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The inhibitory effects of 5-hydroxytryptamine on gastric acid secretion by the rat isolated stomach

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1 The effect of 5-hydroxytryptamine (5-HT) on acid secretion by a rat isolated stomach preparation has been studied.

2 5-HT at 10^{-5} M in the serosal bathing fluid produced significant inhibition of the acid secretory responses to histamine, pentagastrin and isoprenaline but was without effect on basal secretion or that due to bethanechol, dibutryl cyclic adenosine 3',5'-monophosphate (db cyclic AMP) or phosphodiesterase inhibition with ICI 63197. Increasing the concentration of 5-HT to 5×10^{-5} M did not change this pattern of response whilst 5-HT at 10^{-6} M did not cause consistent inhibition.

3 The inhibitory action of 5-HT could be prevented by the antagonist methysergide (2.5×10^{-5} M). This concentration of methysergide alone did not affect responses to secretagogues or basal acid output.

4 Neither propranolol (2.5×10^{-5} M) nor tetrodotoxin (10^{-6} M) antagonized the inhibitory action of 5-HT.

5 Both indomethacin (2.8×10^{-5} M) and ibuprofen (2.4×10^{-4} M) antagonized the action of 5-HT. Indomethacin alone had no effect upon secretagogue responses.

6 5-HT at 10^{-5} M had no inhibitory action when applied to the mucosal side of the preparation.

7 The results indicate that 5-HT can act directly on the stomach of the rat to produce inhibition of acid output. This inhibition is selective and may involve the products of cyclo-oxygenase activity.

Introduction

Exogenous 5-hydroxytryptamine (5-HT) has been found to inhibit acid secretion produced by a variety of stimulants in both conscious and anaesthetized animals. The majority of these studies have been in dog or rat (for review see Thompson, 1971; Jaffe, 1979). 5-HT is found throughout the gut and especially in the stomach and duodenum but a clear role for endogenous 5-HT in the normal regulation of gastric acid secretion has not been established. However, Jaffe, Kopen & Lazan (1977) have shown that acidification of the duodenum of the dog is associated with inhibition of pentagastrin-stimulated acid secretion and a rise in plasma 5-HT concentration. Infusion of 5-HT to give similar plasma levels also inhibited the pentagastrin response by the same amount. In man and rat it has been shown that the 5-HT antagonist, methysergide, stimulates acid secretion (Debnath, Goel & Sanyal, 1975; Caldara, Ferrari, Barbieri, Romussi, Rampini & Telloli, 1980). Thus, there is some evidence that endogenous 5-HT may influence acid secretion under suitable circumstances. Little is known about the mechanism of inhibition of acid secretion by 5-HT (Thompson, 1971). Black, Fisher & Smith (1958) reported that cervical vagotomy abolished the inhibitory effect of infused 5-HT in anaesthetized dogs. However, in conscious dogs, an inhibitory effect of both 5-HT and its metabolic precursor, 5-HTP, has been reported in Heidenhain pouch dogs (Haverback, Bogdanski & Hogben, 1958). This inhibition was less marked than that seen in the innervated stomach. 5-HT is more potent when given via the brain ventricles than when given intraperitoneally in conscious rats (Bugajski, Hano, Danek & Wantuch, 1977) and this may be relevant if high doses of exogenous 5-HT penetrate the blood-brain barrier. 5-HT also has pronounced cardiovascular effects (Page & McCubbin, 1956) which could inhibit acid secretion if they led to a reduction of gastric mucosal blood flow. There appears to be no direct measurement of the effects of 5-HT on gastric mucosal blood flow. The action of 5-HT on a particular vascular bed depends upon the population of 5-HT receptors it contains and possible interaction with α-receptors (Apperley, Humphrey & Levy, 1976; Feniuk, Hare & Humphrey, 1981). It is therefore not possible to predict the action of 5-HT on gastric mucosal blood flow. The situation is further complicated in dog and cat but not in rat by the ability of 5-HT to increase circulating catecholamines (Reid, 1952; Fozzard & Leach,

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1968; Feniuk *et al.*, 1981) as catecholamines also inhibit acid secretion (Holton, 1973; Sanders, 1976) 5-HT has been reported to inhibit gastrin output in dogs (Saik, 1981) but to raise serum gastrin levels in rat (Hierro, Sanchez-Barriga, Solana, Requena & Pena, 1980).

