.c. Gastric collections, at 15 min intervals, were continued for 1 h. The acid content of the gastric solutions was determined by titration with 0.001 N NaOH to pH 7.4 with a pH meter. Pepsin activity was measured by the method of Berstad (1975). Acid or pepsin output was expressed as μEq H^+ or μg, respectively, produced in 15 min by 4 cm^2 of gastric mucosal area forming the base of the chamber.

In the second set of experiments, each animal was given indomethacin (5 or 10 mg kg^{-1}, s.c.) 60 min before 5-HT (5 mg kg^{-1}, s.c.); the latter was followed 30 min later by histamine (10 mg kg^{-1}, s.c.). Gastric secretion was collected after 5-HT administration, according to the collection schedule described for the first set of experiments.

In the third set of experiments, 0.9% NaCl w/v solution (saline) was infused into the jugular vein (at − 15 min) for the first 15 min; this was replaced (at 0 min) by i.v. histamine (5 mg kg^{-1} h^{-1}). After 30 min, 5-HT (2 mg kg^{-1} h^{-1}) was added to the histamine infusion. After two further 15 min gastric collections, phentolamine or propranolol (2 mg kg^{-1} h^{-1}) was added (at 60 min) to the combined histamine and 5-HT infusion. Gastric secretion continued to be collected for another 30 min.

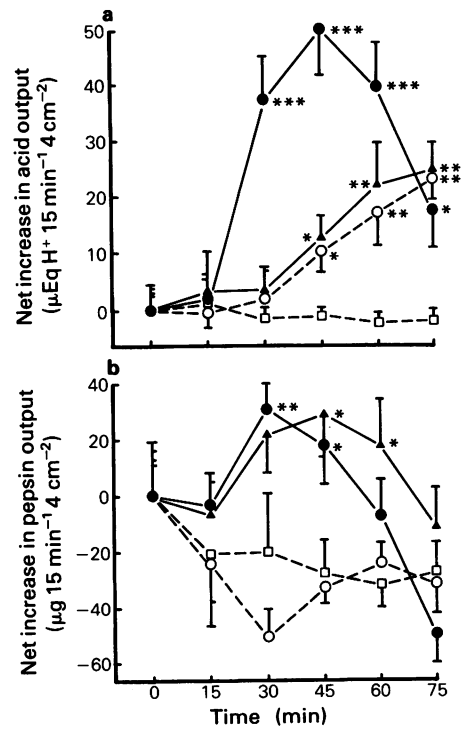

Figure 3 Effects of s.c. injection of secretagogues at 15 min (□ = saline 1 ml kg^{-1}; ○ = histamine 10 mg kg^{-1}; ● = pentagastrin 50 μg kg^{-1} and ▲ = methacholine 1 mg kg^{-1}) on gastric acid (a) and pepsin (b) secretion. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P < 0.05$; **$P < 0.01$, ***$P < 0.001$ when compared with the corresponding saline-injected control.

Determination of 5-hydroxytryptamine, calcium and glucose in blood

Whole blood 5-HT levels after s.c. injection of 0.6, 1 or 5 mg kg^{-1}, or i.v. infusion of 2 mg kg^{-1} h^{-1}, of the amine were determined according to the method developed by Ciarlone (1970). Serum calcium concentration was assayed by an Oxford Autotitrator, and glucose by an enzyme oxidation method (Sigma).

Determination of prostaglandin E_2 in gastric mucosa

The effects of 5-HT or indomethacin on gastric mucosal prostaglandin E_2 levels were determined. Ninety minutes after s.c. injection of these drugs, the gastric mucosa was scraped off with a glass slide. The mucosal content of prostaglandin E_2 was then measured, by the supraperfusion method of Konturek *et al.* (1981).

Drugs and statistical analysis

The following drugs were used: 5-HT, histamine, methacholine, prostaglandin E_2 and indomethacin (Sigma), phentolamine (Ciba), pentagastrin and propranolol (ICI). All drug solutions were freshly prepared; indomethacin was dissolved in 1% $NaHCO_3$ w/v, whereas the others were made up in saline. Statistical significance of differences between means was analysed by Student's *t* test.

