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Neural Involvement in 5-Hydroxytryptamine-induced Net Electrogenic Ion Secretion in the Rat Intestine In-vivo

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Abstract

5-Hydroxytryptamine (5-HT) induces active electrogenic anion secretion by both the small intestine and the colon, responses that can be detected from measurements of transmural electrical activity. This approach was adopted to examine the involvement of neural mechanisms in 5-HT-induced secretion in rat proximal jejunum, distal ileum and proximal colon in-vivo.

Under control conditions, 5-HT caused maximum rises in transintestinal potential difference of $4{\cdot}7 \pm 0{\cdot}3$, $3{\cdot}8 \pm 0{\cdot}4$ and $7{\cdot}6 \pm 0{\cdot}3$ mV, respectively, with corresponding ED50 values of 28 ± 3, 38 ± 4 and 41 ± 4 nmol kg^{-1} ($n = 12$). In each region examined a neural component in the secretory response to 5-HT was identified. Hexamethonium (22 μmol kg^{-1}) reduced the 5-HT response in each region; in the jejunum and colon, it also attenuated the responses to the 5-HT_3 agonist, phenylbiguanide and to 5-methoxytryptamine (5-MeOT), an agonist at all 5-HT receptors except 5-HT_3, indicating that in these regions the nicotinic pathway can be activated by more than one 5-HT receptor subtype. Atropine (0·27 and 2·7 μmol kg^{-1}) was found to have regional effects on the intestinal responses to 5-HT receptor agonists. In the jejunum, evidence for a pro-secretory muscarinic pathway which could be activated by more than one 5-HT receptor subtype was found. In the ileum and colon no muscarinic pro-secretory pathway was identified, indeed in the colon, an anti-secretory pathway may be present. This muscarinic anti-secretory pathway was observed with phenylbiguanide and 5-MeOT, but not 5-HT. Substance P release does not appear to be involved in mediating the intestinal secretory response to 5-HT.

5-HT-induced intestinal anion secretion may involve a direct secretory action on the enterocyte which can be modified by neurally-mediated pro-secretory and anti-secretory pathways, the balance between these processes varying down the length of the gut.

5-Hydroxytryptamine (5-HT) administration induces intestinal fluid and electrolyte secretion in a variety of different species (Cooke 1987). This secretion is a consequence of inhibition of neutral NaCl absorption together with a stimulation of Cl^- or HCO_3^- secretion (Hardcastle et al 1981; Urquhart et al 1988). The anion secretion is electrogenic and therefore the intestinal response to 5-HT can be detected as an increase in transmural electrical activity.

The pathways involved in these actions of 5-HT have yet to be fully elucidated. There is some evidence for a direct action on the transporting cells, the enterocytes. 5-HT has been shown to increase cytosolic Ca^{2+} levels in enterocytes isolated from the chicken (Hirose & Chang 1988) and also to cause a hyperpolarization in an intestinal cell line, an action shared by other secretagogues (Yada & Okada 1984).

There are, however, some indications that at least part of the secretory response to 5-HT is mediated via the enteric nervous system (ENS). Inhibition of neural activity by administration of tetrodotoxin reduces the response to 5-HT in the guinea-pig ileum (Cooke & Carey 1985), rat jejunum (Castro et al 1987) and ileum (Rolfe & Levin 1995) but not in the human jejunum (Budhoo & Kellum 1994) or ileum (Burleigh & Borman 1993). In the colon, tetrodotoxin is reported to be without effect in rat (Zimmerman & Binder 1984; Bunce et al 1991) and hen (Hansen 1992) when stripped preparations, where the outer muscle layers and myenteric plexus have been removed, are used. However, it causes an inhibition of the 5-HT response in unstripped tissues (Siriwardena et al 1991). Such observations suggest that neural mechanisms may, in some circumstances, contribute to the intestinal secretory response to 5-HT.

