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Regulation of ion transport by histamine in human colon

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Abstract

Histamine, added to the basolateral side of voltage clamped human colon in vitro, induced a rapid onset, transient inward short circuit current which was concentration dependent over the range 0.01–3 mM. This response was largely due to electrogenic chloride secretion since it was virtually abolished by bumetanide or by chloride replacement in the bathing solutions. Responses were unaffected by amiloride or acetazolamide. Neither the histamine H_2 receptor agonist dimaprit (1 mM) nor the histamine H_3 receptor agonist *S*-(+)-α-methyl histamine (1 mM) altered short circuit current. Responses to histamine were significantly reduced by the histamine H_1 receptor antagonist mepyramine (1–10 μM) but not altered by the histamine H_2 receptor antagonist cimetidine (100 μM) or by the histamine H_3 receptor antagonist thioperamide (1 μM). Short circuit current responses to histamine were not altered by tetrodotoxin (1 μM). Piroxicam (10 μM) and nordihydroguaiaretic acid (100 μM) were without effect when used individually but significantly reduced responses to histamine when used simultaneously. These results indicate that histamine stimulates chloride secretion across human colonic epithelium by a mechanism which is mediated exclusively via histamine H_1 receptors. This action does not involve intrinsic nerves but appears to be dependent upon eicosanoid synthesis.

Keywords: Colon; Epithelium; Ion transport; Histamine; Secretion; (Human)

1. Introduction

Histamine, an intercellular messenger which exists at high concentrations throughout the mammalian gastro-intestinal tract (Lorenz et al., 1973), is an important mediator of gastric acid secretion although its physiological role in other parts of the gut is less well established. In addition to stimulation of gastric parietal cells (Sachs and Berglindh, 1981), exogenous histamine has a varied pharmacology. It will contract intestinal smooth muscle (Hill et al., 1977), promote epithelial ion transport (Rangachari and McWade, 1986) and fluid secretion (Hardcastle and Hardcastle, 1987; McCabe and Smith, 1984), activate goblet cells to secrete mucus (Neutra et al., 1982), inhibit histamine release from basophils and mast cells (Ting et al., 1980) as well as excite or inhibit separate populations of enteric neurons (Tamura et al., 1988; Tokimasa and Akasu, 1989).

Studies of epithelial ion transport in vitro employing tissues obtained from other species have provided much insight into normal physiology and pathology of clinical relevance to humans. In addition to a histamine H_1 receptor mediated stimulation of ion transport (Rangachari and McWade, 1986; Hardcastle and Hardcastle, 1987; McCabe and Smith, 1984; Cooke et al., 1984; Fromm and Halpern, 1979; Linaker et al., 1981; Wang et al., 1990), histamine H_2 receptor mediated effects of histamine have been reported (Wang and Cooke, 1990). It is clear that histamine exerts a direct action on intestinal chloride secretion since it stimulates cell lines derived from human colonic adenocarcinoma (Barrett and Dharmsathaphorn, 1990; Wasserman et al., 1988). However, histamine may also have indirect effects on epithelial function. Histamine stimulation of ion transport in guinea pig intestinal mucosa, for example, appears to involve a nerve-mediated component (Cooke et al., 1984; Wang et al., 1990).

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Another indirect influence of histamine on mucosal ion transport is through stimulation of eicosanoid metabolism (Hardcastle and Hardcastle, 1988; Wang et al., 1990; Berschneider and Powell, 1992).

In this study, we have used intact human colonic mucosa, stripped of underlying smooth muscle but with attendant lamina propria, to investigate histamine action on ion transport. Selective agonists and antagonists were used to identify the receptor sub-type(s) involved. In separate experiments, nerve blockade or interference with eicosanoid metabolism was used to study whether histamine may have an indirect action on epithelial ion transport.

