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Histamine H_3 receptor-mediated suppression of inhibitory synaptic transmission in the submucous plexus of guinea-pig small intestine

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Abstract

Conventional intracellular microelectrodes and marker injection techniques were used to study the actions of histamine on inhibitory synaptic transmission in the submucous plexus of guinea-pig small intestine. Bath application of histamine (1–300 μM) reversibly suppressed both noradrenergic and non-adrenergic slow inhibitory postsynaptic potentials in a concentration-dependent manner. These effects of histamine were mimicked by the selective histamine H_3 receptor agonist *R*(−)-α-methylhistamine but not the selective histamine H_1 receptor agonist, 6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl) heptanecarboxamide (HTMT dimaleate), or the selective histamine H_2 receptor agonist, dimaprit. The histamine H_3 receptor antagonist, thioperamide, blocked the effects of histamine. Histamine H_1 and H_2 receptor antagonists did not change the action of histamine. Hyperpolarizing responses to focal application of norepinephrine or somatostatin by pressure ejection from micropipettes were unaffected by histamine and *R*(−)-α-methylhistamine. The results suggest that histamine acts at presynaptic histamine H_3 receptors on the terminals of sympathetic postganglionic fibers and intrinsic somatostatinergic nerves in the small intestine to suppress the release of the inhibitory neurotransmitters, norepinephrine and somatostatin.

Keywords: Enteric nervous system; Submucous plexus; Small intestine; Synaptic transmission, inhibitory; Norepinephrine; Somatostatin

1. Introduction

Histamine is an important signal substance in neuroimmune communication in the mammalian intestine. It is stored in intestinal mast cells and released into the extracellular space when the mast cells degranulate in response to antigenic stimulation. Once released, histamine signals the enteric nervous system to initiate a specific immune-related neural program of intestinal behavior consisting of copious secretion of water, mucous and electrolytes across the mucosa in coordination with a powerful propulsive motility pattern that propagates over extensive lengths of bowel. The secreto-/musculomotor defense program functions to expel hazardous substances from the intestinal lumen with accompanying symptoms of diarrhea and abdominal pain (Wood, 1991, 1992, 1993).

Electrophysiological studies in the intestinal myenteric and submucous plexuses revealed two important actions of histamine on neuronal elements of the enteric nervous system. One is at receptors on the neuronal cell bodies and consists of long-lasting excitation that mimics slow synaptic excitation (Nemeth et al., 1984; Tamura and Wood, 1992; Frieling et al., 1993). Histamine H_2 receptors are the primary mediators of the response. The selective histamine H_2 receptor agonist, dimaprit, mimics the excitatory actions of histamine, and the histamine H_2 receptor antagonist, cimetidine, blocks them. The second action is at nicotinic synapses, where histamine acts at the presynaptic histamine H_3 receptor subtype to suppress nicotinic synaptic transmission (Tamura et al., 1988; Frieling et al., 1993). These two actions are found in the circuitry of both the myenteric and submucous plexuses of the small and large intestine.

Several lines of evidence suggest the presence of presynaptic histamine H_3 receptors on noradrenergic nerve endings in both the central nervous system and the peripheral tissues (for review, see Hill et al., 1997). Activation of presynaptic histamine H_3 receptors inhibits the evoked release of norepinephrine from sympathetic nerves in the mouse and rat cerebral cortex (Schlicker et al., 1989, 1992)

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and in peripheral tissues such as guinea-pig mesenteric artery (Ishikawa and Sperelakis, 1987), guinea-pig atria (Luo et al., 1991; Endou et al., 1994), and human saphenous vein (Molderings et al., 1992; Valentine et al., 1999). Neurons in the submucous plexus receive synaptic input from postganglionic sympathetic nerves and appear to be tonically inhibited by sympathetic discharge in vivo (North and Surprenant, 1985). Involvement of sympathetic activity in suppression of fluid and electrolyte secretion and coincident increase in net mucosal absorption is well understood (Hubel, 1985). On the other hand, the role of histamine receptors in sympathetic regulation of intestinal secretion and absorption has been unclear. The present study was undertaken to clarify the involvement of histamine as a modulator of noradrenergic neurotransmission in the submucous plexus. Aside from noradrenergic inhibitory synaptic inputs, non-adrenergic, non-cholinergic inhibitory synaptic potentials (IPSPs) have been reported to occur in submucous neurons (Mihara et al., 1987; Shen and Surprenant, 1993). We confirmed the existence of non-adrenergic IPSPs and investigated the effects of histamine on this form of neurotransmission.

