J. Pharm. Pharmacol. 1995, 47: 744–749
Received November 28, 1994
Accepted July 10, 1995

Evidence that the Secretory Response of Rat Intestine to 5-Hydroxytryptamine In-vivo Involves More than One 5-Hydroxytryptamine-receptor Subtype

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Abstract

The transintestinal potential difference (PD) across rat mid-small intestine and proximal colon was measured in-vivo. The 5-hydroxytryptamine (5-HT)-induced increase in PD, which reflects a stimulation of electrogenic Cl secretion, was mimicked by both 2-methyl-5-hydroxytryptamine (2-CH_3-5-HT), an agonist at 5-HT_3 receptors, and 5-methoxytryptamine (5-MT), an agonist that lacks affinity for 5-HT_3 receptors. The 5-HT_3 antagonist granisetron caused a marked inhibition of the response to 2-CH_3-5-HT in both regions, but only produced a small inhibition of the small intestinal response to 5-HT, with a more pronounced effect in the colon. The failure of granisetron to produce a marked antagonism of the 5-HT-induced rise in the transintestinal PD, coupled with the ability of 5-MT to induce a secretory response, indicates that 5-HT_3 receptors are not the only ones involved in the stimulation of Cl secretion.

The 5-HT_2 antagonist ketanserin failed to influence the response to 5-HT in either the small intestine or the colon, but it did inhibit the action of 5-MT, having a much greater effect in the small intestine. In the presence of granisetron however, ketanserin also inhibited the small intestinal response to 5-HT, having only a minimal effect in the colon. This suggests that 5-HT_2 receptors can also play a role in the activation of Cl secretion.

These observations suggest that both 5-HT_2 and 5-HT_3 receptors contribute to the stimulation of electrogenic Cl secretion by 5-HT, with 5-HT_2 receptors playing a more prominent role in the small intestine and 5-HT_3 receptors being more important in the colon.

The enterocytes lining the intestine respond to 5-hydroxytryptamine (5-HT) challenge with a stimulation of secretion (Kisloff & Moore 1976; Donowitz et al 1977). This results from an increase in the electrogenic secretion of Cl ions together with an inhibition of the electroneutral absorption of NaCl (Hardcastle et al 1981; Zimmerman & Binder 1984; Siriwardena et al 1991). Many studies have been directed towards identifying the receptor responsible for these effects, but, as yet, no concensus has emerged. Evidence has been presented for the involvement of 5-HT_3 receptors in guinea-pig ileum (Baird & Cuthbert 1987) and colon (Cooke et al 1991), although 5-methoxytryptamine (5-MT), an agonist that lacks affinity for 5-HT_3 receptors (Fozard 1985; Leff & Martin 1988; Craig et al 1990), is able to induce a secretory response in rat small intestine (Hardcastle & Hardcastle 1991) and colon (Ayton et al 1995). Studies of the possible involvement of 5-HT_2 receptors in rat distal colon have produced conflicting reports, with one group demonstrating an inhibition of 5-HT-induced secretion by the 5-HT_2 antagonist ketanserin (Siriwardena et al 1991), while another group showed this agent, at a higher concentration, to be without effect (Bunce et al 1991).

More recently the involvement of the 5-HT_4 receptor in the control of intestinal secretion has been investigated, again with no consistent results. In human jejunum (Budhoo & Kellum 1994) and ileum (Borman & Burleigh 1993; Burleigh & Borman 1993) there is evidence for a significant involvement of this receptor subtype, while in the rat it appears to play only a minor role (Franks et al 1993, 1995).