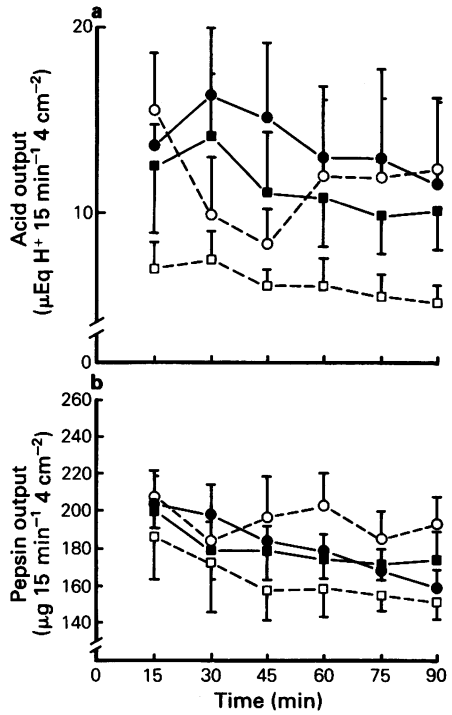

Figure 4 Effects of s.c. injection of 5-hydroxytryptamine (5-HT) at 0 min (■ = saline 1 ml kg^{-1}; ● = 0.6; ○ = 1 and □ = 5 mg kg^{-1} 5-HT) on basal gastric acid (a) and pepsin (b) secretion. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean.

Results

Effects of 5-HT on blood 5-HT, calcium and glucose levels

Figures 1 and 9 show the arterial 5-HT blood levels after s.c. injection (0.6, 1 or 5 mg kg^{-1}) and i.v. infusion (2 mg kg^{-1} h^{-1}) of 5-HT, respectively. The amine, when given s.c., produced dose- and time-dependent increases in blood 5-HT levels. The increases were marked at 90 min after 5-HT administration. Intravenous infusion of the amine also significantly elevated the 5-HT blood level during the 60 min experimental period. The highest dose of 5-HT (5 mg kg^{-1}) did not affect serum calcium and glucose levels (Figure 2).

Effects of 5-HT on the gastric secretory action of secretagogues

Histamine (10 mg kg^{-1}), pentagastrin (50 μg kg^{-1}) or methacholine (1 mg kg^{-1}) markedly increased gastric acid output in the *ex vivo* stomach preparation (Figure 3). Pepsin secretion was elevated by pentagastrin and methacholine but not by histamine administration (Figure 3). Pentagastrin and methacholine increased pepsin secretion from 15 to 45 min after their s.c. injection; basal levels were resumed at 60 min. Histamine slightly depressed pepsin secretion during the first 15 min, but normal values were seen subsequently. 5-HT 0.6, 1 or 5 mg kg^{-1}, injected at 0 min, did not significantly influence basal gastric acid and pepsin secretion during the 90 min observation period, although a suggestive inhibitory effect was seen with the largest dose of the amine (Figure 4). 5-HT 1 and 5 mg kg^{-1} (injected at − 15 min) inhibited histamine-induced acid secretion; a marked action was seen with 5 mg kg^{-1} (Figure 5). The amine dose-dependently inhibited pentagastrin-induced gastric acid secretion; this effect was almost complete with 5 mg kg^{-1} (Figure 6) which also significantly decreased pepsin secretion (Figure 6). All doses of 5-HT depressed methacholine-induced gastric acid secretion (Figure 7); however, only 5 mg kg^{-1} markedly decreased pepsin secretion 45–60 min after its injection at − 15 min (Figure 7).

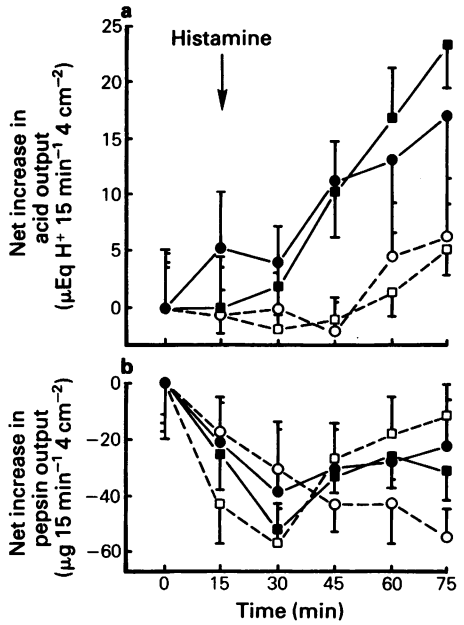

Figure 5 Effects of s.c. injection of 5-hydroxytryptamine at −15 min on histamine-induced (10 mg kg^{-1}, s.c.) gastric acid (a) and pepsin (b) secretion. The symbols are the same as in Figure 4. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P < 0.05$ when compared with the corresponding saline-injected control.

