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Regulation of ion transport by histamine in mouse cecum

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Abstract

Histamine levels are elevated in inflammatory bowel disease. We investigated the mechanism by which histamine affects electrolyte transport in the mouse cecum. Using the Ussing-chamber voltage clamp technique, histamine was found to cause a transient concentration-dependent increase in short-circuit current, a measure of total ion transport across the epithelial tissue. This increase was not affected by amiloride pretreatment, but was significantly inhibited by bumetanide and completely inhibited when chloride was substituted in the bathing buffer by gluconate. A histamine-induced increase in short-circuit current was also significantly reduced by inhibitors of the cyclooxygenase pathway indicating the involvement of prostaglandin E_2 in its action. Prostaglandin E_2 levels were increased in histamine treated tissue and this increase was reversed by indomethacin. These data suggest that histamine causes its effect on mouse cecum largely through increasing arachidonic acid metabolism resulting in increased levels of prostaglandins which in turn increase Cl^- secretion in the epithelial cells. © 1997 Elsevier Science B.V.

Keywords: Ion secretion; Histamine; Intestinal secretion; Epithelial cell

1. Introduction

The regulation of ion transport in the intestine is a complex series of endocrine, paracrine and autocrine interactions between the different cells in the mucosa, submucosa and epithelium. Under normal conditions, these different systems are controlled to allow for normal secretion and absorption of ions across the mucosa. However, in disease states, such as inflammatory bowel disease and intestinal hypersensitivity reactions, the interactions are altered and ion transport becomes abnormal (Sartor and Powell, 1991).

Mast cell activation by antigens have been implicated in the pathophysiology of gastrointestinal inflammation (Baum et al., 1989; Raithel et al., 1989; Nolte et al., 1990). Once activated, mast cells can release a variety of mediators which can act as secretagogues. One of the major mediators is histamine which has been shown to have direct as well as indirect effects on epithelial cell ion transport. Histamine directly increased chloride secretion in the human cell line T-84 by a Ca^{2+} dependent process (Dharmsathaphorn et al., 1989). Binding of histamine to its specific membrane histamine$_1$ receptors caused increased levels of intracellular Ca^{2+} through the activation of phosphoinositol turnover pathway. In the guinea pig distal colon (Wang et al., 1990) and the rat colon (Hardcastle and Hardcastle, 1990), however, histamine has been shown to increase ion secretion through a different mechanism which involves the release of prostaglandins and by augmenting the effects of endogenously released neurotransmitters (Wang et al., 1990). Increased prostaglandin levels (in particular prostaglandin E_2) can bind to their specific receptors on the epithelial cells and increase the activity of adenylyl cyclase causing increased levels of cAMP which in turn can increase apical Cl^- channel activity and hence increase Cl^- secretion (Weymer et al., 1985; Homaidan et al., 1995). All these effects of histamine were achieved by histamine acting through histamine H_1 receptors.

The aim of this study was to determine if histamine plays a role in the regulation of ion transport in normal mouse cecum and to investigate its mechanism of action. No information is available on the actions of histamine on epithelial cell function in the mouse intestine. The C3H/HeJ mouse strain was used since we have recently

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evaluated the normal basal transport mechanisms present on the epithelial cells in the cecum (Tripodi et al., 1996) for a subsequent comparison to an inbred mouse model of colitis the C3H/HeJ/BIR (Sundberg et al., 1994).

2. Materials and methods

2.1. Materials

Histamine, atropine, tetrodotoxin, hexamethonium, indomethacin, piroxicam, amiloride, bumetanide, cimetidine and pyrilamine were obtained from Sigma (St. Louis, MO, USA). CP96345, a substance P receptor antagonist was obtained as a gift from Pfizer (Groton, CT, USA). Thioperamide was obtained from Research Biochemicals (Natick, MA, USA).

2.2. Methods

2.2.1. Transport studies

Healthy female C3H/HeJ mice were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and were maintained on a standard diet with free access to water. The animals were used between 8 and 12 weeks of age. Mice were killed by exposure to 100% CO_2 and the cecum was immediately removed and washed in Krebs-HCO_3 (KBS) buffer. The cecum was cut open along the mesenteric border and full thickness cecal tissue was mounted as a flat sheet between two Lucite modified Ussing chambers having an area of 0.13 cm^2 and oxygenated and maintained at 37°C. The short-circuit current (I_{sc}) which is equivalent to the electrical sum of all ion transport processes occurring simultaneously was determined. An automatic voltage clamp (W.P.I., Sarasota, FL, USA), corrected for fluid resistance between the potential difference sensing bridges, provided continuous short-circuiting of the tissue.