Most studies of 5-HT-induced intestinal secretion have been designed to investigate the involvement of a single 5-HT receptor subtype in the generation of the secretory response. Use of antagonists has revealed however, that the agents that are most effective in inhibiting the response to 5-HT are those that act at more than one receptor subtype, such as mianserin, a 5-HT_{1C} and 5-HT_2 antagonist (Hardcastle et al 1981), cisapride, a 5-HT_2 and 5-HT_3 antagonist (Moriarty et al 1987; Beubler et al 1990) and tropisetron, a 5-HT_3 and 5-HT_4 antagonist (Baird & Cuthbert 1987; Bunce et al 1991), while antagonists acting more selectively are less effective (Bunce et al 1991). Intestinal secretion induced by 5-HT could therefore involve more than one receptor subtype and this study was designed to investigate this possibility further using the rise in electrical activity induced by 5-HT as a reflection of electrogenic Cl secretion. An in-vivo preparation was chosen as it allows cardiovascular function to be monitored and the triphasic change induced by intravenously administered 5-HT (Kalkman et al 1984) provides a useful monitor of the potency and selectivity of agonist and antagonist action.

Materials and Methods

Chemicals

5-Hydroxytryptamine creatinine sulphate and 5-methoxytryptamine were obtained from Sigma Chemical Company Ltd, Poole, UK. 2-Methyl-5-hydroxytryptamine (2-CH_3-5-

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HT) and granisetron were gifts from SmithKline Beecham Pharmaceuticals, Harlow, UK and ketanserin was donated by Janssen Pharmaceutica, Beerse, Belgium.

Animals

Experiments were carried out on male Wistar rats, 230–250 g, obtained from the Sheffield Field Laboratories and allowed free access to food and water. They were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}, i.p.).

Measurement of transintestinal electrical activity and cardiovascular function

The transintestinal potential difference (PD) was measured across 3-cm segments of mid-small intestine and proximal colon. Each segment was tied at the distal end and filled with 154 mM NaCl through a cannula inserted at the proximal end. The PD across each loop was measured between two salt bridge electrodes, one in contact with the luminal fluid and the other, via a wick electrode, with the peritoneal cavity. Electrodes were connected via calomel half cells to two differential input electrometers whose outputs were displayed on a two-channel chart recorder (Linseis L6512). Drugs were administered through a cannula in the femoral vein and each dose (in 0.1 mL) was washed in with 0.2 mL 154 mM NaCl. The response to an agonist was taken as the difference between the maximum PD achieved after each dose and the value immediately before its addition.

Arterial blood pressure (BP) was monitored at the left carotid artery via a saline/heparin-filled cannula connected to a pressure transducer (Druck Ltd, PDCR75). This was linked to a preamplifier (Lectromed type 5241) and a visual display obtained on a two-channel chart recorder (Lectromed Multitrace 2). The BP signal was transmitted to a rate meter (Lectromed type 5250) to provide a continuous display of the heart rate integrated over a 1-s time base.

Body temperature was maintained at 37°C by a homeothermic blanket system with a rectal probe (Harvard Apparatus Ltd).

In each preparation a 5-HT dose-response curve was constructed before the effects of other agonists or antagonists were tested. The interval between the administration of an antagonist and the beginning of the next agonist dose-response curve was 5 min. Preliminary experiments confirmed the consistency of successive control dose-response curves.

Expression of results

Results are expressed as mean values ± s.e.m. of the number of observations indicated and a paired *t*-test was used to compare the effects of other agonists with those of 5-HT and also to assess the significance of antagonist action. In some cases a maximum response to 5-HT could not be demonstrated as high doses caused such a profound fall in BP that the animal died. The greatest change obtained is therefore taken as the maximum response.