2. Materials and methods

Adult male Hartley strain guinea-pigs (400–600 g) were stunned by a blow to the head and exsanguinated from the cervical vessels according to procedures approved by the Ohio State University Laboratory Animal Care and Use Committee. Segments of small intestine were removed 20 cm proximal to the ileocecal junction. Preparations of the submucous plexus for electrophysiological recording were microdissected as described earlier (Zafirov et al., 1993). A 2.0 × 1.0 cm segment of the preparation was mounted in a 2.0-ml recording chamber that was superfused at a rate of 10–15 ml min^{-1} with Krebs solution warmed to 37°C and gassed with 95% O_2/5% CO_2 to buffer at pH 7.3–7.4. The composition of the Krebs solution was (in mM): NaCl, 120.9; KCl, 5.9; $MgCl_2$, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 14.4; $CaCl_2$, 2.5; and glucose, 11.5. The submucous ganglia were visualized with differential interference contrast optics and epilumination. Ganglia selected for study were immobilized with 100-μm-diameter L-shaped stainless steel wires placed on either side of the ganglion.

Methods of intracellular recording from the submucous plexus are described in detail elsewhere (Zafirov et al., 1993). Transmembrane electrical potentials were recorded with conventional ''sharp'' microelectrodes filled with 4% biocytin in 2 M KCl containing 0.05 M Tris buffer (pH 7.4). Resistances of the electrodes were 80–120 MΩ. The preamplifier (M767, World Precision Instruments, Sarasota, FL) was equipped with a bridge circuit for injecting current through the recording electrode. Slow IPSPs were evoked by electrical shocks (20 Hz) applied focally to interganglionic connectives with 20-μm-diameter Teflon®-insulated Pt wire electrodes connected through stimulus-isolation units (Grass SIN5) to Grass S48 stimulators (Grass Instrument Division, Astro-Med, Warwick, RI). Chart records were made on Astro-Med thermal recorders. All data were recorded on videotape for later analysis. Amplitudes of action potentials on the chart records are sometimes attenuated due to slow frequency response of the recorders.

At the end of each recording session, the marker dye biocytin was injected into the impaled neurons from the recording electrodes by the passage of hyperpolarizing current (0.5 nA for 10–30 min). The anal end of the preparations was marked and the tissue was transferred into a disposable chamber filled with fixative containing 4% formaldehyde plus 15% of saturated solution of picric acid and kept at 4°C overnight. The preparations were cleared in three changes of dimethyl sulfoxide and three 10 min washes with phosphate-buffered saline (PBS). The preparations were reacted with avidin coupled to horseradish peroxidase, carried through a diaminobenzidine color-developing reaction and then dehydrated in alcohol. The preparations were mounted in Canada balsam and examined microscopically.

Actions of histamine and related pharmacological agents were studied by pressure microejection or by application in the superfusion solution. Micropipettes (~10 μm tip diameter) manipulated with the tip close to the impaled neurons were used to microeject the substances. Pressure pulses of nitrogen with predetermined force and duration were applied to the micropipettes through electronically controlled solenoid valves.

The pharmacological agents used in this study and sources were: Histamine dihydrochloride, pyrilamine maleate, cimetidine, and somatostatin were obtained from Sigma (St. Louis, MO). Dimaprit dihydrochloride, *R*(−)-α-methylhistamine, L-(−)-norepinephrine bitartrate, phentolamine mesylate were from RBI (Natick, MA). Thioperamide maleate and 6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl) heptanecarboxamide (HTMT dimaleate) were from Tocris Cookson (Ballwin, MO).

Data are expressed as means ± standard error; *n*-values refer to the number of neurons. The concentration–response curves for drug-induced response were constructed using the following least-squares fitting routine: $V = V_{Max}/[1 + (EC_{50}/C)^{nH}]$, where V is the observed response, EC_{50} is the concentration that induces the half-maximal response, and nH is the apparent Hill coefficient.