2. Materials and methods

Human colonic tissue of normal appearance was taken from the margins of pathological specimens removed during surgical resection for colonic carcinoma. Tissues were inspected by a pathologist and immediately transferred in pre-oxygenated Krebs-Henseleit solution to the laboratory. The composition of this solution is (in mM): NaCl (118), KCl (4.7), $CaCl_2$ (2.5), $MgSO_4$ (1.2), KH_2PO_4 (1.2), $NaHCO_3$ (25) and *d*-glucose (11.1); pH 7.4 when gassed with 5% CO_2. Mucosal sheets, stripped of their underlying smooth muscle by blunt dissection, were mounted in Ussing chambers (window area = 0.63 cm^2). Tissues, bathed on either side with Krebs Henseleit solution maintained at 37° C and oxygenated with 95% O_2/5% CO_2, were voltage clamped to zero potential difference using a dual voltage clamp (DVC 1000, World Precision Instruments). Short circuit current was continuously monitored using an analogue to digital data acquisition system (MacLab). Results are expressed as $\mu A/cm^2$. Transmucosal electrical resistance was determined by altering the clamped voltage between ± 2 mV and applying the ohmic relationship. In some experiments the chloride containing salts of the Krebs-Henseleit solution were replaced with (in mM) sodium gluconate (117), potassium gluconate (4.7), calcium sulphate dihydrate (2.5). Drugs were added to either the apical (luminal) side or the basolateral (serosal) side bathing solutions. This protocol was approved by the Ethics Committee of St. Vincent's Hospital.

Paired tissues obtained from a single individual were used to design experiments with matched test and control groups. Statistical comparisons were made by Wilcoxon's signed rank test, Mann-Whitney *U*-test or by analysis of variance, as appropriate. The Spearman method was used to carry out regression analysis.

Drugs used: histamine diphosphate, mepyramine (pyrilamine maleate), bumetanide, amiloride hydrochloride, acetazolamide, piroxicam, mepacrine (quinacrine dihydrochloride), nordihydroguaiaretic acid, tetrodotoxin, carbachol and prostaglandin E_2 were all obtained from the Sigma Chemical Co., Poole, Dorset, UK. Cimetidine, thioperamide, dimaprit and *S*-(+)-α-methyl histamine were obtained from Research Biochemicals, Natick, MA, USA.

3. Results

3.1. Short circuit current responses to histamine receptor agonists

Tissues were mounted in Ussing chambers and were allowed to equilibrate for a period of 30 min after which basal short circuit current and transepithelial resistance had stabilised. The resting or non-stimulated short circuit current in voltage clamped human colon was 86.0 ± 10.8 $\mu A/cm^2$ in tissues obtained from left (descending; $n = 26$) and 103.0 ± 12.9 $\mu A/cm^2$ in right (ascending; $n = 15$) colon. Transmucosal electrical resistance measured in left and right colons was 83.2 ± 7.6 $\Omega \cdot cm^2$ ($n = 26$) and 95.1 ± 7.6 $\Omega \cdot cm^2$ ($n = 15$) respectively. Since responses to histamine, carbachol and prostaglandin E_2 were similar in tissues obtained from right and left colon (Table 1) data were pooled for the purpose of studying agonist stimulated ion transport. Histamine (100 μM) added to the basolateral bathing solution of voltage clamped colonic mucosa produced a monophasic short circuit current response (Fig. 1A). This inward current, which is characteristic of anion secretion and/or cation absorption, was stimulated by histamine in a concentration dependent manner with an EC_{50} of 0.14 ± 0.02 mM ($n = 33$; Fig. 1B). Histamine applied to the apical bathing solution was without effect upon short circuit current. Neither the histamine H_2 receptor agonist, dimaprit, nor the histamine H_3 receptor agonist *S*-(+)-α-methyl histamine, each added basolaterally at a concentration of 1 mM, had any effect on short circuit current with incubation times of 35 min (Fig. 1C).