Unless specified, the bathing solution consisted of Krebs-HCO_3 composed of (in mM): KCl 4.8, $CaCl_2$.5, NaCl 118.1, NaH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, glucose 11, pH 7.4 after gassing with 95% O_2/5% CO_2. Experiments with Cl^--free or sodium-free buffers were performed by substituting Cl^- ions with gluconate or substituting Na^+ ions with choline. The Cl^--free buffer composed of (in mM): Na-gluconate 118, K_2SO_4.7, $CaSO_4$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 1.2, glucose 11.1 and $NaHCO_3$ 25, pH 7.4 after gassing with 95% O_2/5% CO_2. The Na^+-free buffer composed of (in mM): choline-Cl 118, KCl 4.7, $CaCl_2$.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, glucose 11.1, choline-HCO_3 25, pH 7.4 after gassing with 95% O_2/5% CO_2.

The cecum was divided into 4 pieces and the tissues paired and used if their conductances did not differ by more than 25%. Unless specified all drugs were added to the serosal side of the cecal tissue.

Statistical analyses were performed with Student's *t*-tests for paired and unpaired data; half-maximal and maximal effects of histamine on transport were determined by the method of Woolf–Hanes (Segel, 1976) by plotting the concentration/change in I_{sc} versus concentration. In these calculations, the half-maximal concentration and the maximal effect for each experiment were determined and the results are presented as the means of these values ± S.E. Unless specified all results are reported as mean ± S.E.

2.2.2. Measurement of prostaglandin E_2 levels in tissue treated with histamine

Unstriped cecal pieces of tissue were washed with KBS, placed on ice and cut into small but equal pieces. For all assays, pieces of tissue were transferred to polypropylene vials containing 5 ml of oxygenated KBS at 37°C in a slow shaking water bath. The tissue was continuously oxygenated during the experiment. The tissue was treated with histamine for different time periods. Aliquots were transferred from the supernatant to Eppendorf tubes at specific times and centrifuged at 4°C, for 2 min at 9000 rpm in the Eppendorf centrifuge. Samples were kept at −70°C for later determination of prostaglandin E_2 levels using radioimmunoassay (RIA). Commercially available RIA kits for the measurement of prostaglandin E_2 were used (Advanced Magnetics, MA, USA). The sample was precipitated with cold acetone, centrifuged and the precipitate was discarded. Petroleum ether was then added to the supernatant and the aqueous phase separated and acidified to pH 3–4 and then extracted further with ethyl acetate. The sample was lyophilized and reconstituted in a known amount of assay buffer. In brief, the assay involved incubating the sample with the corresponding antiserum overnight at 4°C and then centrifuging for 15 min at 4°C at $1000 \times g$. The supernatant was then transferred to scintillation vials, scintillant was added and the vial was counted in a liquid scintillation counter.

3. Results

3.1. Effects of histamine on basal short-circuit current (I_{sc})

Serosal addition of different concentrations of histamine caused a concentration dependent increase in I_{sc} with an EC_{50} of 50 μM. The peak increase in I_{sc} was 45 ± 5.6 μA/cm^2 at 100 μM histamine ($n = 4$, Fig. 1a) and was reached in 5 min after the addition of histamine. As has been observed before (McCabe and Smith, 1984; Wang et al., 1990), histamine's response was transient. It reached a peak increase in I_{sc} in less than 10 min and was completely back to the base level in around 15 min (Fig. 1b).

3.2. Effects of histamine in the presence of neuronal blockers

To determine the mechanism by which histamine causes its effects on electrolyte transport, the cecal tissue was