3. Results

3.1. Effects of histamine on noradrenergic IPSPs

Short train stimulation (20 Hz, 0.2 s or less) applied to the interganglionic fiber tracts evoked IPSPs in most of the submucous plexus neurons examined (60/70, 86%). The alpha adrenoceptor antagonist, phentolamine (1 μM) abol-

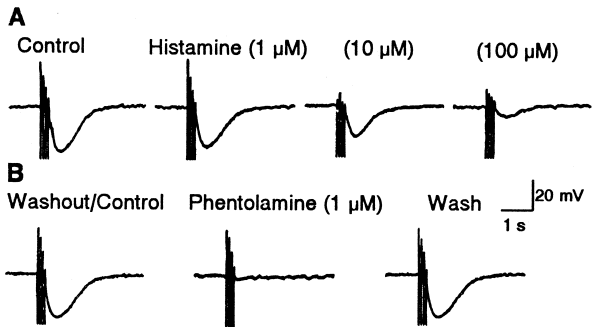

Fig. 1. Effects of histamine on noradrenergic IPSPs in a submucous neuron. (A) Noradrenergic IPSPs evoked by short train stimulation (20 Hz, four pulses) applied to an interganglionic fiber tract were suppressed progressively by increasing concentrations of histamine from 1 to 100 μM. (B) The inhibitory action of histamine was reversed during washout and was followed by demonstration of blockade of the IPSP by the α-adrenoceptor antagonist phentolamine (1 μM).

ished the IPSPs (Figs. 1B and 2A). This was consistent with earlier reports that the noradrenergic IPSPs in guinea-pig submucous plexus neurons are mediated by α-adrenergic receptors (North and Surprenant, 1985; Zafirov et al., 1993). The mean amplitude and duration of the noradrenergic IPSPs were 22.93 ± 1.25 mV (range: 11–38 mV, $n = 30$) and 1.22 ± 0.08 s (range: 0.7–2 s, $n = 30$) when evoked by a stimulus of 20 Hz for 0.2 s. All of the neurons possessing noradrenergic IPSPs were S-type neurons with uniaxonal morphology.

Bath application of histamine (1–300 μM) reversibly suppressed the amplitude of the noradrenergic IPSPs (Fig. 1A). Suppression of the IPSPs began within 30 s–1 min after entry of histamine into the tissue chamber. Maximum inhibition was observed within 2–4 min and washout for periods of 5–10 min were sufficient for complete recovery. Suppression of the noradrenergic IPSPs was concentration dependent with an EC_{50} of 9.18 ± 1.13 μM for 48 submucous plexus neurons (Figs. 1A and 2B). Histamine did not evoke excitatory responses in nine of the 60 neurons tested, but did suppress the noradrenergic IPSPs in the nine neurons.