Thus, the complex actions of 5-HT *in vivo* provide a number of possible means to inhibit acid secretion. As part of an investigation of this problem we have studied the action of 5-HT on acid secretion by a rat isolated stomach preparation where many of the uncertainties associated with *in vivo* studies are avoided. Preliminary accounts of some of this work have been presented to the British Pharmacological Society (Canfield & Spencer, 1981) and the Bayliss & Starling Society (Canfield & Spencer, 1982).

Methods

Isolated stomach preparations

The rat isolated stomach preparation has been described previously (Canfield & Price, 1981) and was not modified for these experiments. All drugs were added to the serosal bathing solution unless otherwise stated. Experiments were performed within the following general design: stomachs were randomly allocated to one of four groups as required; controls (C) which received only secretagogues; T_1 which had 5-HT; T_2 which had 5-HT plus drug under test and T_3 which received the drug under test from T_2. In groups T_1–T_3 the drug treatment was present throughout the entire experiment and started 1 h before the first secretagogue. Within each group, every stomach received only one exposure to a sub-maximal concentration of the secretagogue under study and no more than three secretogues were given to any stomach. The order of addition of secretagogues was randomized. As 5-HT did not inhibit the response to bethanechol, the use of this stimulant verified the viability of tissues where 5-HT was present (T_1). Responses to secretagogues are expressed as secretory ratio, R (response/basal secretion) as described previously (Canfield & Price, 1981). Comparisons between treatments were made by the Mann-Witney U-test and considered significant if $P<0.05$.

Drugs

The following were used; pentagastrin, propranolol, ICI 63197 (ICI Ltd); histamine acid phosphate, indomethacin, dibutryl adenosine 3, 5 – cyclic monophosphate (db cyclic AMP), 5-hydroxytryptamine creatine sulphate complex, tetrodotoxin (Sigma); isoprenaline sulphate (Macarthys); bethanechol chloride (Glenwood Laboratories); ibuprofen (Boots Ltd); methysergide maleate (Sandoz).