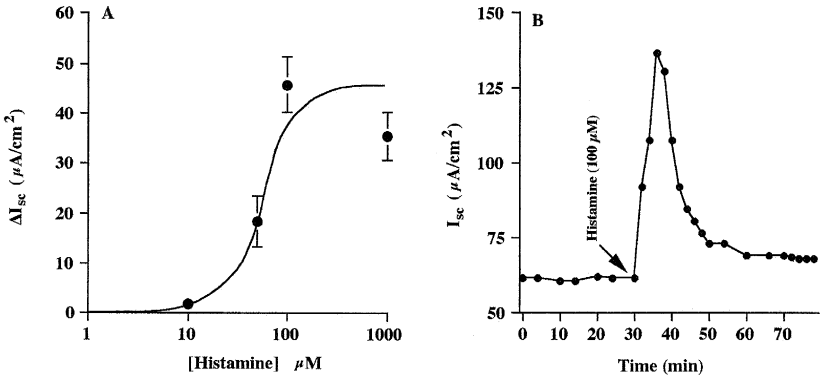

Fig. 1. (A) Concentration-dependent response of the effect of histamine on mouse cecal short-circuit current ($n = 4$ for 1 μM, $n = 6$ for 50 μM, $n = 34$ for 100 μM and $n = 4$ for 1000 μM). Histamine was added to the serosal surface of the tissue and the data based on the maximum increase in short-circuit current is shown for each concentration tested. (B) The effect of histamine on short-circuit current as a function of time from a single representative experiment.

treated with either tetrodotoxin, a neuronal Na^+ channel inhibitor which prevents neural input to the epithelial cells, or hexamethonium, a cholinergic inhibitor. Histamine (100 μM) was added to the serosal side of the cecum after pretreating the tissue with either of the inhibitors and the peak change in I_{sc} measured and compared to the histamine-induced peak change in I_{sc} in control untreated paired cecal tissues. Tetrodotoxin (10 μM) significantly reduced the histamine-induced increase in I_{sc} by $66.9 \pm 17.6\%$ (42.3 ± 10.8 μA/cm^2 in tissue treated with histamine alone versus 14.4 ± 6.9 μA/cm^2 in tissue pretreated with tetrodoxine before histamine addition, $P < 0.05$, $n = 4$). Hexamethonium (100 μM), however, had no effect on the increase in I_{sc} caused by histamine (37.2 ± 2.2 μA/cm^2 in tissues treated with histamine alone versus 36.8 ± 3.0 μA/cm^2 in paired tissues pretreated with hexamethonium before histamine addition, $n = 4$, NS, Fig. 2). Similarly, atropine pretreatment of the tissue had no effect on histamine induced increase in I_{sc} (43.7 ± 4.2 μA/cm^2 in tissues treated with histamine alone versus 44.9 ± 5.4 μA/cm^2 in paired tissues pretreated with atropine before histamine addition, $n = 4$, NS). These data suggest that histamine is exerting part of its effects through non-cholinergic intrinsic nerves.

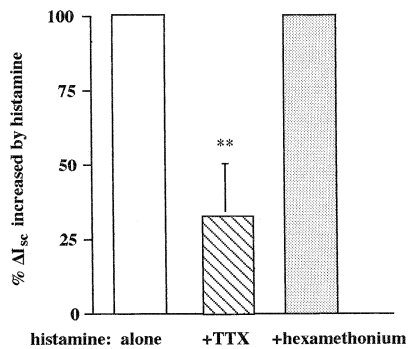

Fig. 2. The effect of histamine on short-circuit current alone and after incubating the tissue with 10 μM TTX or 100 μM hexamethonium. The data (mean ± S.E.M., $n = 4$, ** $P < 0.05$, P-value represents the comparison of the histamine response on short-circuit current in the presence of the inhibitor to its effect alone) are presented as percentage change in short-circuit current caused by histamine.

CP96345, a substance P receptor antagonist, was used to test if histamine exerts part of its effect through releasing substance P. Pretreatment of the cecal tissue with CP96345 (10 nM), a concentration which was sufficient to block the substance P effect on I_{sc} completely, had no effect on the histamine-induced increase in I_{sc}, indicating that histamine does not cause its effects through substance P (43.7 ± 4.2 μA/cm^2 in tissues treated with histamine alone versus 42.6 ± 3.9 μA/cm^2 in paired tissues pretreated with hexamethonium before histamine addition, $n = 4$, NS). The reverse, however, was true. The addition of histamine receptor antagonist pyrilamine (10 μM) inhibited the effect of substance P (10 μM) on I_{sc} by $89.4 \pm 4.0\%$ ($n = 4$, $P < 0.05$), suggesting that substance P, as has been reported previously (Kuwahara and Cooke, 1990), partially causes its effect through stimulating mast cells to release histamine. CP96345 at 10 nM was sufficient to completely inhibit the I_{sc}-induced increase caused by substance P (data not shown).