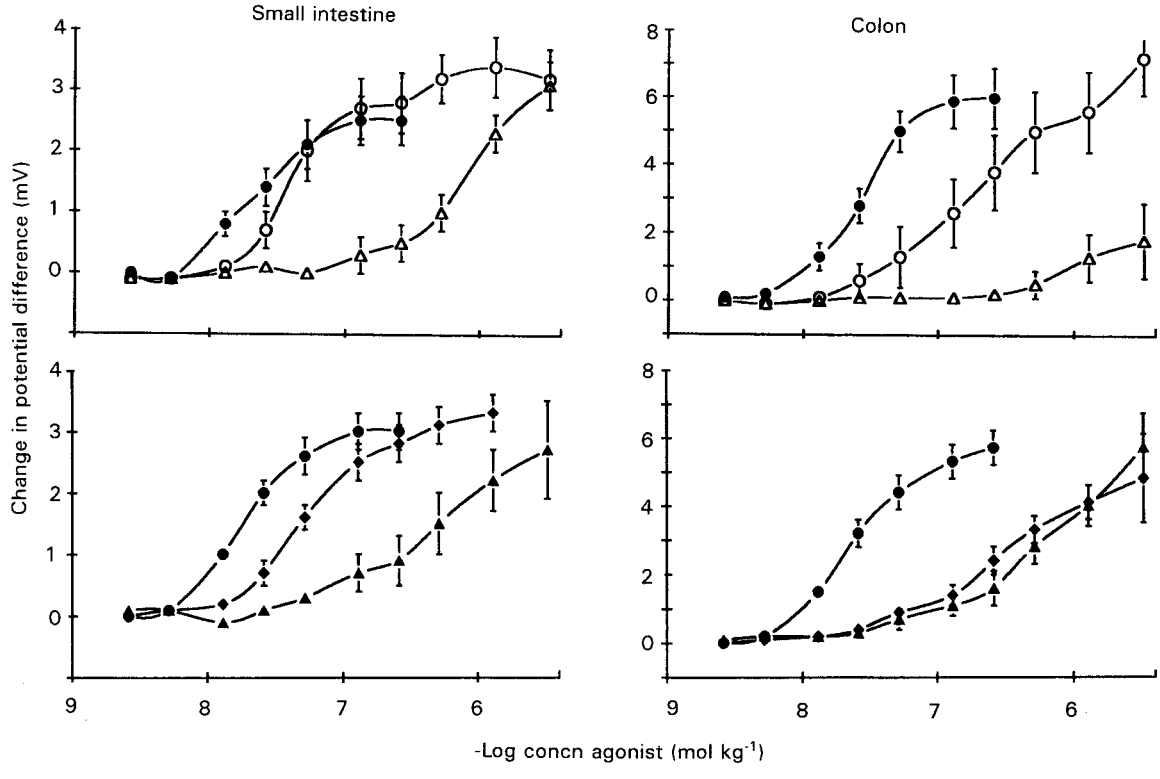

FIG. 1. Effects of 5-HT (●, n = 14), 2-CH_3-5-HT (○, n = 6) and 5-MT (◆, n = 14) on the PD across rat small intestine and colon in-vivo. The effects of granisetron ($8{\cdot}6 \times 10^{-8}$ mol kg^{-1}) on the response to 2-CH_3-5-HT (△, n = 6) and ketanserin ($7{\cdot}6 \times 10^{-8}$ mol kg^{-1}) on the response to 5-MT (▲, n = 7) are also shown. The rises in PD are plotted as a function of log agonist dose and each point represents the mean ± s.e.m. of the number of observations indicated. In some cases the size of the error bar is less than that of the symbol.

Results

The basal PD was 5·7 ± 0·3 mV in the small intestine and 10·3 ± 0·5 mV in the colon (n = 33), the serosa being positive with respect to the mucosa in both cases. 5-HT induced dose-dependent rises in transintestinal electrical activity (Fig. 1) with maximum PD changes of 3·3 ± 0·2 mV in the small intestine and 6·0 ± 0·3 mV in the colon and ED50 values of 2·4 ± 0·2×10^{-8} mol kg^{-1} and 2·8 ± 0·2×10^{-8} mol kg^{-1} respectively (n = 33).

Under basal conditions the heart rate was 404 ± 6 beats min^{-1}, systolic pressure was 148 ± 3 mmHg and diastolic pressure was 114 ± 3 mmHg (n = 33). Intravenously administered 5-HT causes a triphasic change in cardiovascular activity: an initial bradycardia and hypotension mediated by 5-HT_3 receptors, followed by a transient hypertension (pressor phase) mediated by 5-HT_2 receptors and finally a prolonged hypotension (depressor phase) mediated by 5-$HT_{1\text{-like}}$ receptors (Kalkman et al 1984). In the present study, 5-HT induced an initial bradycardia with a maximum fall in heart rate of 180 ± 12 beats min^{-1}, a transient rise in systolic pressure with a maximum increase of 65 ± 5 mmHg and a prolonged fall in diastolic pressure with a maximum decrease of 63 ± 2 mmHg. Corresponding ED50 values were 1·2 ± 0·1×10^{-7}, 1·2 ± 0·1×10^{-7} and 2·0 ± 0·2 x 10^{-8} mol kg^{-1} (n = 33).