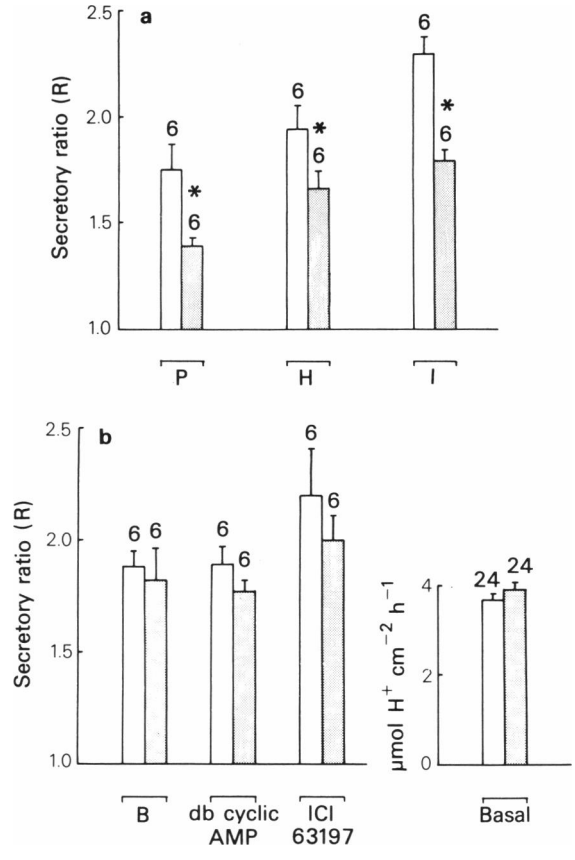

Figure 1 The effect of 5-hydroxytryptamine, 10^{-5} M (stippled columns) compared with control stomachs (open columns) during stimulation with pentagastrin (P, 2.2×10^{-7} M), histamine (H, 1.6×10^{-4} M), isoprenaline (I, 1.3×10^{-6} M), bethanechol (B, 8.5×10^{-6} M) db cyclic AMP (1.4×10^{-4} M), ICI 63197 (2.4×10^{-4} M) and under basal conditions. Columns are mean values with s.e.mean bars; number of observations shown over each column. Significance difference between means shown by $*P<0.05$.

Results

Inhibitory effects of 5-hydroxytryptamine

Figure 1a shows the effect of 5-HT (10^{-5} M) on basal secretion and the responses to various secretagogues. 5-HT caused significant inhibition of the responses to pentagastrin, histamine and isoprenaline but was without effect (Figure 1b) on basal secretion or responses to bethanechol, db cyclic AMP or the phos-

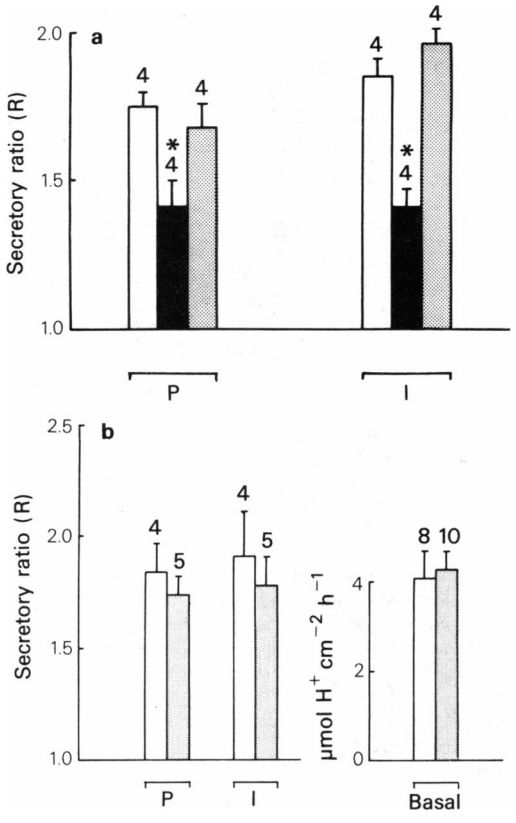

Figure 2 (a) Control values (open columns), with 5-hydroxytryptamine (5-HT) at 5×10^{-5} M (solid columns) and 5-HT plus methysergide (2.5×10^{-5} M, stippled columns). (b) Controls (open columns) and in presence methysergide (2.5×10^{-5} M stippled columns). Stimulants were pentagastrin (P, 2.2×10^{-7} M) and isoprenaline (I, 6.3×10^{-7} M). Columns are mean values with s.e.mean bars; number of observations above each column. Significant difference between control and test means shown by $^{*}P < 0.05$.

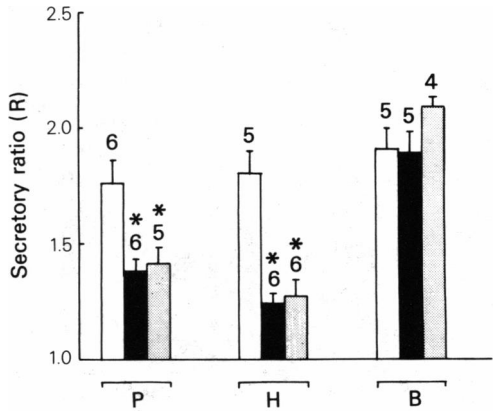

Figure 3 The effect of propranolol (2.5×10^{-5} M, stippled columns) on the inhibition by 5-hydroxytryptamine (2×10^{-5} M, solid columns) on responses to pentagastrin (P, 2.2×10^{-7} M), histamine (H, 1.1×10^{-4} M) and bethanechol (B, 8.5×10^{-6} M). Open columns are control values. Columns are mean values with s.e.mean bars; number of observations over each column.