Effects of 5-HT and indomethacin on gastric glandular mucosal prostaglandin E_2 content

Table 1 shows the effects of 5-HT or indomethacin on prostaglandin E_2 levels in the gastric mucosa. The highest dose of 5-HT (5 mg kg^{-1}) used in this study did not influence the prostaglandin E_2 profile in the gastric mucosa. Only indomethacin 10 mg kg^{-1} significantly decreased the prostaglandin E_2 content to about half that of the saline-pretreated control.

Effects of indomethacin and adrenoceptor antagonists on the inhibitory action of 5-HT on histamine-induced gastric acid output

The same doses of indomethacin (given at −75 min) did not significantly affect histamine-induced gastric acid secretion. Indomethacin pretreatment also did not influence the inhibitory action of s.c. 5-HT on histamine-induced gastric acid secretion (Figure 8). Figure 9 shows the blood levels of 5-HT, achieved during the 60 min observation period when the amine was infused i.v. at 0 min, at a rate of 2 mg kg^{-1} h^{-1}. In the experiment where all drugs were infused i.v., neither phentolamine nor propranolol (given at 60 min) influenced the depressant effect of 5-HT (given at 30 min) on histamine-induced gastric acid secretion (Figure 10).

Discussion

The *ex vivo* chamber preparation appears to be suitable for studying the secretory functions of the stomach. Basal secretion of gastric acid and pepsin are well maintained during the observation period. Also, the responses to secretagogues are consistent and can be measured accurately. The main advantages of using this method are that it permits (a) measurements of secretions from a fixed area of glandular mucosa, (b) a constant volume of solution to be added to, and removed from, the chamber, (c) direct observation of mucosal changes and (d) direct addition of phar-

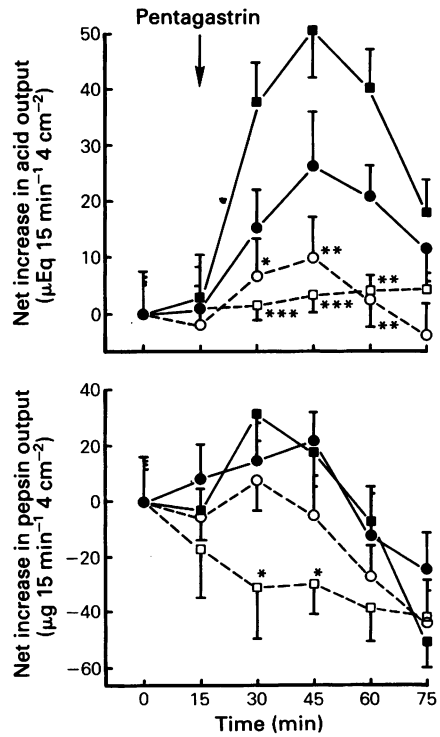

Figure 6 Effects of s.c. injection of 5-hydroxytryptamine at −15 min on pentagastrin-induced (50 μg kg^{-1}, s.c.) gastric acid (a) and pepsin (b) secretion. The symbols are the same as in Figure 4. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ when compared with the corresponding saline-injected control.