The selective 5-HT_3 agonist 2-CH_3-5-HT (Richardson et al 1985) caused dose-dependent rises in the PD across both the small intestine and the colon (Fig. 1). The maximum changes obtained were greater than those observed with 5-HT, although the ED50 values were also greater (Table 1). The selectivity of 2-CH_3-5-HT action at 5-HT_3 receptors was confirmed by cardiovascular data. This agent induced a maximum fall in heart rate that did not differ from that induced by 5-HT (5-HT = 233 ± 34 beats min^{-1}, 2-CH_3-5-HT = 171 ± 40 beats min^{-1} (n = 6), $P > 0.05$), but it failed to cause either a pressor or depressor phase in BP. In contrast, 5-MT, an agonist that lacks affinity for 5-HT_3 receptors (Fozard 1985; Leff & Martin 1988; Craig et al 1990), failed to induce a fall in heart rate, but caused pressor and depressor phases that did not differ from those obtained in response to 5-HT (maximum pressor response: 5-HT = 72 ± 9 mmHg; 5-MT = 75 ± 9 mmHg, $P > 0.05$; maximum depressor response: 5-HT = 61 ± 4 mmHg; 5-MT = 66 ± 4 mmHg, $P > 0.05$, n = 14). 5-MT also caused a rise in the PD across both the small intestine and the colon (Fig. 1), although in comparison with 5-HT the maximum response it produced was smaller in the colon (Table 1). In both regions of the intestine the ED50 values were greater than those for 5-HT (Table 1).

The 5-HT_3 antagonist granisetron (Sanger & Nelson 1989), at a dose of 8·6×10^{-8} mol kg^{-1}, caused a small, but significant inhibition of the secretory response to 5-HT in the small intestine where it increased the ED50 by a factor of 1.8 (Fig. 2, Table 2). Granisetron had a more pronounced inhibitory effect in the colon (Fig. 2), causing a 4.1-fold increase in the ED50 and also reducing the maximum PD change to a level that did not differ from that obtained with 5-MT ($P > 0.05$, Table 2). The selectivity of granisetron action was confirmed by its ability to antagonize the 5-HT-induced bradycardia (maximum response: control = 156 ± 14 beats min^{-1}; + granisetron = 81 ± 27 beats min^{-1}, $P < 0.01$, n = 7) without any significant inhibition of the pressor and depressor phases. Increasing the dose of granisetron to 8·6×10^{-7} mol kg^{-1} caused no further inhibition of either the intestinal or heart rate responses to 5-HT ($P > 0.05$ in all cases).

The effect of 2-CH_3-5-HT on the PD in the small intestine was inhibited by granisetron (8·6 × 10^{-8} mol kg^{-1}) which increased the ED50 value by a factor of 11·8 (Fig. 1, Table 2). In the colon, granisetron reduced the maximum rise in PD induced by 2-CH_3-5-HT to a level that did not differ significantly from zero ($P > 0.05$, Fig. 1, Table 2).

The 5-HT_2 antagonist ketanserin (Bradley et al 1986), at a dose of 7·6×10^{-8} mol kg^{-1}, abolished the pressor response to both 5-HT (maximum response: control = 39 ± 4 mmHg; + ketanserin = 0 ± 0 mmHg, $P < 0.001$, n = 6) and 5-MT (maximum response: control = 93 ± 11 mmHg; + ketanserin = 0 ± 0 mmHg, $P < 0.001$, n = 7), without any effect on the fall in heart rate induced by 5-HT ($P > 0.05$) or the depressor responses to 5-HT and 5-MT ($P > 0.05$ in both cases). It did not however, alter the increased electrical activity induced by 5-HT in either the small intestine or the colon (Fig. 2, Table 2), but it did inhibit the intestinal effects of 5-MT in both regions of the gut, increasing the ED50 and, in the small intestine, reducing the maximum PD change as well (Fig. 1, Table 2). Increasing the dose of ketanserin to 3·0 × 10^{-7} mol kg^{-1} and 1·2 × 10^{-6} mol kg^{-1} caused no further inhibition of the intestinal response to 5-MT.