Since our tissue supply was from a heterogeneous (human) population, it was not altogether surprising that responses to histamine were somewhat variable in tissues obtained from different individuals. However,

Table 1
Effects of secretagogues on different segments of human colon

Treatment	Left colon	Right colon
Histamine (100 μM)	43.4 ± 6.3 ($n = 46$)	35.6 ± 6.3 ($n = 21$)
Carbachol (100 μM)	90.6 ± 4.9 ($n = 83$)	92.2 ± 11.3 ($n = 24$)
Prostaglandin E_2 (1 μM)	20.3 ± 7.9 ($n = 10$)	17.8 ± 9.6 ($n = 5$)

Comparison of short circuit current responses ($\mu A/cm^2$) to various secretagogues in left and right human colon. The EC_{50} values for histamine stimulation of ion transport were 0.15 ± 0.03 mM ($n = 24$) and 0.12 ± 0.03 mM ($n = 9$) for left and right side colons respectively.

when short circuit current responses to histamine (300 μM) were compared in a series of paired tissues obtained from single individuals (41.1 ± 9.4 $\mu A/cm^2$ and 42.7 ± 11.1 $\mu A/cm^2$; $n = 7$), the correlation coefficient was 1.00 ($P < 0.001$). Similar results were obtained using other secretagogues. In consequence all experiments were performed using matched preparations from a single individual for test and control groups.

3.2. Pharmacological characterisation of the histamine receptor

Using paired preparations, cumulative concentration-response curves to histamine were constructed in the presence or absence of histamine receptor antagonists. Mepyramine (1–10 μM), a histamine H_1 receptor antagonist reduced the response to histamine (Fig. 2A) but did not affect responses to the cholinergic agonist, carbachol (100 μM), which were 98.3 ± 17.2% of the response to carbachol in paired control tissues ($n = 19$).

In the presence of the histamine H_2 receptor antagonist cimetidine (100 μM, $n = 5$) or the histamine H_3 receptor antagonist thioperamide (1 μM, $n = 5$) concentration-response curves to histamine (0.01–1 mM) were not altered when compared with those obtained in matched control preparations (Fig. 2B and C). Responses to histamine were not altered by even higher

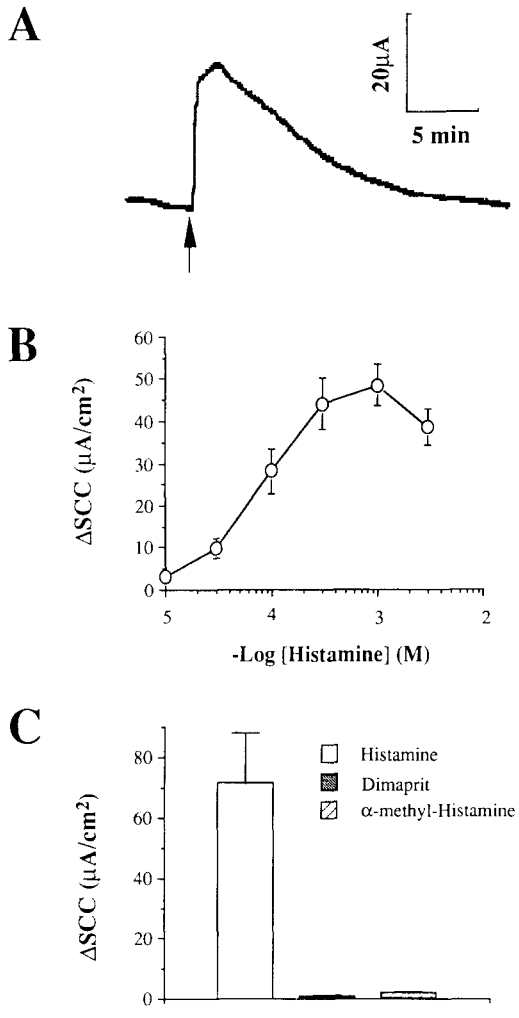

Fig. 1. (A) Representative short circuit current response to histamine in human colonic mucosa. Histamine (100 μM) added, as indicated by the arrow, to the basolateral bathing solution of voltage clamped colonic mucosa produced a monophasic response. (B) Basolateral addition of histamine stimulated short circuit current in a concentration dependent manner with an EC_{50} of 0.14 ± 0.02 mM ($n = 33$). (C) The H_2 selective agonist, dimaprit (1 mM; $n = 5$), and the H_3 selective agonist, α-methyl-histamine (1 mM; $n = 3$) were without effect on ion transport in human colon over a 35 min incubation period.