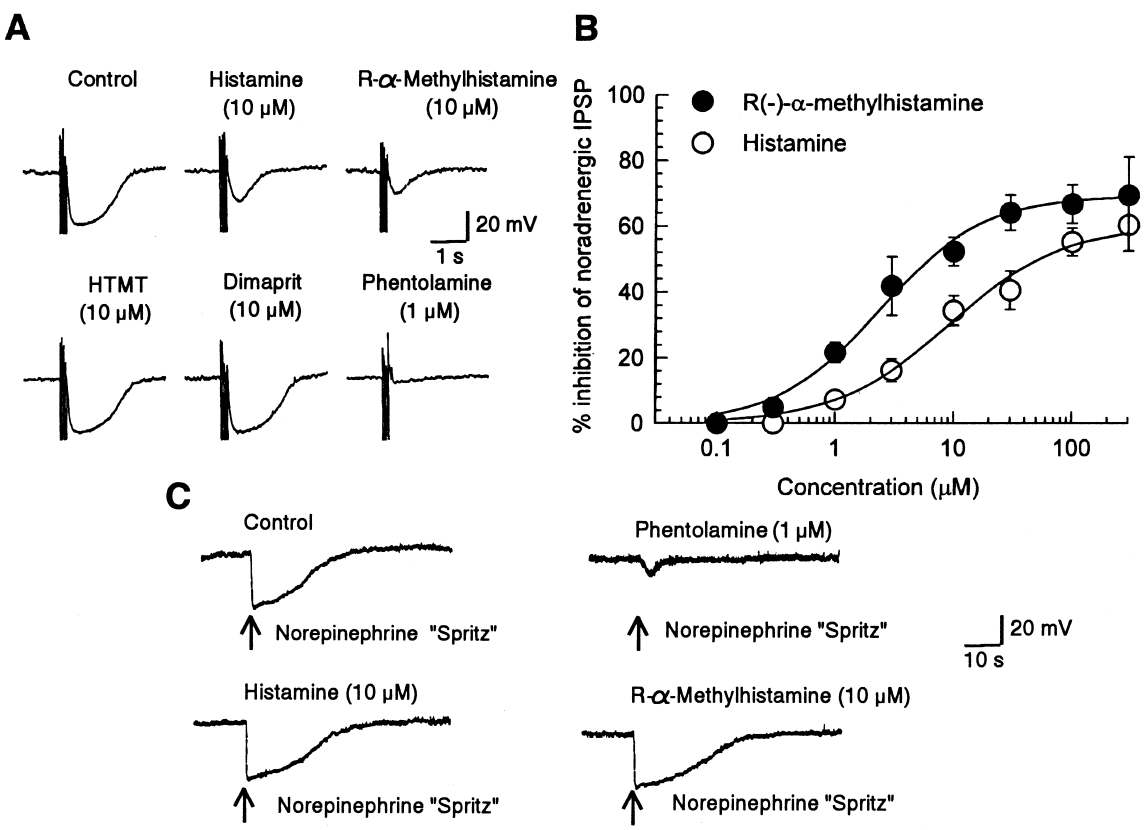

Fig. 2. Effects of histamine and selective histamine receptor agonists on noradrenergic IPSPs and the hyperpolarizing responses to micropressure application of norepinephrine. (A) Focal electrical stimulation (20 Hz, 0.2 s) evoked noradrenergic IPSPs in a submucous plexus neuron. Application of histamine (10 μM) in the superfusion solution suppressed the noradrenergic IPSPs. The inhibitory action of histamine was mimicked by the selective histamine H_3 receptor agonist, $R(-)$-α-methylhistamine (10 μM), but not the selective histamine H_1 receptor agonist, HTMT (10 μM), or the histamine H_2 receptor agonist, dimaprit (10 μM). Phentolamine (1 μM) reversibly abolished the IPSPs, indicating that the IPSPs were noradrenergic. (B) Concentration–response curves for histamine and $R(-)$-α-methylhistamine suppression of noradrenergic IPSPs. The EC_{50} for histamine and $R(-)$-α-methylhistamine were 9.18 ± 1.13 and 2.39 ± 0.24 μM, respectively. Each point represents the mean ± s.e. for 4–15 neurons. (C) Control response to a microejection pulse (''spritz'') of 10 μM norepinephrine was membrane hyperpolarization. The hyperpolarizing response to norepinephrine was suppressed by phentolamine (1 μM). Neither histamine nor $R(-)$-α-methylhistamine suppressed hyperpolarizing responses to micropressure application of norepinephrine.

Histamine receptor agonists and antagonists were tested to identify the receptor subtype responsible for suppression of the slow IPSPs. The selective histamine H_3 receptor agonist, $R(-)$-α-methylhistamine, suppressed the noradrenergic IPSPs with an EC_{50} of 2.39 ± 0.24 μM, in 36 of the 42 submucous plexus neurons examined (Fig. 2A and B). The histamine H_1 receptor agonist HTMT (10 μM, $n = 7$, Fig. 2A) and the histamine H_2 receptor agonist dimaprit (10 μM, $n = 7$, Fig. 2A) did not reduce the amplitude of the stimulus-evoked noradrenergic IPSPs. Bath application of the histamine H_1 receptor antagonist pyrilamine (30 μM, $n = 7$, Fig. 3C) or the histamine H_2 receptor antagonist cimetidine (30 μM, $n = 7$, Fig. 3D) did not prevent suppression of the noradrenergic IPSPs by histamine (10 μM). However, bath application of the histamine H_3 receptor antagonist thioperamide (30 μM, Fig. 3E and H) abolished the suppression of noradrenergic IPSPs by histamine and $R(-)$-α-methylhistamine. Thioperamide itself had no significant effect on the noradrenergic IPSPs. Concentration–response curves for $R(-)$-α-methylhistamine were shifted rightward in a concentration-dependent manner by thioperamide (3, 10 and 30 μM; Fig. 4).