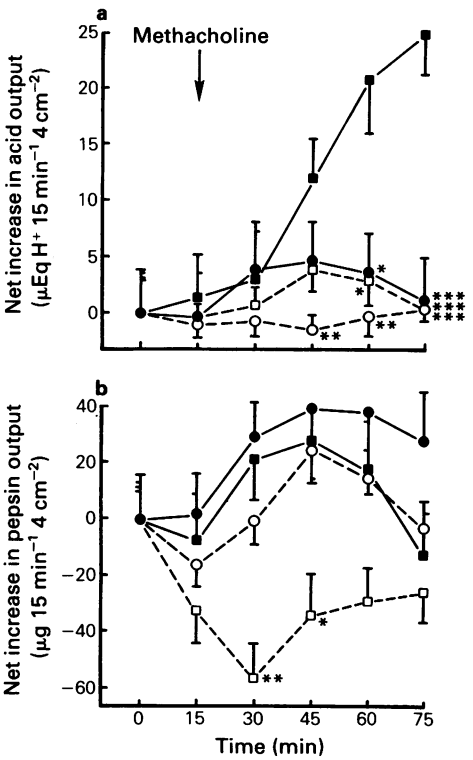

Figure 7 Effects of s.c. injection of 5-hydroxytryptamine at − 15 min on methacholine-induced (1 mg kg^{-1}, s.c.) gastric acid (a) and pepsin (b) secretion. The symbols are the same as in Figure 4. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P<0.05$; **$P<0.01$; ***$P<0.001$ when compared with the corresponding saline-injected control.

macological agents to the chamber solution. The preparation is basically an *in vivo* technique since the stomach is still attached to the body and drugs studied can be injected systemically. However, it does not have the disadvantage of an *in vivo* perfused preparation where perfusate collection volumes can vary because of peristalsis, and where irregular stomach distension, with consequent retention of contents, is liable to occur. The i.v. infusion of 5-HT 2 mg kg^{-1} h^{-1} used in this study compares closely with the i.v. bolus doses of 5-HT (5–20 μg kg^{-1}) found by Canfield & Hughes (1983) to inhibit pentagastrin-stimulated acid secretion in rats, when the infusion dose is calculated on the basis of one bolus dose given within 10 s. The s.c. doses of 5-HT (0.6–5 mg kg^{-1}) are within the range of the i.p. doses (1–10 mg kg^{-1}) shown by Thompson (1971) to suppress gastric secretion in these animals. A s.c. route of administration of 5-HT was used in the first two sets of experiments in order to study its inhibitory effects, whereas an i.v. infusion route, providing a

Table 1 Effects of 5-hydroxytryptamine (5-HT) or indomethacin pretreatment (90 min before rats were killed) on gastric mucosal prostaglandin E_2 levels

Pretreatment s.c.	*Prostaglandin E_2* (ng mg^{-1} protein)
Saline 1 ml kg^{-1}	6.58 ± 0.46
5-HT 5 mg kg^{-1}	5.24 ± 0.29
Indomethacin 5 mg kg^{-1}	6.05 ± 0.51
10 mg kg^{-1}	3.85 ± 0.35*

Values indicate means ± s.e.mean of 6 rats.
*$P<0.01$ when compared with the saline-pretreated group.

rapid rise in the blood level of the amine, to achieve a significantly high level in the shortest time, allowed further studies on its mechanism of action.

The patterns of pepsin secretion in response to stimulation by the three secretagogues studied were not similar. Pepsin secretion following histamine administration was different from that after pentagastrin or methacholine. Histamine produced a slight depressant effect on pepsin secretion while pentagastrin and methacholine markedly elevated pepsin output from 15 to 45 min after injection. The significance of these differences is unclear. Truncal vagotomy in