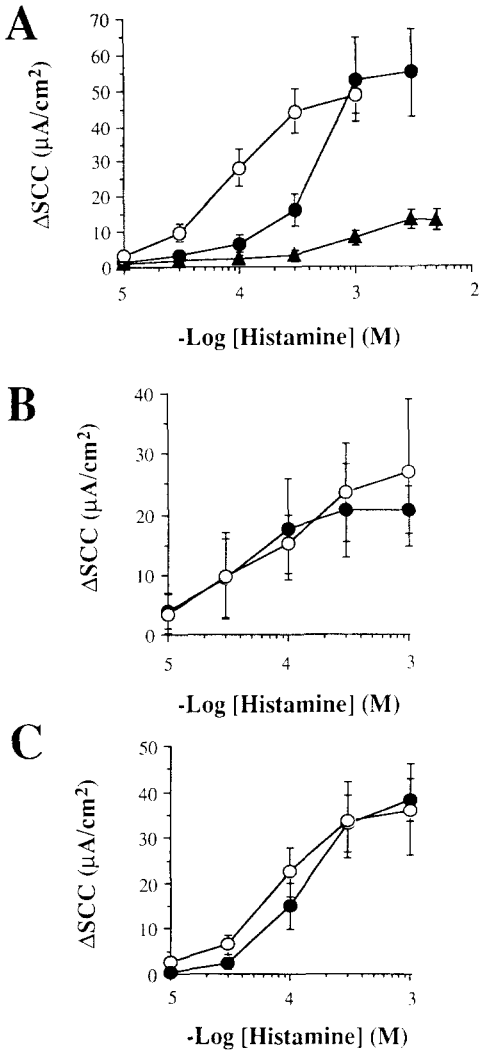

Fig. 2. (A) The histamine H_1 receptor antagonist mepyramine (1 μM; closed circles; $n = 6$) significantly attenuated ($P < 0.05$) and at higher concentrations (10 μM; closed triangles; $n = 9$) almost abolished responses to histamine ($P < 0.005$). (B) The histamine H_2 antagonist, cimetidine (100 μM; closed circles) and (C) the H_3 antagonist, thioperamide (1 μM; closed circles) were both without effect on responses to histamine ($n = 5$). Comparisons were made using analysis of variance.

Table 2
Influence of drugs on basal short circuit current

Treatment	Δ Short circuit current ($\mu A/cm^2$)
Control ($n = 91$)	-4.1 ± 0.4
Mepyramine (1 μM; $n = 6$)	-5.4 ± 2.2
Mepyramine (10 μM; $n = 6$)	-5.4 ± 2.1
Cimetidine (100 μM; $n = 5$)	-2.2 ± 0.8
Thioperamide (1 μM; $n = 5$)	-2.1 ± 0.7
Thioperamide (100 mM; $n = 9$)	-14.3 ± 6.3 [a]
Bumetanide (100 μM; $n = 24$)	-17.9 ± 2.7 [c]
Amiloride (10 μM; $n = 6$)	-16.7 ± 5.3 [c]
Acetazolamide (1 mM; $n = 5$)	-9.4 ± 4.4
Tetrodotoxin (1 μM; $n = 33$)	-12.1 ± 4.3 [b]
Piroxicam (10 μM; $n = 20$)	-15.7 ± 3.5 [c]
Nordihydroguaiaretic acid (100 μM; $n = 12$)	-9.6 ± 3.2 [b]
Mepacrine (50 μM; $n = 6$)	-7.3 ± 1.7 [a]
Nordihydroguaiaretic acid + piroxicam ($n = 4$)	-16.0 ± 5.8 [c]

Effects of drugs on basal short circuit current in human colon. Reductions in short circuit current were measured over a 10 min period after drug addition and compared with variation in untreated controls. Comparisons were made using the Mann-Whitney U-test ([a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.005$).

concentrations of thioperamide (100 μM) which reduced basal short circuit current (Table 2).