Microejection of norepinephrine onto the cell somas evoked an IPSP-like hyperpolarizing response in the submucous neurons (Fig. 2C). Like the stimulus-evoked IPSPs, the hyperpolarizing responses to norepinephrine were suppressed by the α-adrenergic antagonist phentolamine (Fig. 2C). Neither histamine nor $R(-)$-α-methylhistamine altered the hyperpolarizing response evoked by norepinephrine (Fig. 2C). This suggested that the site of action of histamine was at presynaptic inhibitory receptors on the noradrenergic nerve terminals, and that suppression of the IPSPs resulted from inhibition of norepinephrine release from the terminals.

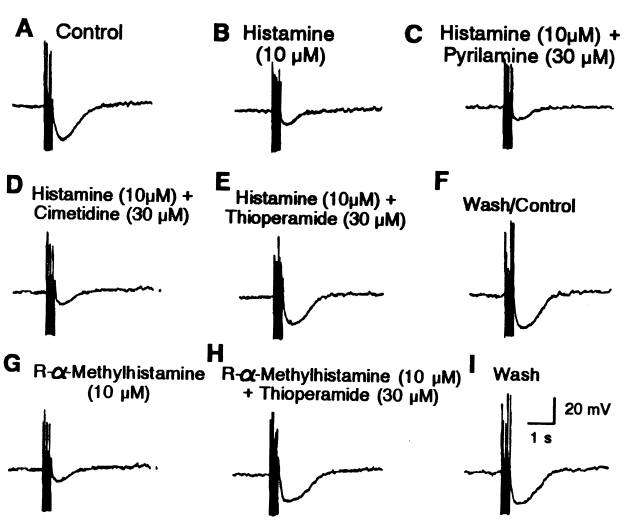

Fig. 3. Effects of histamine and selective histamine receptor antagonists on IPSPs in a submucous neuron. (A) Control noradrenergic IPSP. (B) Suppression of the IPSP by histamine (10 μM) in the superfusion solution. (C, D) Pyrilamine (30 μM) and cimetidine (30 μM) did not change the inhibitory action of histamine. (E) Thioperamide (30 μM) blocked the action of histamine. (F) Recovery of the IPSP after washout. (G) $R(-)$-α-methylhistamine (10 μM) suppressed the IPSP. (H) The inhibitory action of $R(-)$-α-methylhistamine was also blocked by thioperamide (30 μM). (I) Recovery after washout.

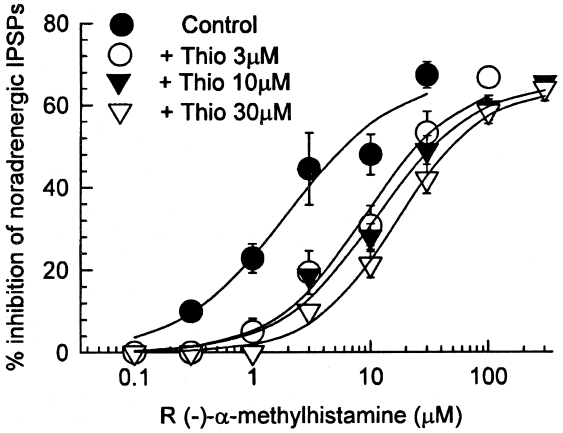

Fig. 4. Concentration–response curves for $R(-)$-α-methylhistamine were shifted rightward in the presence of three concentrations of thioperamide (3, 10 and 30 μM).

3.2. Effects of histamine on non-adrenergic IPSPs

Non-adrenergic IPSPs were observed in only 15 of the 85 submucous plexus neurons examined. Prolonged trains of electrical stimuli (20 Hz, 0.6–2 s) were required to evoke non-adrenergic IPSPs compared to that of noradrenergic IPSPs (20 Hz, 0.2 s or less). The α-adrenoceptor antagonist phentolamine (10 μM) was present in the bathing solution to block the noradrenergic component of IPSPs during investigation of the non-adrenergic IPSPs. The mean amplitude of the non-adrenergic IPSPs was 14.57 ± 1.13 mV (range: 10–20 mV, $n = 7$), and the mean duration was 5.07 ± 0.64 s (range: 3–7.5 s, $n = 7$), when evoked by a stimulus of 20 Hz for 1 s. All of the neurons possessing non-adrenergic IPSP input were S-type neurons with uniaxonal morphology.