3.3. The nature of the ion involved in histamine action

To determine the nature of the ion(s) whose transport is affected by histamine treatment, treatment of the tissue with bumetanide, or ion substitution studies were performed. Chloride or sodium ions were substituted for gluconate and choline respectively to determine if either was involved in the action of histamine. Amiloride, an inhibitor of the apical Na^+ channel and the Na^+/H^+ exchanger, was not used in this study since we found no evidence of the presence of an amiloride-sensitive Na^+ channels in the mouse cecum (Tripodi et al., 1996). Mucosal Na^+ ion substitution experiments, however, were performed and found to have no effect on histamine-induced increase in I_{sc}, suggesting that histamine is not affecting Na^+ ion movement in the mouse cecum. Chlo-

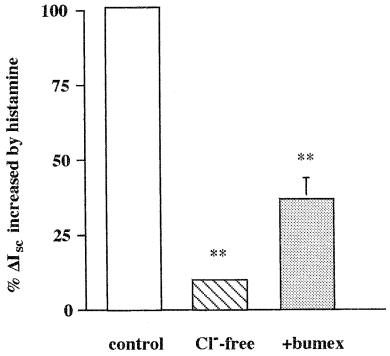

Fig. 3. The effect of histamine on short-circuit current alone and in the presence of chloride-free buffer or bumetanide (bumex, 50 μM). The data (mean ± SE, $n = 4$, ** $P < 0.05$, P-value represents the comparison of the histamine response on short-circuit current in the presence of the inhibitor to its effect alone) are presented as percentage change in short-circuit current caused by histamine.

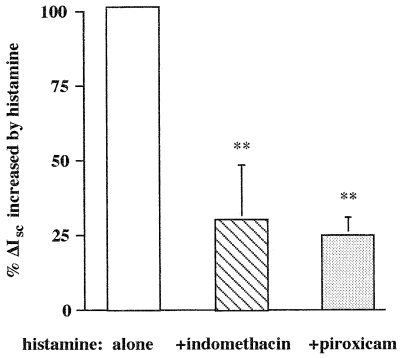

Fig. 4. The effect of histamine on short-circuit current alone and in the presence of indomethacin (2 μM) or piroxicam (10 μM). The data (mean ± S.E.M., $n = 4$, ** $P < 0.05$, P-value represents the comparison of the histamine response on short-circuit current in the presence of the inhibitor to its effect alone) are presented as percentage change in short-circuit current caused by histamine.

ride ion replacement by gluconate, however, caused a significant reduction in histamine's response on I_{sc}. The I_{sc} was reduced by 89.6 ± 5.2% ($P < 0.005$, $n = 4$, Fig. 3). Similar results were obtained when the tissue was pretreated with bumetanide (50 μM), an inhibitor of the basolateral $Na^+/K^+/2Cl^-$ transporter. Bumetanide reduced histamine induced increase in I_{sc} by 63.3 ± 7.0% ($P < 0.005$, $n = 4$, Fig. 3). These data suggest that the majority of histamine's effect is to increase chloride ion secretion to cause the observed increase in I_{sc}.

Mucosal addition of 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid (DIDS) at 1 mM, an inhibitor of the Cl^-/HCO_3^- exchanger, had no effect on histamine's induced increase in I_{sc} (26.9 ± 6.7 μA/cm^2 in untreated tissue versus 25.0 ± 5.8 μA/cm^2 in tissue pretreated with DIDS, $n = 4$, NS). These data suggest therefore, that the observed effects of histamine are exerted directly on the apical Cl^- channel and not through affecting the Cl^-/HCO_3^- exchanger.

3.4. Effect of histamine in the presence of arachidonic acid metabolism

To determine the mechanism by which histamine is increasing secretion, the tissue was pretreated with indomethacin or piroxicam, inhibitors of the cyclooxygenase pathway, to prevent the production of prostaglandins. Indomethacin (2 μM) caused a significant decrease in the histamine (100 μM)-induced increase in I_{sc} by 69.8 ± 18.2% ($n = 4$, $P < 0.005$; 53.8 ± 5.4 μA/cm^2 in control tissue versus 16.3 ± 5.1 μA/cm^2 in the indomethacin treated tissue). Similar results were obtained when the tissue was pretreated with piroxicam (10 μM). Piroxicam decreased the histamine-induced increase in I_{sc} by 75.1 ± 5.6% ($n = 9$, $P < 0.0005$, Fig. 4) suggesting that histamine is causing the majority of its effects through stimulating arachidonic acid metabolism.