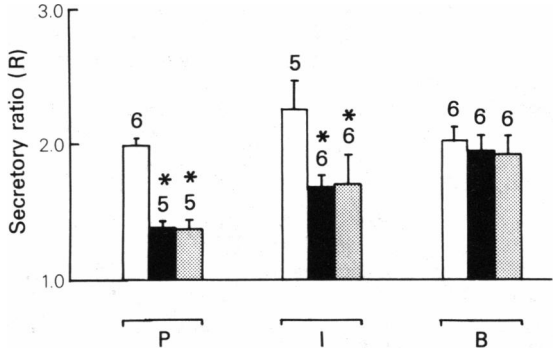

Figure 4 The effect of tetrodotoxin (TTX, 10^{-6} M) on the inhibitory action of 5-hydroxytryptamine (5-HT, 10^{-5} M) shown by stippled columns; 5-HT alone by solid columns and control by open columns during stimulation with pentagastrin (P, 2.2×10^{-7} M), isoprenaline (I, 1.3×10^{-6} M) and bethanechol (B, 8.5×10^{-6} M). Columns show mean values with s.e.mean bars; number of observations above each column. TTX had no significant effect on responses.

phodiesterase inhibitor ICI 63197. Increasing the concentration of 5-HT to 5×10^{-5} M still did not lead to inhibition of the responses to bethanechol (control $R = 1.68 \pm 0.08$; test $R = 1.72 \pm 0.09$ mean and s.e.mean, $n = 6$ for both) or dibutryl cyclic AMP (control $R = 2.07 \pm 0.19$, test $R = 1.96 \pm 0.08$, $n = 5$ for both groups). However it did cause further inhibition of the responses to both histamine (test $R = 1.43 \pm 0.05$, $n = 9$) and isoprenaline (test $R = 1.43 \pm 0.04$, $n = 6$) but had no additional effect upon pentagastrin (test $R = 1.37 \pm 0.07$, $n = 6$). Lower concentrations of 5-HT (10^{-6} M) caused inhibition of pentagastrin and isoprenaline responses in some stomachs but no consistent significant effect was observed.

Antagonism of effects of 5-hydroxytryptamine

Figure 2a shows that the inhibitory action of 5-HT on pentagastrin- and isoprenaline-stimulated secretion was completely reversed by the antagonist, methysergide (2.5×10^{-5} M). This concentration of methysergide alone (Figure 2b) had no effect on basal secretion or on the response to secretagogues. Methysergide at 10^{-6} M had no antagonistic action on 5-HT inhibition. R values (mean ± s.e.mean) for 5-

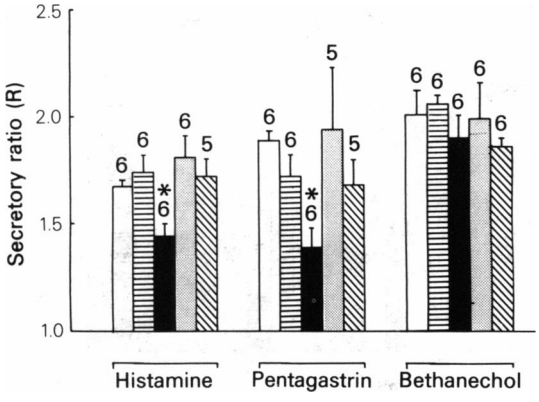

Figure 5 The effect of indomethacin (Indo, 2.8×10^{-5} M) and ibuprofen (2.4×10^{-4} M) on the inhibitory effect of 5-hydroxytryptamine (5-HT, 2×10^{-5} M) during stimulation with pentagastrin (2.2×10^{-7} M) histamine (1.6×10^{-4} M) and bethanechol (8.5×10^{-6} M). Columns are means with s.e.mean bars and number of observations above each column. Open columns are secretagogues alone, horizontally hatched columns secretagogue + Indo, solid columns secretagogue + 5-HT, stippled columns secretagogue + 5-HT + Indo and diagonally hatched columns secretagogue + 5-HT + ibuprofen. A significant difference from control values (open columns) is shown by $^*P < 0.05$.