Application of histamine (10 μM) in the superfusion solution reversibly suppressed the non-adrenergic IPSPs by 48 ± 2.67% of control ($n = 5$, Fig 5A). Suppression of non-adrenergic IPSPs was abolished by thioperamide (30 μM), the selective histamine H_3 receptor antagonist ($n = 5$, Fig 5A). The histamine H_1 receptor antagonists, pyrilamine ($n = 4$, not shown), and the H_2 receptor antagonist, cimetidine ($n = 4$, not shown), had no effects on histamine-induced suppression of non-adrenergic IPSPs. The selective histamine H_3 receptor agonist $R(-)$-α-methylhistamine (10 μM) mimicked histamine by suppressing the non-adrenergic IPSPs by 62.8 ± 8.44% of control ($n = 5$, Fig. 5A). This effect was also blocked by thioperamide (30 μM, not shown).

Micropressure application of somatostatin, a putative mediator of non-adrenergic slow IPSPs in the submucous

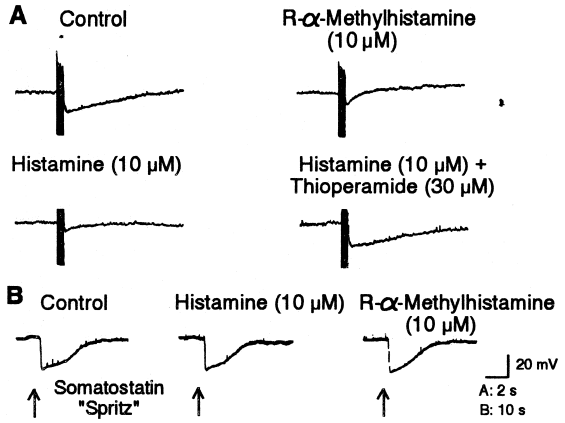

Fig. 5. Histamine suppressed non-adrenergic IPSPs but not the hyperpolarizing response to somatostatin in a submucous neuron. Phentolamine (10 μM) was present in the superfusion solution to block noradrenergic IPSPs. (A) Histamine (10 μM) in the superfusion solution suppressed the non-adrenergic IPSPs. The selective histamine H_3 agonist, $R(-)$-α-methylhistamine (10 μM), mimicked the inhibitory action of histamine. The histamine H_3 receptor antagonist, thioperamide (30 μM), blocked the inhibitory action of histamine. (B) Micropressure application (''spritz'') of 10 μM somatostatin-evoked membrane hyperpolarization in the same neuron as in A. Neither histamine (10 μM) nor $R(-)$-α-methylhistamine (10 μM) suppressed hyperpolarizing responses to micropressure application of somatostatin.

plexus (Shen and Surprenant, 1993), evoked IPSP-like hyperpolarizing responses (Fig. 5B). Neither histamine nor $R(-)$-α-methylhistamine altered the hyperpolarizing response evoked by somatostatin (Fig. 5B). This suggested that the blocking actions of histamine on the non-adrenergic IPSPs resulted from presynaptic inhibition of somatostatin release.

4. Discussion

The present study found that histamine suppressed both adrenergic and non-adrenergic inhibitory synaptic transmission in the submucous plexus of guinea-pig small intestine by interacting with histamine H_3 receptors located on the presynaptic terminals of postganglionic sympathetic nerves and intrinsic somatostatinergic nerves. The presence of significant amounts of histamine in mucosal mast cells in the gut wall (Wood, 1992) suggests that histamine could be released during anaphylaxis or inflammation to influence neuronal excitability and synaptic transmission in the submucous plexus.

One population of slow IPSPs in the submucous plexus reflects the intramural release of norepinephrine from sympathetic postganglionic nerve fibers (North and Surprenant, 1985; Zafirov et al., 1993; Wood, 1994). Our findings suggest that histamine acts to suppress norepinephrine release from the sympathetic innervation. This appeared to be a direct action at the presynaptic inhibitory receptors on the sympathetic nerve terminals because histamine did not suppress the hyperpolarizing action of exogenously applied norepinephrine and the suppression of noradrenergic IPSPs occurred in neurons without any histamine-induced depolarization.