3.5. The effect of histamine on prostaglandin E_2 production

Treatment of the tissue with histamine (100 μM) caused an increase in prostaglandin E_2 production (Fig. 5) compared with a time control (2.7 ± 0.8 μg/mg protein in control tissue versus 6.3 ± 2.0 μg/mg protein in treated tissue, $n = 3$, $P < 0.05$ at 15 min after the addition of histamine). The increase in prostaglandin E_2 by histamine was completely abolished when the tissue was treated by indomethacin ([prostaglandin E_2] = 3.1 ± 0.7 μg/mg protein in tissue treated with indomethacin and histamine).

3.6. Identification of the histamine receptor subtype

The serosal addition of cimetidine, an H_2 receptor agonist, had no significant effect on the I_{sc} response to histamine (ΔI_{sc} = 33.3 ± 14.3 μA/cm^2 in control tissue

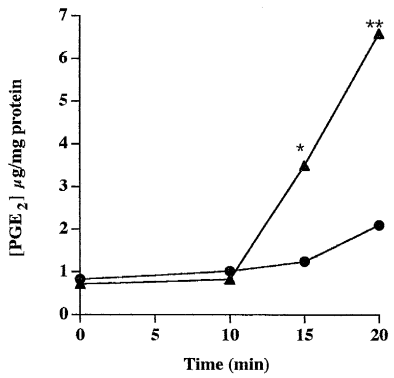

Fig. 5. A representative experiment (one of 3 experiments) showing the effect of histamine on the production of prostaglandin E_2 (△) as a function of time compared with a time control (●). Histamine was added at time 5 min (* $P < 0.05$, ** $P < 0.005$, P-value represents the comparison of the histamine response on the production of PGE_2 as compared to untreated time control).

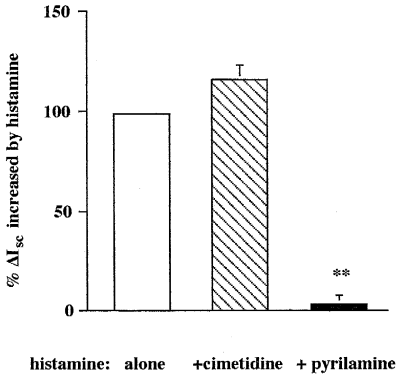

Fig. 6. The effect of histamine on short-circuit current alone and in the presence of cimetidine (10 μM) and pyrilamine (10 μM). The data (mean ± S.E.M., $n = 4$, ** $P < 0.05$, P-value represents the comparison of the histamine response on short-circuit current in the presence of the inhibitor to its effect alone) are presented as percentage change in short-circuit current caused by histamine.

versus 39.7 ± 18.6 μA/cm^2 in cimetidine treated tissue, $n = 3$, NS). However, the addition of pyrilamine 10 μM, a H_1 (histamine$_1$) receptor antagonist, significantly reduced the histamine-induced increase in I_{sc} by $96.4 \pm 3.6\%$ ($n = 4$, $P < 0.0005$, Fig. 6). These results suggest that histamine is causing its effect on ion secretion through binding to Histamine$_1$ receptors on inflammatory cells, neurons or even epithelial cells to ultimately cause the observed increase in Cl^- secretion. Thioperamide (100 nM), an H_3 receptor antagonist, significantly augmented the histamine-induced increase observed in I_{sc} (histamine induced $\Delta I_{sc} = 20 \pm 4.6$ μA/cm^2 in control tissue versus $\Delta I_{sc} = 63.8 \pm 9.2$ μA/cm^2 in thioperamide treated tissue, $n = 3$, $P < 0.05$).

4. Discussion

Histamine is involved in many immune and inflammatory functions including the down-regulation of mitogen- and antigen-induced lymphocyte proliferation, modification of cytokine-induced complement and fibrinogen synthesis and inhibition of immunoglobulin production (Falus and Meretey, 1992; Schreiber et al., 1992 ;Beyak and Vanner, 1995). Baenkler et al. (1987) demonstrated the potential role of histamine in inflammatory bowel disease by showing increased amounts of histamine in the lamina propria of biopsies from Crohn's and ulcerative colitis patients. Similarly, Fox et al. (1990) showed that intestinal mast cells from actively inflamed intestine released greater amounts of histamine and prostaglandin D_2 than from matched uninflamed tissue.