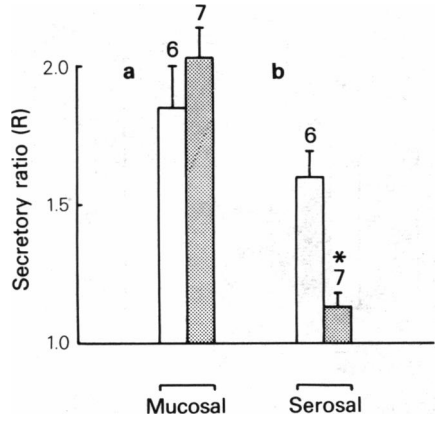

Figure 6 The response to pentagastrin (2.2×10^{-7} M) alone (open columns) and in the presence of 5-hydroxytryptamine (5-HT, 10^{-5} M, stippled columns). In (a) columns shows effect of 5-HT in mucosal solution on first application of pentagastrin; (b) show second application of pentagastrin to same tissues but with 5-HT now in serosal solution. Columns show mean values with s.e.mean bars and number of observations above each column. A significant difference between means is shown by $^*P < 0.05$.

HT and 5-HT plus methysergide were, pentagastrin (2.2×10^{-7} M) $R = 1.40 \pm 0.06$, 1.56 ± 0.17; histamine (1.6×10^{-4} M) $R = 1.49 \pm 0.08$, 1.41 ± 0.04 and bethanechol (8.5×10^{-6} M) $R = 2.02 \pm 0.27$, 2.40 ± 0.29 ($n = 6$ for each mean). It has been suggested that propranolol may inhibit peripheral 5-HT receptors (Schechter & Weinstock, 1976). Figure 3 shows that propranolol (2.5×10^{-5} M) did not affect the inhibitory action of 5-HT in this preparation. The response to bethanechol, which is not inhibited by 5-HT, served as control for the viability of these tissues. Propranolol itself has previously been shown to be without effect on non-adrenergic secretagogue responses (Canfield & Price, 1981). The inhibitory action of 5-HT was also unaffected by blockade of the intrinsic neural plexi with tetrodotoxin (TTX, 10^{-6} M). This is shown in Figure 4 and as before, the results with bethanechol demonstrate the viability of the stomachs and suggest that TTX itself has no effect alone, at least on the response to bethanechol.

Figure 5 shows that the two anti-inflammatory drugs, indomethacin and ibuprofen, are able to reverse the inhibitory effects of 5-HT on the response to histamine and pentagastrin. Indomethacin alone was without effect upon responses to pentagastrin, histamine and bethanechol as shown and was also without effect on isoprenaline (1.3×10^{-6} M); the control value $R = 2.33 \pm 0.13$, test with indomethacin $R = 2.46 \pm 0.13$, ($n = 7$ for both groups).

Mucosal application of 5-hydroxytryptamine

The enterochromaffin (EC) cells *in vivo* may release 5-HT into the lumen of the stomach so it was of interest to test the ability of 5-HT to inhibit acid secretion from the mucosal side. The results are shown in Figure 6. When 5-HT (10^{-5} M) was on the mucosal side, there was no significant effect on the response to pentagastrin compared with controls which did not have 5-HT. Following this the tissues were washed, 5-HT removed from the mucosal and placed on the serosal side of the test tissues for a further hour before a second application of the same concentration of pentagastrin. As shown, 5-HT on the serosal side caused significant inhibition compared with the second response in the control tissues.