Although ketanserin alone had no effect on the intestinal

Table 1. Comparison of the effects of 5-HT with those of 2-CH_3-5-HT and 5-MT on the transintestinal electrical activity of rat small intestine and colon in-vivo. The rise in PD is given as the maximum response (PD_{max}) in mV and the ED50 in mol kg^{-1}. Each value represents the mean ● s.e.m. of the number of observations indicated. The significance of the differences between the effects of 5-HT and those of 2-CH_3-5-HT and 5-MT was assessed by a paired *t*-test.

	n	Small intestine		Colon	
		PD_{max}	ED50	PD_{max}	ED50
5-HT	6	2·7 ± 0·4	2·6 ± 0·4 × 10^{-8}	6·2 ± 0·9	2·8 ± 0·3 × 10^{-8}
2-CH_3-5-HT		3·6 ± 0·5	7·1 ± 1·4 × 10^{-8}	7·7 ± 1·0	5·4 ± 2·3 × 10^{-7}
		$P < 0.05$	$P < 0.01$	$P < 0.01$	$P < 0.05$
5-HT	14	3·2 ± 0·3	2·1 ± 0·3 × 10^{-8}	5·8 ± 0·5	2·8 ± 0·3 × 10^{-8}
5-MT		3·3 ± 0·3	7·1 ± 1·3 × 10^{-8}	4·1 ± 0·5	2·2 ± 0·3 × 10^{-7}
		$P > 0.05$	$P < 0.01$	$P < 0.001$	$P < 0.001$