In this study, we report the effects of histamine on ion transport in normal mouse cecum. In the mouse cecum, we recently reported that the basal short-circuit current is positive and only reflects net sodium absorption with little or no net anion secretion (Tripodi et al., 1996; Homaidan and Tripodi, data not shown). Secretagogues that stimulate chloride secretion cause an increase in I_{sc}. Histamine was found to cause a transient concentration-dependent increase in I_{sc}. The transient nature of the histamine response prevented the measurement of ion fluxes. However, from ion substitution experiments it was found that the increase in I_{sc} was completely dependent on Cl^- ions with no effect on Na^+ ion movement through the apical Na^+ channel. Histamine stimulates ion secretion through a mechanism which involves the production of prostaglandin E_2. This increase in prostaglandin E_2 is consistent with the previous report by Hardcastle and Hardcastle (1990).

The histamine induced increase in I_{sc} was bumetanide sensitive. Bumetanide inhibits the $Na^+/K^+/2Cl^-$ cotransporter present on the basolateral membrane of the epithelial cells. This cotransporter is the driving force for Cl^- movement across the epithelial cell and for Cl^- secretion through the apical chloride channel. Hence, decreasing the levels of Cl^- in the cell by pretreating the tissue with bumetanide for example, consequently prevents Cl^- secretion from the apical side. A similar reduction with bumetanide has been reported in the guinea pig distal colon (Wang et al., 1990). Additional evidence that Cl^- secretion was responsible for the histamine-induced increase in I_{sc} was provided by the ion substitution experiments which caused complete inhibition of the histamine induced increase in I_{sc} in the mouse cecum. A similar reduction but to a lesser extent has been reported in the rat proximal colon (Hardcastle and Hardcastle, 1990).

One of the pathways that histamine has been shown to affect ion transport is by increasing the levels of prostaglandins (Hardcastle and Hardcastle, 1990). The evidence for this was that both indomethacin and mepacrine, an inhibitor of phospholipase A_2 activity, were able to inhibit the histamine-induced increase in the I_{sc} in a concentration-dependent manner, yet neither of them affected the rise of I_{sc} induced by treatment of prostaglandin E_2. Similar findings were observed in our study, which showed reduction in the histamine-induced increase in I_{sc} when the tissue was pretreated with cyclooxygenase inhibitors. That histamine mediates its effects, at least partially through prostaglandin E_2 production was also demonstrated by measuring the levels prostaglandin E_2 in tissue treated with histamine, suggesting that histamine is causing Cl^- secretion, at least in part due to increased levels of prostaglandin E_2.

Histamine affects ion secretion in the mouse cecum through histamine H_1 receptors which is in accord with previous reports (Linaker et al., 1981; Wang et al., 1990). The I_{sc} response to histamine was abolished by histamine H_1 receptor antagonist pyrilamine but was unaffected by cimetidine, an histamine H_2 receptor agonist. In a recent report, histamine has been shown to act at presynaptic receptors on cholinergic axons to decrease the strength of transmission which may function as a brake on runaway excitation caused by postsynaptic histamine H_2 receptor

stimulation (Wood, 1992). It has been hypothesized that this presynaptic inhibition functions to suppress the neural stimulation during normal digestion (Wood, 1992). Wang and Cooke (1990) found that the histamine H_3 receptor blocker, burimamide, increases the amplitude of histamine induced secretion in guinea pig distal colon. This is in accord with what we observed in the present study, where thioperamide, an histamine H_3 receptor antagonist increased the histamine-induced increase in I_{sc} suggesting therefore, a role for presynaptic inhibitory histamine H_3 receptor.

In conclusion, this study demonstrates for the first time that histamine has profound effects on the secretory function of the normal mouse cecum. Since histamine levels have been shown to be increased in inflammatory bowel disease, an understanding of its mechanism of action on electrolyte transport in the cecum of the C3H/HeJ mouse is essential before any attempt to study the changes that are involved in the disease state in the inbred model of colitis in the same strain of mice the C3H/HeJ/BIR (Sundberg et al., 1994). This study serves as a basis for the study of ion transport in the mouse cecum and its regulation and the potential changes that might occur in secretion in colitis.

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