Discussion

5-HT significantly reduced the acid secretion in response to pentagastrin, histamine and isoprenaline in this isolated stomach preparation. This inhibition was not a non-selective effect as responses to bethanechol, db cyclic AMP and phosphodiesterase inhibition (ICI 63197) were unchanged. The inhibition could be prevented by the accepted 5-HT an-

tagonist methysergide. The action of methysergide was not a non-specific potentiation of acid output as it had no effect on basal secretion or responses to pentagastrin and isoprenaline. The contrast between the lack of antagonistic effect of methysergide at 10^{-6} M and the complete reversal of inhibition at 2×10^{-5} M was unexpected. The present results do not suggest an explanation for this and work is currently in progress with a variety of 5-HT antagonists in an attempt to characterize the 5-HT receptor-type mediating the inhibition. Thus it is concluded that the rat isolated stomach contains 5-HT receptors which when activated cause inhibition of acid secretion due to some secretagogues. This finding could explain the reported *in vivo* inhibition of acid output in response to pentagastrin and histamine but would not explain reports of *in vivo* inhibition of cholinergically stimulated secretion. It may be that 5-HT has more than one mode of action *in vivo*. In rat, it is a potent inhibitor of vagally induced acid secretion when administered intracerebroventricularly (Bugajski *et al.*, 1977) and in amphibia has been reported to modify acetylcholine release from nerve endings (Hirai & Koketsu, 1980).

The concentration of 5-HT needed to inhibit acid secretion in this study is higher than that used generally in smooth muscle and vascular studies *in vitro*. The smooth muscle of the fundic region of the rat stomach is exceptionally sensitive to 5-HT (Vane, 1957). However, it may be that higher concentrations of 5-HT are necessary to affect secretory rather than muscular processes as the concentrations used in this study are similar to those shown to modify processes in the rat intestine *in vitro* (Hardcastle, Hardcastle & Redfern, 1981). There are a number of other possible explanations for this situation. Black and his co-workers (Angus & Black, 1979; Angus, Black & Stone, 1980) have determined pK_B values for metiamide and atropine against histamine and bethanechol stimulation of acid secretion respectively in the mouse stomach *in vitro*. The values for both antagonists were significantly lower than values obtained in other *in vitro* systems and these workers suggest that this may be a consequence of the act of secretion such that the concentration of drug at the receptor may not be in equilibrium with the concentration in the tissue bath. This problem has not been examined in the rat preparation but it has previously been found necessary to use high concentrations of atropine, metiamide and β-adrenoceptor antagonists to obtain significant effects. (Canfield, Hughes, Price & Spencer, 1981). It may also be that the access of 5-HT to the stomach is restricted in this preparation. Gershon & Tamir (1981) have shown that a barrier to the passage of 5-HT exists between the mucosa and the neural plexi in the guinea-pig intestine. 5-HT on the serosal side was taken up by the neural plexi but very little appeared in mucosal EC cells whereas, 5-HT from mucosal surface penetrated EC cells but not significantly into the nervous tissue. We do not know if a similar barrier exists in the rat stomach but when 5-HT was placed on the mucosal side it had no inhibitory action. Whilst this strongly suggest the 5-HT does not enter from the mucosal side it does not exclude the possibility of a barrier to passage from the serosal surface. A third possibility is that there is a substantial uptake or breakdown of 5-HT by the intact stomach wall. It would be desirable to investigate the effects on the 5-HT inhibition of both selective uptake and monoamine-oxidase (MAO) inhibitors. A further possibility is that the immature animals used in this study do not have a fully developed 5-HT receptor system. There is evidence, for example, that the sympathetic innervation to the gut in rats of this age is incomplete (Yoshida, Taniyama & Tanaka, 1979). We are currently investigating this aspect of the problem. Thus, the reason for requiring high concentrations of 5-HT remain to be investigated but the results presented here suggest that the action of 5-HT is not a non-specific consequence of high drug concentration.