3.3. Determination of the charge carrying ion

Pharmacological agents which interfere with specific ion transporting pathways were used to identify the charge carrying ion involved in responses to histamine in human colon. The effect of each drug on basal short circuit current is shown in Table 2.

Histamine stimulation of short circuit current was virtually abolished in the presence of bumetanide (100 μM; Table 3), indicating these responses to be due largely to electrogenic chloride secretion. This was confirmed by the significant attenuation of short circuit current responses to histamine in chloride-free bathing solutions (Table 3). Both amiloride (10 μM) and acetazolamide (1 mM) were without significant effect on reponses to histamine which is consistent with the process being independent of electrogenic sodium absorption and bicarbonate secretion.

3.4. To investigate involvement of nerves in histamine induced short circuit current

Concentration-response curves to histamine in the presence of tetrodotoxin (1 μM; $n = 9$) were not significantly different from controls (Fig. 3). In addition, short circuit current responses to 100 μM carbachol were unaltered by tetrodotoxin (83.0 ± 7.9 $\mu A/cm^2$ in treated preparations compared with 75.1 ± 8.3 $\mu A/cm^2$ in paired controls; $n = 27$).

3.5. Involvement of eicosanoids in histamine induced short circuit current

We used a pharmacological approach to investigate the potential role of arachidonic acid metabolism in ion transport responses to histamine. The effect of each drug on basal short circuit current is shown in Table 2.

Responses to histamine were attenuated by prior treatment of the tissue with the phospholipase A_2 inhibitor mepacrine (50 μM). Piroxicam (10 μM) and nordihydroguaiaretic acid (100 μM), which are inhibitors of the arachidonic acid metabolising enzymes cyclooxygenase and lipoxygenase respectively, were without significant effect on short circuit current responses to histamine when tested individually (Table 4). However, a combination of cyclooxygenase and lipoxygenase inhibition resulted in a significant reduction in responses to histamine without affecting responses to 100 μM carbachol (control response = 68.9 ± 12.5 $\mu A/cm^2$; test response = 73.8 ± 13.8 $\mu A/cm^2$;

Table 3
Determination of charge carrying ion

Treatment	Control response ($\mu A/cm^2$)	Test response ($\mu A/cm^2$)
Bumetanide (100 μM; $n = 5$)	20.2 ± 8.1	2.2 ± 1.3 [a]
Amiloride (10 μM; $n = 6$)	44.3 ± 9.7	61.1 ± 14.4
Acetazolamide (1 mM; $n = 5$)	27.8 ± 4.9	27.1 ± 14.4
Chloride-free ($n = 6$)	39.2 ± 9.0	3.8 ± 1.7 [c]

Effects of agents which interfere with ion transport processes on short circuit current responses to histamine in human colon. Inhibitors were added 10 min prior to addition of histamine (100 μM). Comparisons were made using Wilcoxon's signed rank test ([a] $P < 0.05$, [c] $P < 0.005$).

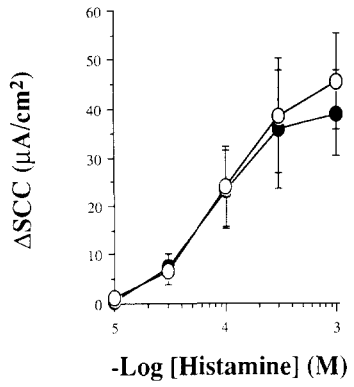

Fig. 3. Concentration-response curves to histamine in the presence of tetrodotoxin (1 μM; closed circles) were not significantly different from those obtained in paired control preparations (open circles; $n = 9$).

$n = 4$ in each case). These results indicate a role for eicosanoids in the full expression of responses to histamine stimulation of ion transport.