5-HT is known to act on enteric neurones where it can regulate the release of acetylcholine (Cooke et al 1991), an agent that also acts to induce Cl^- secretion (Isaacs et al 1976; Browning et al 1977). The possible involvement of a cholinergic pathway in the 5-HT intestinal secretory response has been investigated by several groups using the non-selective muscarinic receptor antagonist atropine, but it has failed to produce consistent effects. Some studies in the small intestine have found that atropine inhibits the response to 5-HT (Cooke & Carey 1985; Castro et al 1987), while others have demonstrated an enhanced response in its presence (Beesley & Levin 1991). Similarly in the colon, reported actions of atropine range from no effect (Zimmerman & Binder 1984; Bunce et al 1991; Hansen 1992) to an enhanced response (Nzegwu & Levin 1990). These findings suggest that cholinergic mechanisms may have both pro-secretory and anti-secretory effects that modify the response to 5-HT.

There also appear to be links between the actions of 5-HT and substance P. Substance P is a neurotransmitter found within the ENS coexisting with acetylcholine in cholinergic nerves and 5-HT and gastrin releasing peptide (GRP) in

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myenteric neurones (Cooke 1986). In the rat, the majority of the substance P containing-neurones are intrinsic in origin (Holzer et al 1980). Substance P is thought to induce intestinal secretion by a direct action on the enterocyte (Cooke 1989) and via the ENS through release of vasoactive intestinal polypeptide (VIP) (Lundgren et al 1989), 5-HT and neurotensin (Cooke 1987). Substance P is also involved in mediating atropine-sensitive, 5-HT-induced intestinal smooth muscle contractions (Chahl 1983). Thus the actions of substance P and 5-HT in the gastrointestinal tract appear to be closely associated.

The influence of neural mechanisms on the secretory response of rat small intestine and colon to 5-HT receptor agonists was determined using an in-vivo preparation, thus ensuring the integrity of the neural network. A preliminary report of the findings has been presented (Franks et al 1993).

Materials and Methods

Animals

Male Wistar rats, 230–250 g, were obtained from the Sheffield Field Laboratories and allowed free access to food and water. They were anaesthetized with sodium pentobarbitone (70 mg kg^{-1}, i.p.).

Measurement of transintestinal electrical activity

The transintestinal potential difference (PD) across 5-cm segments of the proximal jejunum, terminal ileum and proximal colon were measured in-vivo as described by Franks et al (1993), using agar/KCl bridges connected via calomel half cells to differential input electrometers. Blood pressure was measured at the femoral artery using a Druck pressure transducer (type S/N 3389) and heart rate was calculated from the pulse pressure by a Lectromed rate meter (model 5250). Blood pressure, heart rate and transintestinal PDs were displayed both on a four-channel chart recorder (Electromed, Multitrace 4), and a computer using CED CHART software and analysed by computer utilizing CED SPIKE2 software. All drugs were administered in 0·1 mL through the femoral vein and washed in with 0·2 mL 154 mM NaCl.

Non-cumulative 5-HT receptor agonist dose-response curves were constructed using ascending doses in the absence and presence of either atropine (0·27 and 2·7 μmol kg^{-1}), hexamethonium (22 μmol kg^{-1}) or [D-Pro^4, Trp^{7,9,10}] substance P (fragment 4-11) (16·6 nmol kg^{-1}). As rats differed in their sensitivity to 5-HT and 5-HT receptor agonists, each animal acted as its own control. Extending the dose-response curves after antagonist treatment was not undertaken as the higher doses of 5-HT caused a profound decrease in blood pressure and further increasing the dose would have led to the death of the animal.

The effects of atropine and hexamethonium on the intestinal responses to prostaglandin E_2 (PGE_2) and acetylcholine were also investigated to establish the selectivity of their actions.

Expression of results

The results are expressed as the mean ± s.e.m. of the number of observations indicated. Statistical significance was tested using Student's paired *t*-test as no desensitization of the 5-HT response is observed in-vivo (Hardcastle et al 1994). A *P* value of less than 0·05 was considered to be significant.

Chemicals

5-Hydroxytryptamine-creatinine sulphate complex, 5-methoxytryptamine hydrochloride, hexamethonium bromide, atropine methyl nitrate, substance P and [D-Pro^4, Trp^{7,9,10}] substance P (fragment 4-11) were obtained from Sigma Chemical Co., Poole, UK; *O*-acetylcholine chloride was from BDH Chemicals Ltd, Poole, UK, and 1-phenylbiguanide from Aldrich Chemical Co. Ltd, Dorset, UK.