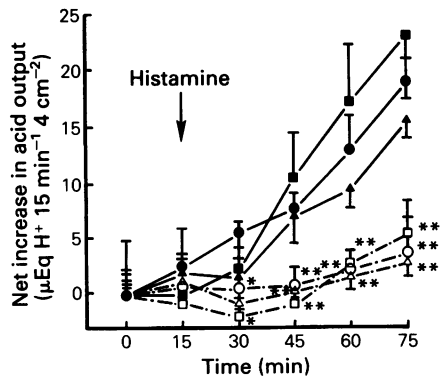

Figure 8 Effects of indomethacin pretreatment (injected s.c. 90 min beforehand) on the inhibitory action of 5-hydroxytryptamine (5-HT, injected s.c. 30 min beforehand) on histamine-induced (10 mg kg^{-1}, s.c.) gastric acid secretion (■ = 1% $NaHCO_3$ 1 ml kg^{-1} + histamine 10 mg kg^{-1}; ● = indomethacin 5 mg kg^{-1} + histamine 10 mg kg^{-1}; ▲ = indomethacin 10 mg kg^{-1} + histamine 10 mg kg^{-1}; □ = 1% $NaHCO_3$ 1 ml kg^{-1} + 5-HT 5 mg kg^{-1} + histamine 10 mg kg^{-1}; ○ = indomethacin 5 mg kg^{-1} + 5-HT 5 mg kg^{-1} + histamine 10 mg kg^{-1} and △ = indomethacin 10 mg kg^{-1} + 5-HT 5mgkg^{-1} + histamine 10 mg kg^{-1}). Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P<0.05$; **$P<0.001$ when compared with the corresponding values of rats not given 5-HT.

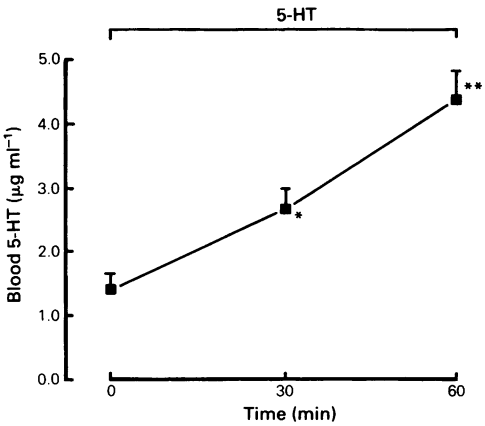

Figure 9 Effect of i.v. infusion of 5-hydroxytryptamine (5-HT) at 2 mg kg^{-1} h^{-1} on arterial blood 5-HT level. Each symbol indicates the mean of 6 rats; vertical lines represent s.e.mean. *$P<0.05$; **$P<0.001$ when compared with its own basal blood level at 0 min.

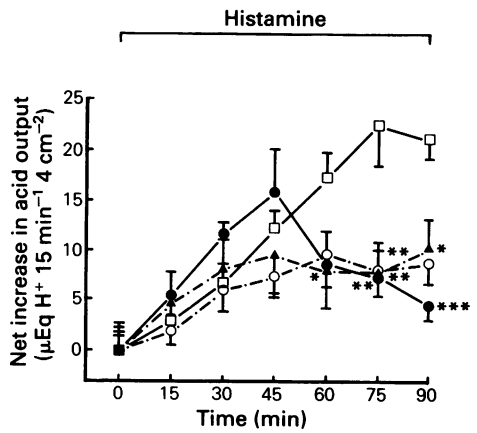

Figure 10 Effects of phentolamine and propranolol treatments (infused i.v. at 60 min) on the inhibitory action of 5-hydroxytryptamine (5-HT, infused i.v. at 30 min) on histamine-induced (infused i.v.) gastric acid secretion (□ = histamine 5 mg kg^{-1} h^{-1}; ▲ = histamine 5 mg kg^{-1} h^{-1} + 5-HT 2 mg kg^{-1} h^{-1}; ○ = histamine5 mg kg^{-1} h^{-1} + 5-HT 2 mg kg^{-1} h^{-1} + phentolamine 2 mg kg^{-1} h^{-1} and ● = histamine 5 mg kg^{-1} h^{-1} + 5-HT 2 mg kg^{-1} h^{-1} + propranolol 2 mg kg^{-1} h^{-1}). Each symbol indicates the mean of 7 rats; vertical lines represent s.e.mean. *$P<0.05$; **$P<0.01$, ***$P<0.001$ when compared with the corresponding values of rats given only histamine infusion.

dogs reduced pepsin secretion in response to both histamine and gastrin (Emas & Grossman, 1967). However, in rats, gastrin apparently stimulates pepsin secretion only in the denervated Heidenhain pouch (Svensson, 1970). The discrepancy in these findings needs clarification. Based on the findings in dogs and rats, truncal vagotomy in the present study, would, therefore, have been expected to reduce greatly the secretion of pepsin elicited by histamine but perhaps not that by pentagastrin. The ability of 5-HT to inhibit pepsin secretion induced by pentagastrin and methacholine is interesting. This action could be the net effect of (a) the direct influence of 5-HT on pepsin-secreting cells and/or (b) 5-HT-induced inhibition of gastric acid secretion which in turn leads to less pepsin secretion. The former possibility appears unlikely because 5-HT was found not to modify basal pepsin secretion.