Mechanism of inhibitory effect

The lack of effect of TTX suggests that 5-HT inhibition does not work through the intrinsic nerve supply of the stomach. It is also unlikely to involve an action at an adrenoceptor as the inhibition was not modified by propranolol and it has been previously shown that drugs acting at α-adrenoceptors do not influence acid secretion in this preparation (Canfield & Price, 1981). The ability of both indomethacin and ibuprofen to reverse the inhibitory action of 5-HT raises the possibility of an involvement of prostaglandins in the inhibition. Several workers have drawn attention to the similarity of the actions of 5-HT and prostaglandins on the gastro-intestinal tract. Two groups have suggested that prostaglandins exert their effects on gastric secretion by releasing 5-HT but neither group was able to show an effect of prostaglandins on the release or content of 5-HT in the stomach (Angulo & Thompson, 1968; 1969; Debnath, Bhattacharya, Sanyal, Poddar & Ghosh, 1978). Debnath & Sanyal (1976) have also claimed that the inhibitory action of prostaglandin E_1 (PGE_1) on acid secretion in the pylorus-ligated rat was antagonized by methysergide. However, these experiments would appear to lack controls for the stimulatory action of methysergide itself (Debnath *et al.*, 1975; Caldara *et al.*, 1980). As Soll (1980) has demonstrated a direct inhibitory effect of prostaglandins on isolated parietal cells from the dog, there is no necessity to propose 5-HT as a mediator of the action of prostaglandins. There is some evidence to support the converse hypothesis;

that 5-HT causes release of prostaglandins, in the rat lung (Alabaster & Bahkle, 1976) and the rat stomach (Coceani, Pace-Asciak & Wolfe, 1968). More recently 5-HT has been shown to stimulate prostacyclin production in smooth muscle cell cultures (Coughlin, Moskowitz, Antoniades & Levine, 1981). The effect was blocked by 5-HT antagonists and the authors suggest that 5-HT promotes the release of arachidonic acid from cellular phospholipids. This effect of 5-HT had an EC_{50} of 10^{-6} M and was maximal at 10^{-5} M; concentrations similar to those used in this present study on the stomach. Our results with the isolated stomach are consistent with a hypothesis that 5-HT releases prostaglandins but not with the converse hypothesis. If 5-HT acts via prostaglandins then one would expect both substances to have the same inhibitory effects on acid secretion in the isolated stomach. It has been shown previously that PGE_2 inhibits the response to pentagastrin but not isoprenaline in this preparation (Canfield *et al.*, 1981). Other workers, using different isolated stomach preparations, have reported that prostaglandin derivatives do not inhibit the response to db cyclic AMP and have inconsistent effects on cholinergic stimulation (Main & Pearce, 1978; Frame & Main, 1980; Boughton-Smith & Whittle, 1981). Thus there are similarities in the inhibitory effects of 5-HT and prostaglandins but they are not identical. The present results are consistent with the view that 5-HT inhibition of acid secretion *in vitro* may be mediated by prostaglandin release but further experimental evidence is needed to substantiate such an hypothesis. Whilst indomethacin undoubtedly inhibits cyclo-oxygenase it may also have other less specific actions involving cellular calcium metabolism (Northover, 1977) which may be able to influence acid secretion. It has been reported to potentiate db cyclic AMP-stimulated acid secretion in the rat both *in vivo* and *in vitro* (Main & Melarange, 1978; Donaldson & Main, 1981) but not to affect basal or histamine-stimulated secretion. These results confirm that indomethacin does not potentiate histamine nor did it potentiate the responses to pentagastrin, isoprenaline or bethanechol. This action of indomethacin thus appears restricted to db cyclic AMP-stimulation but remains unexplained. Without further experiments it is not possible to be certain that the ability of indomethacin and ibuprofen to prevent 5-HT inhibition in this preparation is solely the result of cyclo-oxygenase inhibition.

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