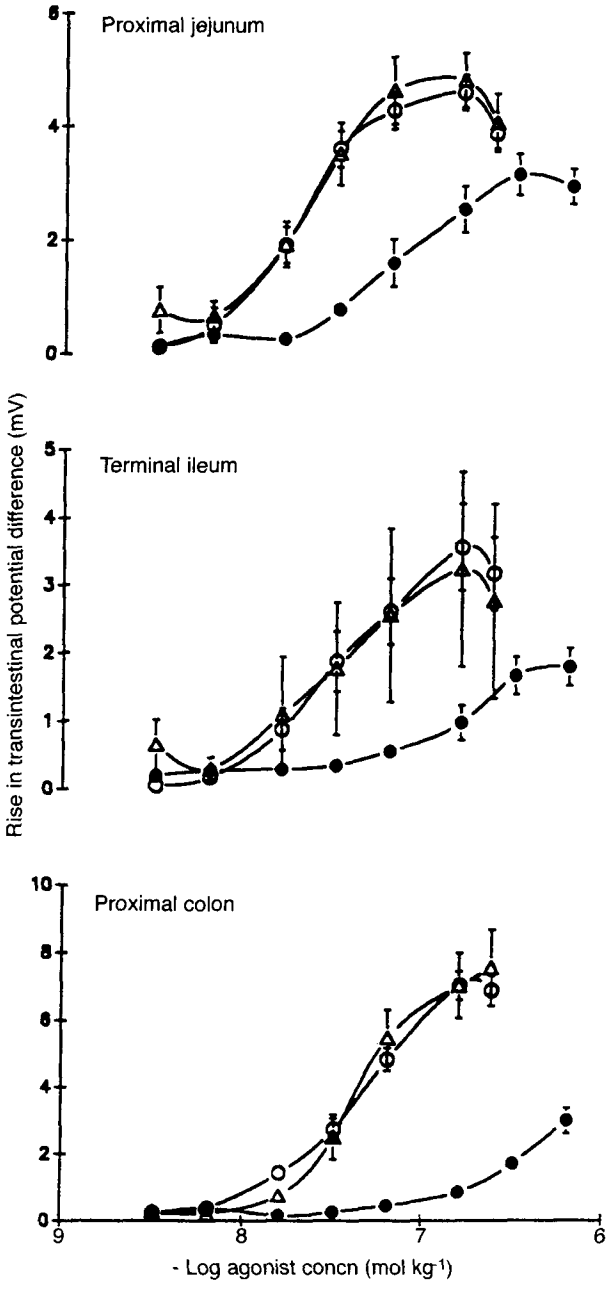

FIG. 1. Dose–response curves to 5-HT receptor agonists in proximal jejunum, terminal ileum and proximal colon. 5-HT (○, n = 12), phenylbiguanide (△, n = 6) and 5-MeOT (●, n = 6). Rise in transintestinal PD (mV) is plotted against dose of agonist (mol kg^{-1}), with each point representing the mean ± s.e.m. of the number of observations indicated.

Table 1. Effect of atropine ($2{\cdot}7\,\mu mol\,kg^{-1}$) on the 5-HT-, phenylbiguanide- and 5-MeOT-induced rises in transintestinal PD in the jejunum, ileum and colon. Each value represents the mean PD_{max} (mV) evoked by the 5-HT receptor agonists ± s.e.m. of 6 observations.

		5-HT	Phenylbiguanide	5-MeOT
Jejunum	Control	4·1 ± 0·4	4·9 ± 0·5	3·2 ± 0·3††
	+ atropine	2·8 ± 0·4*	2·8 ± 0·4**	2·8 ± 0·3**
Ileum	Control	2·9 ± 0·5	3·3 ± 1·3	1·8 ± 0·3†
	+ atropine	2·2 ± 0·5	3·4 ± 1·2	1·8 ± 0·2
Colon	Control	8·1 ± 0·4	7·5 ± 1·0	3·0 ± 0·4††
	+ atropine	8·4 ± 0·7	9·1 ± 0·6*	4·0 ± 0·3*

*$P < 0{\cdot}05$, **$P < 0{\cdot}01$ compared with control, †$P < 0{\cdot}05$, ††$P < 0{\cdot}001$ compared with 5-HT experiments.