4. Discussion

In this study we have demonstrated that histamine produces a concentration dependent, transient rise in inward current in voltage clamped human colonic mucosa as previously reported (Hubel et al., 1987; Crowe and Perdue, 1993). Although it has been demonstrated that there are segmental variations in basal human colonic ion transport (Rask-Madsen and Hjelt, 1977; Sellin and DeSoignie, 1987; Hubel et al., 1987), this does not appear to be the case for agonist stimulated ion transport since we found no regional differences in responses to either Ca^{2+} (histamine, carbachol) mediated or cAMP-mediated (prostaglandin E_2) secretagogues.

The short circuit current response to histamine in human colon is mediated by histamine H_1 receptors since it was reduced in the presence of the H_1 selective antagonist, mepyramine. Antagonism by mepyramine did not appear to be competitive in nature at the higher concentration tested. Mepyramine had no effect on cholinergic stimulation of colonic ion transport indicating there was no anticholinergic effect of mepyramine or loss of tissue viability. There appears to be no involvement of histamine H_2 or H_3 receptors in histamine stimulated ion transport since agonists which are specific for histamine H_2 (dimaprit) or H_3 receptors (*S*-(+)-α-methyl histamine) failed to mimic the action of histamine itself. This is further supported by the lack of effect of cimetidine, a histamine H_2 specific antagonist (Brimblecombe et al., 1975) and thioperamide, a H_3 specific antagonist (Arrang et al., 1987), on responses to histamine indicating these receptor subtypes do not substantially contribute to histamine stimulation of electrogenic ion transport in this tissue. This is comparable to other mammalian epithelia in which histamine H_1 receptors are the principal targets of exogenous histamine (Rangachari and McWade, 1986; Hardcastle and Hardcastle, 1987; McCabe and Smith, 1984; Cooke et al., 1984; Fromm and Halpern, 1979; Linaker et al., 1981; Wang et al., 1990). We found no evidence of a H_2 receptor mediated chloride secretion which was recently reported in guinea pig distal colon (Wang and Cooke, 1990) nor did we detect any influence of histamine H_3 receptors which exist on submucosal neurons in guinea pig (Frieling et al., 1993).

In a pharmacological approach to identify the charge carrying ion species responsible for the change in short circuit current we used a number of drugs which selectively interfere with specific ion transport processes in epithelial cells. These were bumetanide, a loop diuretic which inhibits the $Na^+/K^+/Cl^-$ co-transport upon which electrogenic chloride secretion depends (Halm and Frizzell, 1990); amiloride which blocks electrogenic sodium absorption (Rask-Madsen and Hjelt, 1977) and acetazolamide which prevents bicarbonate secretion by inhibiting carbonic anhydrase (Hopfer and Liedtke, 1987). These data are consistent with the fact that basal ion transport is largely accounted for by a combination of sodium absorption and chloride secretion although the relative contribution of each of these processes appears to vary in different segments of the large intestine (Sellin and DeSoignie, 1987; Hubel et al., 1987). Although basal colonic chloride secretion is regulated by intracellular bicarbonate in other species (Dagher et al., 1992) and therefore may be indirectly influenced by carbonic anhydrase, which exists in epithelial cells (Lonnerholm et al., 1988), we found no

Table 4
Interference with arachidonic acid metabolism

Treatment	Control response (μA/cm²)	Test response (μA/cm²)
Piroxicam (10 μM; $n = 5$)	27.8 ± 4.9	22.3 ± 9.0
Nordihydroguaiaretic acid (100 μM; $n = 7$)	61.6 ± 13.1	47.5 ± 9.0
Piroxicam + nordihydroguaiaretic acid ($n = 4$)	42.5 ± 10.3	7.9 ± 4.6 [a]
Mepacrine (50 μM; $n = 6$)	56.2 ± 18.1	23.7 ± 11.9 [a]

Effects of agents which interfere with arachidonic acid metabolism on short circuit current responses to histamine (100 μM) in human colon. Drugs were added 10 min before challenge with histamine. Comparisons were made using Wilcoxon's signed rank test ([a] $P < 0.05$).

significant reduction of resting short circuit current by acetazolamide. Ion transport stimulated by histamine appears, therefore, to be largely due to electrogenic secretion of chloride ions since it was virtually abolished by bumetanide and was not reduced by amiloride or acetazolamide. That chloride secretion is a major contributor to the ion transport response to histamine was further supported by the reduction of histamine-evoked responses in chloride-free solutions. However, the complete picture may be more complex since histamine modulates K^+ channel activity in a human intestinal epithelial cell line (Itoh et al., 1994) and such activity may be essential for fluid secretion in chloride-secreting epithelia (Dawson and Richards, 1990).