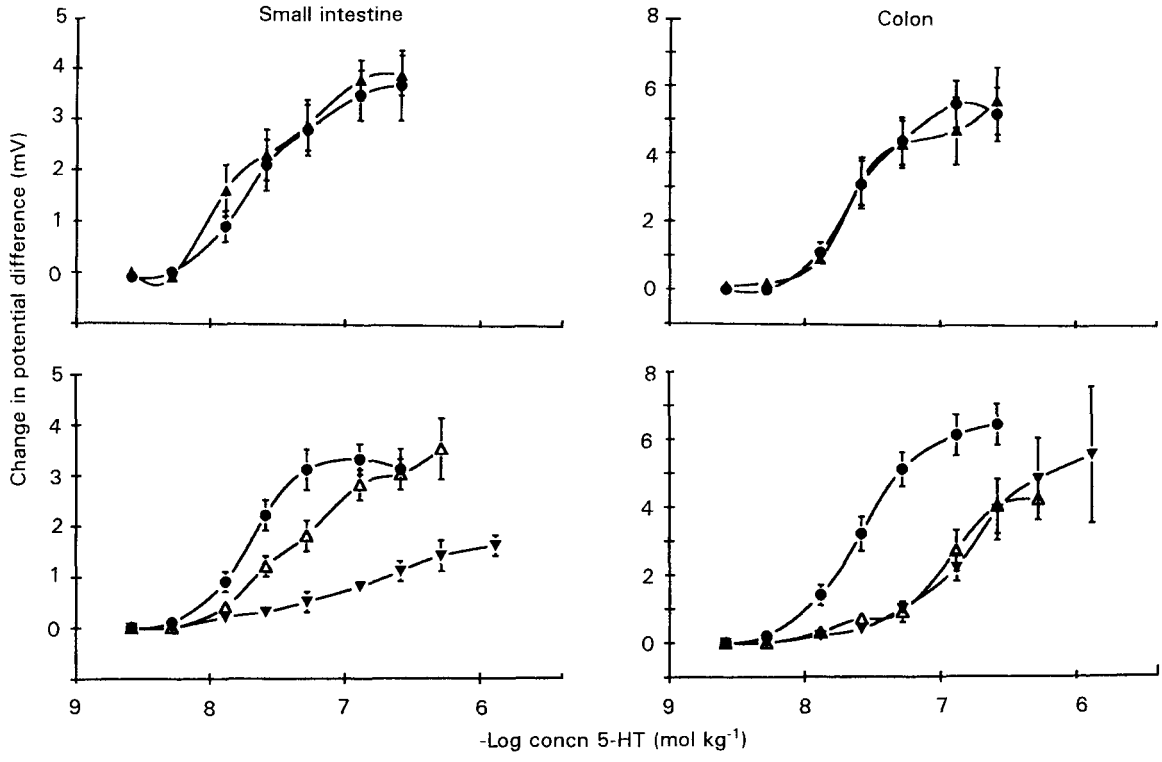

FIG. 2. Effects of ketanserin (▲, 7·6 × 10^{-8} mol kg^{-1}, n = 6) and granisetron (△, 8·6 × 10^{-8} mol kg^{-1}, n = 7) on the increased transintestinal electrical activity induced by 5-HT (●) in rat small intestine and colon in-vivo. The effects of ketanserin in the presence of granisetron (▼, n = 7) are also shown. The rises in PD are plotted as a function of log agonist dose and each point represents the mean ± s.e.m. of the number of observations indicated. In some cases the size of the error bar is less than that of the symbol.

responses to 5-HT, in the presence of granisetron (Fig. 2, Table 2) it demonstrated inhibitory actions that were similar to those that it exerted on the effects of 5-MT.

Discussion

It is now clear that multiple 5-HT receptor subtypes exist (Hoyer & Schoeffter 1991), but those responsible for 5-HT-induced intestinal secretion have yet to be fully elucidated. The situation is complicated by the fact that there appear not only to be species differences (McClean et al 1993), but also variations along the length of the intestinal tract (Ayton et al 1995), an observation that is extended in the present study. This investigation suggests in addition, that more than one 5-HT-receptor subtype contributes to the overall secretory response, supporting views previously expressed (Scott et al 1992; Ayton et al 1995).

The involvement of different 5-HT receptor subtypes was investigated by examining the actions of various agonists and antagonists. The 5-HT_3 agonist 2-CH_3-5-HT increased the PD in both the small intestine and the colon, inducing maximum responses that were larger than those obtained with 5-HT (Fig. 1, Table 1). Its actions appear to be selective at the 5-HT_3 receptor as its effects were antagonized by granisetron (Fig. 1) and it only elicited an initial bradycardia and fall in blood pressure. The enhanced maximum rise in PD could be explained if receptors other than 5-HT_3 activated an antisecretory pathway designed to modulate the secretory response. Such an inhibitory component in the response to 5-HT has been implicated in both the small intestine (Beesley & Levin 1991) and the colon (Nzegwu & Levin 1990) where an enteric neural cholinergic adrenergic pathway (ENCAP) was proposed, although the 5-HT receptor responsible was not investigated.

The data with 2-CH_3-5-HT suggest that 5-HT_3 receptors play a major role in the activation of intestinal secretion by 5-HT. This is not however, supported by the actions of granisetron on the response to 5-HT itself. Granisetron causes only a small inhibition in the small intestine, although it has a more marked effect in the colon (Fig. 2, Table 2). Moreover, 5-MT, an agonist that lacks affinity for 5-HT_3 receptors, was also able to induce a secretory response (Fig. 1, Table 1), an effect that is also observed in-vitro (Bunce et al 1991; Hardcastle & Hardcastle 1991; Hardcastle et al 1993; Hansen 1994). Because of its affinity for 5-HT_4 receptors (Hoyer & Schoeffter 1991) the ability of 5-MT to induce a secretory response has been taken as evidence that this receptor subtype is implicated in the control of intestinal secretion (Hansen 1994). It should not be overlooked however, that 5-MT can also activate 5-HT_{1-like} and 5-HT_2 receptors and this is confirmed in the present study by its ability to induce pressor and prolonged depressor responses in the cardiovascular system.