Results

5-HT induced a dose-dependent rise in transintestinal PD in the jejunum, ileum and colon (Fig. 1, Table 1). Basal PDs were 5·5 ± 0·5, 3·1 ± 0·5 and 10·3 ± 0·3 mV, with maximal rises in transintestinal PD (PD_{max}) of 4·7 ± 0·3, 3·8 ± 0·4 and 7·6 ± 0·3 mV, and ED50 values of 28 ± 3, 38 ± 4 and 41 ± 4 nmol kg^{-1}, respectively (n = 12 in each case).

Intravenous administration of 5-HT induces a triphasic cardiovascular response, with each phase being dose-dependent and mediated by activation of a different receptor type (Kalkman et al 1984). The first phase is a rapid and transient hypotension and bradycardia mediated by 5-HT_3 receptors on vagal afferents of the heart, known as the Bezold-Jarisch reflex. The second phase is a transient hypertension mediated by 5-$HT_{2A-like}$ (i.e. ketanserin-sensitive) receptors, followed by the third phase, a prolonged hypotension mediated by 5-HT_{1-like} receptors. The maximum cardiovascular responses to 5-HT were −215 ± 18 beats min^{-1}, +27 ± 4 mmHg and −47 ± 2 mmHg respectively (n = 11).

Phenylbiguanide, a selective agonist at 5-HT_3 receptors (Fozard 1990), evoked a rise in transintestinal PD in each of the three regions which was similar in magnitude and potency to that induced by 5-HT (Fig. 1, Table 1; $P > 0{\cdot}05$ in all cases; n = 6). Phenylbiguanide also caused a fall in heart rate similar to that induced by 5-HT ($P > 0{\cdot}05$), but failed to elicit a transient hypertension or prolonged hypotension (3 ± 1 and 6 ± 1 mmHg respectively, n = 5 in each case).

5-Methoxytryptamine (5-MeOT), an agonist at 5-$HT_{1,2\,and\,4}$, but not at 5-HT_3 receptors (Fozard 1990; Bockaert et al 1992), also induced a rise in transintestinal PD in the jejunum, ileum and colon (Fig. 1). However, in each case the PD_{max} was smaller (Table 1) and the ED50 values larger (87 ± 15 nmol kg^{-1}, $P < 0{\cdot}01$; 115 ± 26 nmol kg^{-1}, $P < 0{\cdot}05$; 240 ± 34 nmol kg^{-1}, $P < 0{\cdot}01$ respectively, n = 6) than those obtained with 5-HT, indicating that 5-MeOT is a less potent secretagogue than 5-HT.

Table 2. The effect of atropine on the acetylcholine-induced rise in transintestinal PD in the jejunum, ileum and colon.

	PD_{max} (mV)		
	Control	$0{\cdot}27\,\mu mol\,kg^{-1}$ atropine	$2{\cdot}7\,\mu mol\,kg^{-1}$
Jejunum	7·3 ± 0·5	5·5 ± 0·7*	4·7 ± 0·7*
Ileum	2·0 ± 0·6	1·2 ± 0·3	1·2 ± 0·2
Colon	5·9 ± 1·0	10·0 ± 0·4	9·3 ± 0·9
	ED50 (nmol kg^{-1})		
	Control	$0{\cdot}27\,\mu mol\,kg^{-1}$ atropine	$2{\cdot}7\,\mu mol\,kg^{-1}$
Jejunum	60 ± 4	720 ± 90***	1087 ± 240**
Ileum	99 ± 55	970 ± 300	1040 ± 150**
Colon	96 ± 10	1280 ± 110**	1120 ± 130***

Each value represents the mean ± s.e.m. of 4 observations. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$ compared with control.