In contrast to previous studies in non-human mammalian species which have implicated a role for the enteric nervous system in amplifying ion transport responses to histamine (Cooke et al., 1984; Wang et al., 1990; Frieling et al., 1993), tetrodotoxin was without effect on histamine stimulated chloride secretion implying that such responses do not involve activation of the enteric nervous system in human tissue. Functional nerves which regulate chloride secretion are retained in the preparation we used (Keely et al., 1994; Stack et al., 1995). Tetrodotoxin, which blocks fast Na^+ channels on nerves, significantly attenuated basal short circuit current in colon, probably as a result of a contribution to resting state ion transport by intrinsic neurons (Cooke et al., 1983; Andres et al., 1985; Hubel et al., 1987).

Our results indicate that continuous synthesis of prostaglandins contributes to basal electrical tone in human colon since mepacrine, which inhibits phospholipase A_2 (Lapetina et al., 1981), piroxicam, which is a potent inhibitor of cyclooxygenase (Carty et al., 1980) and nordihydroguaiaretic acid, which reduced leukotriene but not prostaglandin formation in human colonic mucosa (Dreyling et al., 1986) all reduce basal short circuit current in this preparation. Eicosanoids have previously been implicated as mediators of histamine-induced fluid and electrolyte secretion by rat colon (Hardcastle and Hardcastle, 1988; Wang et al., 1990). However, the involvement of arachidonic acid metabolites in intestinal ion transport responses to histamine may not be simple. For example, rather than having a direct effect on epithelial cells histamine stimulates the synthesis of eicosanoids in fibroblasts which then act in a paracrine fashion to stimulate chloride secretion in adjacent epithelial cells (Berschneider and Powell, 1992). Furthermore, endogenously formed prostaglandins, in addition to having a direct stimulatory effect on chloride secretion, may act synergistically with other secretagogues to promote chloride secretion by opening basolateral K^+ channels to augment an electrical gradient favourable to apical chloride efflux (Hardcastle and Hardcastle, 1986).

Both prostaglandins and leukotrienes are involved in secretory responses to histamine in human colon since simultaneous inhibition of both pathways of arachidonic acid metabolism resulted in a significant reduction in responses. This indicates that there may be a reciprocal interaction between the cyclooxygenase and lipoxygenase pathways of eicosanoid synthesis. Inhibition of either enzyme alone may result in a compensatory stimulation of the remaining pathway, possibly due to increased availability of arachidonic acid substrate. Thus inhibition of responses to histamine do not occur unless synthesis of both prostaglandins and leukotrienes is inhibited. Such interactions between the cyclooxygenase and lipoxygenase pathway have been previously reported in human colon (Wardle et al., 1993).

In summary, we have shown that histamine stimulates ion transport across human colonic mucosa by a histamine H_1 receptor-mediated process. The action of histamine does not appear to involve intrinsic nerves but appears to be dependent on eicosanoid generation. The change in short circuit current may be accounted for, in large part, by electrogenic chloride secretion. Since chloride secretion in vivo creates a gradient for compensatory movement of cations, followed by osmotic flow of water (Welsh et al., 1982) with consequent net secretion of fluid by the colon, this is considered to be at least one of the mechanisms underlying secretory diarrhea. Such excess fluid secretion may result as a consequence of local release of histamine from mast cells within the lamina propria (Crowe and Perdue, 1993; Castro, 1982) of the gastrointestinal mucosa or alternatively when serum levels of histamine are elevated in systemic mastocytosis (Austen, 1992).

Acknowledgements

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