Our results suggest that suppression of noradrenergic synaptic transmission by histamine is mediated by histamine H_3 receptors in the submucous plexus. The potent and specific histamine H_3 agonist, $R(-)$-α-methylhistamine, mimicked the presynaptic inhibitory action of histamine. The much stronger blocking action of thioperamide over pyrilamine or cimetidine is additional evidence for histamine H_3 receptor involvement. The parallel rightward shifts of the $R(-)$-α-methylhistamine concentration–response curves found with increasing concentrations of thioperamide are suggestive of competitive antagonism at the histamine H_3 receptor.

Our observations of non-adrenergic IPSPs in the submucous plexus confirm the findings of others who have reported that a subset of the IPSPs are mediated by transmitter(s) other than norepinephrine (Hirst and Silinsky, 1975; Mihara et al., 1987). Unlike the adrenergic IPSP, the non-adrenergic IPSP was seldom observed in our study. The non-adrenergic transmitter has not been identified unequivocally; nevertheless, somatostatin emerges as the most likely candidate (Shen and Surprenant, 1993).

Histamine suppressed the non-adrenergic IPSPs and this can be interpreted to be presynaptic inhibition because histamine did not suppress the hyperpolarizing action of exogenously applied somatostatin. Our evidence suggests that inhibition of the non-adrenergic IPSPs is mediated by the histamine H_3 receptor. Nevertheless, confirmation will

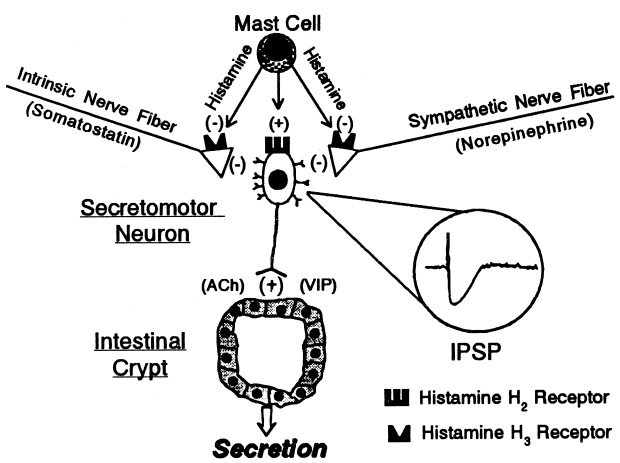

Fig. 6. Conceptual model for actions of histamine in the submucous plexus. Histamine acts at histamine H_2 receptors on the cell soma to increase excitability of secretomotor neurons and at presynaptic inhibitory histamine H_3 receptors to suppress release of norepinephrine from sympathetic nerves and somatostatin from intrinsic inhibitory inputs to secretomotor neurons. Stimulation of submucosal secretomotor neurons by histamine is expected to evoke secretion from mucosal crypts and may account in part for diarrheal symptoms associated with the release of histamine during gastrointestinal type I hypersensitivity reactions. Inactivation of inhibitory synaptic inputs to secretomotor neurons facilitates secretion by removing braking action of sympathetic nerves and may also contribute to diarrheal symptoms.

require full concentration–response curves obtained for different concentration of the antagonist. This was not feasible in the present study because of the scarcity of non-adrenergic IPSPs.

An aspect of the physiologic significance of histamine H_3 receptors at inhibitory synapses in the submucous plexus is illustrated in Fig. 6. Secretomotor neurons located in the submucous plexus release vasoactive intestinal peptide and acetylcholine to stimulate the secretion of water and electrolytes from the intestinal crypts (Cooke and Reddix, 1994). The secretomotor neurons receive inhibitory synaptic inputs from noradrenergic sympathetic postganglionic neurons (North and Surprenant, 1985) and from intrinsic somatostatinergic neurons in the enteric microcircuits (Mihara et al., 1987; Shen and Surprenant, 1993). Activation of the inhibitory synaptic inputs evokes IPSPs (both adrenergic and non-adrenergic) in the secretomotor neurons. This suppresses firing in the secretomotor neurons and acts as a brake on mucosal secretion. Histamine acts presynaptically to suppress the inhibitory synaptic transmission to the secretomotor neurons and/or synaptically connected interneurons. This coupled with excitation of the submucous neurons by activation of excitatory histamine H_2 receptors on the cell soma (Frieling et al., 1993) leads to maximal secretomotor neuron firing rates and hyperstimulation of mucosal secretion.

Acknowledgements

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