Effects of atropine

Atropine inhibited the secretory response to acetylcholine in each of the regions examined (Table 2). In the jejunum and colon, atropine ($0{\cdot}27$ and $2{\cdot}7\,\mu mol\,kg^{-1}$) caused similar increases in the ED50 values. The ileal response to acetylcholine was small, as has been found previously by Young & Levin (1989). In this region only the higher dose of atropine significantly increased the ED50 value. The ileal and colonic PD_{max} values were unaltered by either $0{\cdot}27$ or $2{\cdot}7\,\mu mol\,kg^{-1}$ atropine (the apparent increase in colonic PD_{max} in the presence of atropine was due to the true PD_{max} not being obtained in this region under control conditions owing to the profound decrease in blood pressure evoked by acetylcholine), although in the jejunum the PD_{max} was decreased (Table 2).

Atropine ($0{\cdot}27$ and $2{\cdot}7\,\mu mol\,kg^{-1}$) reduced the 5-HT-induced jejunal PD_{max} from 4·2 ± 0·2 to 2·6 ± 0·3 mV ($P < 0{\cdot}01$) and 2·7 ± 0·4 mV ($P < 0{\cdot}05$) respectively. Atropine ($0{\cdot}27\,\mu mol\,kg^{-1}$) reduced the ileal PD_{max} from 2·6 ± 0·3 to 1·7 ± 0·6 mV ($P < 0{\cdot}05$), whilst $2{\cdot}7\,\mu mol\,kg^{-1}$ was without effect ($P > 0{\cdot}05$). ED50 values in both the jejunum and ileum were unaffected by atropine ($P > 0{\cdot}05$ in all cases). Atropine had no effect on colonic PD_{max} or ED50 values ($P > 0{\cdot}05$, n = 6 in each case).

Atropine ($2{\cdot}7\,\mu mol\,kg^{-1}$) also reduced the PD_{max} induced by phenylbiguanide and 5-MeOT in the jejunum by 43 ± 6 and 13 ± 2% (Table 1), respectively compared with 31 ± 8% inhibition of the response to 5-HT. Neither the phenylbiguanide- nor the 5-MeOT-induced rises in transintestinal PD were reduced by atropine in the ileum (Table 1). In the colon, atropine potentiated the maximum phenylbiguanide and 5-MeOT responses by 31 ± 15 and 39 ± 13%, respectively, in contrast to its lack of effect on the 5-HT response (Table 1). Atropine did not alter ED50 values for either phenylbiguanide or 5-MeOT ($P > 0{\cdot}05$ in all cases).

Effects of hexamethonium

Hexamethonium ($22\,\mu mol\,kg^{-1}$) induced a fall in blood pressure (systolic: −56 ± 4 mmHg; diastolic: −51 ± 3 mmHg) and heart rate (−42 ± 3 beats min^{-1}, n = 6 in each case), which was sustained throughout the rest of the experiment indicating an effective ganglionic blockade.

Hexamethonium ($22\,\mu mol\,kg^{-1}$) decreased the 5-HT-induced PD_{max} in the jejunum, ileum and colon (Table 3). The jejunal ED50 value was also increased from 26 ± 3 to 49 ± 5 nmol kg^{-1} (n = 6, $P < 0{\cdot}05$) but neither the ileal nor colonic ED50 values were altered by hexamethonium (n = 6, $P > 0{\cdot}05$).

The same dose of hexamethonium also significantly

Table 3. Effect of hexamethonium (22 μmol kg^{-1}) on the 5-HT-, phenylbiguanide- and 5-MeOT-induced rises in transmural PD in the jejunum, ileum and colon.

		5-HT	Phenylbiguanide	5-MeOT
Jejunum	Control	4·8 ± 0·5	4·1 ± 0·1	2·9 ± 0·4
	+hexamethonium	3·2 ± 0·4*	2·0 ± 0·2**	2·2 ± 0·4**
Ileum	Control	4·3 ± 0·7	2·0 ± 0·6	1·1 ± 0·2
	+hexamethonium	3·0 ± 0·3*	1·0 ± 0·1	1·4 ± 0·2
Colon	Control	6·2 ± 0·5	4·7 ± 0·8	3·6 ± 0·5
	+hexamethonium	4·6 ± 0·5*	2·1 ± 0·3**	2·3 ± 0·2*

Each value represents the mean PD_{max} induced by the 5-HT receptor agonists ± s.e.m. of 6 observations. *$P < 0·05$, **$P < 0·01$ compared with control.

decreased the jejunal and colonic PD_{max} values obtained with phenylbiguanide and 5-MeOT, but had no effect on either response in the ileum (Table 3). As with 5-HT, jejunal ED50 values for phenylbiguanide and 5-MeOT were increased (from 19 ± 4 to 43 ± 10 nmol kg^{-1}, n = 6, $P < 0·05$, and from 63 ± 8 to 109 ± 20 nmol kg^{-1}, n = 6, $P < 0·01$), but neither ileal nor colonic ED50 values for these two agonists were altered by hexamethonium ($P > 0·05$ in all cases).