The possibility that the 5-HT_2 receptor could be involved in the intestinal secretory response was tested using the 5-HT_2 antagonist ketanserin (Bradley et al 1986). In-vitro studies in rat colon have produced conflicting results concerning the antagonism of the 5-HT response by this agent,

Table 2. Actions of 5-HT antagonists on the transintestinal electrical response of rat small intestine and colon in-vivo to 5-HT stimulation. The effects of granisetron ($8{\cdot}6 \times 10^{-8}$ mol kg^{-1}) on the responses to 5-HT and 2-CH_3-5-HT and those of ketanserin ($7{\cdot}6 \times 10^{-8}$ mol kg^{-1}) on the responses to 5-HT, 5-MT and 5-HT in the presence of granisetron are shown. The rise in PD is given as the maximum response (PD_{max}) in mV and the ED50 in mol kg^{-1}. Each value represents the mean ± s.e.m. of the number of observations indicated. The significance of the differences between the responses in the absence and presence of antagonists was assessed by a paired *t* test. * Effect of ketanserin on the responses to 5-HT in the presence of granisetron.

	n	Small intestine		Colon	
		PD_{max}	ED50	PD_{max}	ED50
5-HT	7	3·4 ± 0·4	$2{\cdot}3 \pm 0{\cdot}2 \times 10^{-8}$	6·6 ± 0.5	$2{\cdot}9 \pm 0{\cdot}4 \times 10^{-8}$
+ granisetron		3·1 ± 0·4	$4{\cdot}2 \pm 0{\cdot}3 \times 10^{-8}$	4·4 ± 0.7	$1{\cdot}2 \pm 0{\cdot}1 \times 10^{-7}$
		$P > 0{\cdot}05$	$P < 0{\cdot}01$	$P < 0{\cdot}01$	$P < 0{\cdot}001$
+ granisetron					
+ ketanserin		2·1 ± 0·4	$1{\cdot}8 \pm 0{\cdot}4 \times 10^{-7}$	5·2 ± 1·3	$1{\cdot}9 \pm 0{\cdot}2 \times 10^{-7}$
		$P < 0{\cdot}001$*	$P < 0{\cdot}01$*	$P > 0{\cdot}05$*	$P < 0{\cdot}05$*
2-CH_3-5-HT	6	3·6 ± 0·5	$7{\cdot}1 \pm 1{\cdot}4 \times 10^{-8}$	7·7 ± 1·0	$5{\cdot}4 \pm 2{\cdot}3 \times 10^{-7}$
+ granisetron		3·1 ± 0·3	$8{\cdot}4 \pm 1{\cdot}5 \times 10^{-7}$	2·2 ± 0·9	–
		$P > 0{\cdot}05$	$P < 0{\cdot}01$	$P < 0{\cdot}01$	
5-HT	6	3·9 ± 0·7	$3{\cdot}0 \pm 0{\cdot}7 \times 10^{-8}$	5·8 ± 0·7	$2{\cdot}8 \pm 0{\cdot}3 \times 10^{-8}$
+ ketanserin		3·9 ± 0·4	$2{\cdot}4 \pm 0{\cdot}7 \times 10^{-8}$	5·7 ± 0·8	$2{\cdot}7 \pm 0{\cdot}4 \times 10^{-8}$
		$P > 0{\cdot}05$	$P > 0{\cdot}05$	$P > 0{\cdot}05$	$P > 0{\cdot}05$
5-MT	7	3·2 ± 0·6	$6{\cdot}6 \pm 1{\cdot}2 \times 10^{-8}$	4·5 ± 0·8	$1{\cdot}9 \pm 0{\cdot}4 \times 10^{-7}$
+ ketanserin		2·5 ± 0·6	$5{\cdot}4 \pm 1{\cdot}4 \times 10^{-7}$	5·1 ± 0·8	$5{\cdot}0 \pm 0{\cdot}7 \times 10^{-7}$
		$P < 0{\cdot}05$	$P < 0{\cdot}05$	$P > 0{\cdot}05$	$P < 0{\cdot}01$