Inhibition of gastric acid secretion by 5-HT has been observed in both *in vivo* and *in vitro* studies (Black *et al.*, 1958; Bugajski *et al.*, 1977; Canfield & Hughes, 1983; Canfield & Spencer, 1983; Jaffe *et al.*, 1977). The inhibitory mechanisms of 5-HT have been extensively studied in the rat isolated stomach (Canfield & Spencer, 1983). This depressive action is thought to be selective and to be mediated possibly through the products of cyclo-oxygenase activity. However, such a conclusion is not supported by the present study. On the one hand, 5-HT 5 mg kg^{-1}, and also in doses of 0.6 and 1 mg kg^{-1} (Cho, unpublished findings), did not affect gastric mucosal prostaglandin E_2 content. On the other hand, the higher dose (10 mg kg^{-1}) of indomethacin pretreatment, which significantly decreased the gastric mucosal prostaglandin E_2 content (Table 1), did not modify the inhibitory action of 5-HT. The drug also did not significantly affect the secretory responses evoked by histamine (Figure 8); it does not influence basal gastric acid secretion (Cho, unpublished findings). Furthermore, indomethacin-induced reduction in gastric mucosal prostaglandin E_2 levels did not enhance acid secretion. It is not known whether indomethacin has a direct action on gastric acid secretion. Nevertheless, it would appear that the physiological role of the prostaglandins in controlling gastric acid secretion is questionable. The finding that the smaller dose of indomethacin (5 mg kg^{-1}) did not lower gastric glandular mucosal PGE_2 content (Table 1) is at variance with that of Konturek *et al.* (1983). The discrepancy could be due to the possibility that scraping the mucosa, as done in the present study, may have influenced PGE_2 levels in the samples.

It is interesting to note that in dogs, inhibition of gastric acid secretion by infusions of 5-HT depends on intact vagal innervation (Black *et al.*, 1958). This finding is not supported by the present study using rats, because truncal vagotomy did not prevent the inhibitory action of 5-HT. The question of whether the depressive action of 5-HT is a selective one on the stomach (Canfield & Spencer, 1983), mediated indirectly by depressing the vegetative brain centres (Bugajski *et al.*, 1977) or by releasing hormones that

inhibit gastric secretion, e.g. corticotropin-releasing factor from the hypothalamus (Jones & Hillhouse, 1977; Tache *et al.*, 1983), needs to be investigated.

Preliminary studies have shown that histamine-evoked acid secretion is depressed by adrenaline, when the latter is added to the i.v. histamine infusion. The observation that neither phentolamine nor propranolol influenced the inhibitory action of 5-HT confirms the conclusions of Canfield & Spencer (1983), and indicates that adrenaline is not an inhibitory mediator for 5-HT. Although 5-HT has been found to lower blood pressure (Henning & Rubenson, 1971), s.c. injections of the amine in doses used in the current experiments do not significantly affect the systemic blood pressure and heart rate when observed over a similar experimental period (Cho, unpublished findings). Thus, it is unlikely that the inhibitory action of 5-HT on gastric secretory function is mediated through systemic vascular effects.

It has been suggested that 5-HT-induced hyperglycaemia may play a role in antagonizing the gastric acid secretory effect of insulin (Hano *et al.*, 1975). This mechanism of inhibiting acid secretion is unlikely because s.c. injection of the biggest dose of 5-HT did not affect serum glucose levels. Although 5-HT administration did not influence arterial blood calcium, the possibility of the amine acting on calcium-mediated receptors, which stimulate acid secretion (Berglindh *et al.*, 1980; Christiansen *et al.*, 1979), remains to be excluded.

The findings in this study suggest that inhibition of gastric acid and pepsin output by 5-HT is not vagal-, prostaglandin- or adrenaline-mediated. Neither the glucose nor calcium level in the serum appears to be responsible for the suppressive action of 5-HT. A selective action on the stomach, or an indirect central effect, could be involved in its ability to inhibit gastric function.

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