Effects of atropine and hexamethonium on PGE_2-induced rise in transmural PD

PGE_2 induced a dose-dependent rise in transintestinal PD in the jejunum, ileum and colon (PD_{max}: 4·2 ± 0·2, 2·9 ± 0·2 and 6·6 ± 0·4 mV; ED50: 44 ± 4, 42 ± 3 and 65 ± 5 nmol kg^{-1}, respectively, n = 4). Neither atropine (2·7 μmol kg^{-1}) nor hexamethonium (22 μmol kg^{-1}) had any effect on PGE_2-induced secretion in any region ($P > 0·05$, n = 4 in both cases).

Effects of substance P antagonist

[D-Pro^4, Trp^{7,9,10}] substance P (fragment 4-11) (16·6 nmol kg^{-1}), a potent substance P antagonist (Mizrahi et al 1982), increased the ED50 value for substance P in each of the intestinal regions examined but only reduced the PD_{max} in the jejunum (Table 4). The same dose of [D-Pro^4, Trp^{7,9,10}] substance P had no effect on the 5-HT-induced rise in transmural PD in the jejunum or ileum. The colonic response to 5-HT, was however, slightly attenuated in the presence of the substance P antagonist (Table 4).

Discussion

The receptors responsible for 5-HT-induced intestinal secretion have yet to be fully identified, but evidence is emerging that several different 5-HT receptor subtypes contribute to the response (Scott et al 1992; Ayton et al 1995; Hardcastle & Hardcastle 1995). The present investigation adds further weight to this view as both phenylbiguanide, an agonist that acts selectively at 5-HT_3 receptors, and 5-MeOT, an agonist that lacks affinity for 5-HT_3 receptors, were able to mimic the secretory effects of 5-HT in all the regions of the intestinal tract tested. It is, therefore, unlikely that a single type of 5-HT receptor can be solely responsible for the intestinal secretory response to 5-HT.

The site of 5-HT action in initiating the secretory response also remains to be located, but the results reported in this study indicate the involvement of neural mechanisms in the intestinal secretory response to 5-HT challenge. The ganglionic-blocking agent, hexamethonium, inhibited the response to 5-HT in all the regions of intestine examined, indicating the involvement of a nicotinic pathway. 5-HT-induced secretion was mimicked by both phenylbiguanide, an agonist at 5-HT_3 receptors (Fozard 1990) and 5-MeOT an agonist at 5-$HT_{1,2 and 4}$ but not 5-HT_3 receptors (Fozard 1990; Bockaert et al 1992). Thus, the secretory process can be stimulated by more than one receptor subtype. Inhibition

Table 4. Effect of the substance P antagonist, [D-Pro^4, Trp^{7,9,10}] substance P (fragment 4-11), (16·6 nmol kg^{-1}) on the substance P- and 5-HT-induced rises in transintestinal PD in the jejunum, ileum and colon.

	PD_{max} (mV)			
	Substance P	+antagonist	5-HT	+antagonist
Jejunum	5·7 ± 0·6	4·4 ± 0·7**	4·4 ± 0·5	4·3 ± 0·5
Ileum	2·4 ± 0·5	2·4 ± 0·6	2·4 ± 0·5	2·7 ± 0·5
Colon	9·7 ± 0·4	9·2 ± 0·6	7·6 ± 0·7	8·2 ± 0·8
	ED50 (nmol kg^{-1})			
	Substance P	+antagonist	5-HT	+antagonist
Jejunum	0.53 ± 0.07	0.87 ± 0.09**	32 ± 10	26 ± 4
Ileum	0.42 ± 0.06	0.85 ± 0.13*	28 ± 6	36 ± 5
Colon	0.31 ± 0.06	0.68 ± 0.03**	30 ± 6	42 ± 8*