with one group reporting no effect (Bunce et al 1991) and another demonstrating an inhibition (Siriwardena et al 1991; Siriwardena & Kellum 1993). In-vivo ketanserin has been shown to have no effect on the electrical response of the small intestine to 5-HT, although it partially inhibits the stimulation of fluid secretion (Beubler et al 1990, Beubler & Horina 1990), suggesting that different receptor subtypes could be involved in these two aspects of the intestinal response to 5-HT challenge. The lack of effect of ketanserin on the electrical response of the small intestine to 5-HT in-vivo has been confirmed in the present study and extended to the proximal colon (Fig. 2, Table 2). Ketanserin did, however, inhibit the response to 5-MT in the small intestine, suggesting that in this region of the gut 5-HT_2 receptors could play a role in the stimulation of secretion in the absence of 5HT_3-receptor activity. Further evidence for this view comes from the observation that ketanserin can also inhibit the response to 5-HT when 5-HT_3 receptors have been antagonized by granisetron (Fig. 2, Table 2). This is also consistent with the fact that cisapride, an antagonist at 5-HT_2 and 5-HT_3 receptors (Schuurkes & Van Nueten 1985; Dunbar et al 1986; Van Nueten & Schuurkes 1989), has been shown to inhibit the electrical response of the small intestine to 5-HT both in-vivo (Beubler et al 1990) and in-vitro (Cooke & Carey 1984, 1985; Moriarty et al 1987).

In contrast, the colonic response to 5-MT, as well as that to 5-HT in the presence of granisetron, was only minimally affected by ketanserin (Figs 1, 2, Tables 1, 2), so in this region of the gut there is little evidence for 5-HT_2-receptor involvement even in the absence of 5-HT_3-receptor activity. These findings are consistent with in-vitro data reported for distal colon by Bunce et al (1991), although Siriwardena et al (1991) have demonstrated an inhibition of the electrical response to 5-HT by ketanserin.

The present study has investigated the Cl-secretory response of rat small intestine and proximal colon to stimulation by 5-HT. The fact that this response is mimicked by both 2-CH_3-5-HT and 5-MT indicates that more than one receptor subtype must contribute to the overall response. In both regions 5-HT_3 receptors play a role and in the small intestine there is also evidence for 5-HT_2 receptor involvement. Studies with 5-HT antagonists also suggest that more than one 5-HT-receptor subtype is involved in intestinal secretion, since agents that are most effective in blocking the response are those that act at more than one receptor subtype. These include the 5-HT_2 and 5-HT_3 antagonist cisapride (Cooke & Carey 1984, 1985; Beubler at al 1990; Bunce et al 1991), the 5-HT_3 and 5-HT_4 antagonist tropisetron (Baird & Cuthbert 1987; Cooke et al 1991; Bunce et al 1991) and the 5-HT_{1C} and 5-HT_2 antagonist mianserin (Hardcastle et al 1981).

The 5-HT-induced secretory response involves not only a stimulation of electrogenic Cl secretion, but also an inhibition of NaCl absorption, an electrically silent process whose activity is not detected when electrical techniques are used to monitor the response. There is evidence that the effects of 5-HT on these two mechanisms may also involve different receptor subtypes. When the effects of antagonists on both the electrical changes and fluid secretion induced by 5-HT were compared, it was found that ketanserin reduced the fluid secretion but had no effect on the electrical response, while cisapride had the converse effect (Beubler et al 1990). Moreover, fluid secretion induced by 5-HT can be partially inhibited by either ketanserin, a 5-HT_2 antagonist (Bradley et al 1986), or tropisetron, a 5-HT_3 and 5-HT_4 antagonist (Buchheit et al 1992), but when the two antagonists are present together the stimulation of fluid secretion is totally abolished (Beubler & Horina 1990).

The mechanisms involved in the stimulation of intestinal secretion by 5-HT appear to be complex, with evidence accumulating to support the concept that several different 5-HT-receptor subtypes are involved. Not only are different subtypes likely to be concerned with the control of the two ion-transport processes that contribute to the secretory response, but, as the present study shows, the regulation of a single mechanism, namely that for the electrogenic

secretion of Cl, involves more than one 5-HT-receptor subtype.

Acknowledgements

We would like to thank Bernadette Ayton for her skilled technical assistance. We are grateful to SmithKline Beecham Pharmaceuticals, Harlow, Essex and to Janssen Pharmaceutica, Beerse, Belgium for the gift of chemicals.

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