Values represent the mean ± s.e.m. of 6 observations, *$P < 0·05$, **$P < 0·01$ compared with control.

of the response to both these agonists in the jejunum and colon by hexamethonium indicates that the nicotinic pathway can also be activated by more than one subtype. The involvement of such a neural pathway in 5-HT-induced intestinal secretion has also been demonstrated in guinea-pig ileum (Kellum et al 1992) and colon (Cooke et al 1991). In this species however, the majority of the responses to 5-HT is mediated by neuronal mechanisms that are initiated by 5-HT_3 receptors (Cooke et al 1991). In the present study the ileum behaved differently with respect to hexamethonium in that only the response to 5-HT was significantly attenuated. This suggests that either 5-HT is acting at a receptor that is not activated by either phenylbiguanide or 5-MeOT, or that the neural pathway in this region requires the stimulation of 5-HT_3 receptors in conjunction with another 5-HT receptor subtype. The effects of hexamethonium cannot be attributed to a non-specific inhibition of the secretory process since this agent failed to influence the secretory response to PGE_2.

The effects of atropine revealed regional differences in the intestinal response to 5-HT-receptor agonists. In the jejunum, atropine inhibited the response to all the agonists tested, indicating the involvement of a muscarinic cholinergic component in the secretory response. In the ileum, atropine was without effect on secretion induced by any agonist, while in the colon it had no effect on the response to 5-HT but augmented the effects of phenylbiguanide and 5-MeOT. This suggests that there is no pro-secretory muscarinic cholinergic pathway in the ileum or colon, but in the latter region an anti-secretory pathway may be present. Such a mechanism has been suggested in the rat small intestine (Beesley & Levin 1991) and colon (Nzegwu & Levin 1990) where both hexamethonium and atropine enhanced the response to 5-HT in-vitro. This led to the proposal of an enteric neural cholinergic adrenergic pathway (ENCAP) that can limit the magnitude of the secretory response. The operation of such a pathway in the in-vivo situation appears to differ, since no enhanced secretory response was observed with 5-HT, and atropine only induced a potentiation of the response in the colon when phenylbiguanide or 5-MeOT were applied. This suggests that 5-HT itself may activate some receptor that is unaffected by phenylbiguanide or 5-MeOT and that this acts independently of a muscarinic pathway. As with hexamethonium, the action of atropine was not due to any non-specific effects on secretion as it failed to alter PGE_2-induced secretion.

These results with atropine and hexamethonium differ from those reported in an earlier study of rat intestine in-vivo (Hardcastle et al 1981) where neither of these agents altered the response to 5-HT. It should, however, be pointed out that a different region of the small intestine was used and a lower dose of hexamethonium administered in the previous study. It is clear from the present investigation that there are variations in the mechanisms involved in the 5-HT response along the length of the gut. Similarly, it has recently been shown that the secretory response of proximal and distal regions of rat colon are mediated by different 5-HT receptors (Ayton et al 1995).

The substance P antagonist, [D-Pro^4, $Trp^{7,9,10}$] substance P (fragment 4-11), significantly decreased the secretory response to substance P in each of the three regions of gut. The same dose of antagonist had no effect on the secretory response to 5-HT in the small intestine, but caused a small rightward shift of the 5-HT dose-response curve in the colon. It is, therefore, unlikely that substance P is involved in either the jejunum or ileum, although it may make a small contribution to the colonic 5-HT secretory response.

The possible involvement of substance P in the colon and not the small intestine is surprising since in the rat the majority of enteric substance P fibres innervate the small intestine (Holzer et al 1980).

This study has demonstrated that there is a neural component in the secretory response to 5-HT in all of the intestinal regions investigated. There is also evidence for both pro-secretory and anti-secretory pathways that may be activated by different combinations of 5-HT-receptor subtypes. 5-HT-induced intestinal secretion may therefore involve both a direct secretory action on the enterocyte, which can be modified by both pro-secretory and anti-secretory neural pathways, the balance between these processes varying along the length of the gut.

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