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INTRACELLULAR STUDY OF EFFECTS OF HISTAMINE ON ELECTRICAL BEHAVIOUR OF MYENTERIC NEURONES IN GUINEA-PIG SMALL INTESTINE

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SUMMARY

1. The actions of histamine on myenteric neurones were investigated with intracellular recording methods in guinea-pig small intestine.

2. The actions of histamine at the ganglion cell soma were: membrane depolarization, increased input resistance, suppression of post-spike hyperpolarizing potentials, augmented excitability and repetitive spike discharge. Excitability was enhanced also at spike initiation sites remote from the cell body.

3. Both H_1 and H_2 receptors were involved in the response to histamine. Dimaprit mimicked the responses to histamine in 80% and 2-methylhistamine in 50% of the trials. Cimetidine was an antagonist for histamine in 82% and for dimaprit in all of the trials. Pyrilamine blocked the actions of histamine in 59% of the cells and always blocked the action of 2-methylhistamine.

4. Histamine mimicked slow synaptic excitation in the neurones, but was ruled out as a neurotransmitter for the slow excitatory post-synaptic potential (e.p.s.p.).

5. Histamine either did not affect the responses to 5-hydroxytryptamine, substance P and acetylcholine or it potentiated the responses to these putative neurotransmitters for slow synaptic excitation.

6. The results support the possibility that histamine released from mast cells by circulating peptidergic messengers, by neurotransmitters or during anaphylaxis could influence enteric nervous function.

INTRODUCTION

Histamine is present in the central nervous systems of a variety of vertebrate and invertebrate species (Reite, 1972) and has been investigated for a role as a neurotransmitter substance in both groups of animals (Snyder & Taylor, 1972; Weinreich, 1977; Schwartz, Pollard & Quach, 1980; Haas & Konnerth, 1983). The evidence for neurotransmitter function in the vertebrate central nervous system is meagre and indirect; whereas, direct electrophysiological results implicate histamine as a neurotransmitter in cerebral ganglia of *Aplysia californica* (McCaman & Weinreich, 1982).

Histamine is present in autonomic ganglia; however, in contrast to the central

nervous system, most of the histamine in the autonomic nervous system is located in mast cells within the connective tissue (Torp, 1961). Little is known about the direct effects of histamine on electrical behaviour of autonomic ganglion cells, but there is evidence that histamine alters synaptic transmission in the ganglia (Trendelenburg, 1954; Gertner & Kohn, 1959; Brezenoff & Gertner, 1972; Brimble & Wallis, 1973; Nandiwada, Lokhandwala & Jandhyala, 1980; Yamada, Tokimasa & Koketsu, 1982; Lindl, 1983).

The enteric nervous system is considered to be a third division of the autonomic nervous system which is structurally and functionally distinct from the sympathetic and parasympathetic divisions (Gershon & Erde, 1981; Wood, 1981). Like other parts of the nervous system, there are indications that the functional integrity of the enteric system may be influenced by neuronal actions of histamine. In the small intestine, histamine is present in mast cells with greatest amounts in the mucosal regions and with small but significant amounts in mast cells that are situated in close association with the ganglia of the myenteric plexus (Dale & Zilletti, 1970). Application of histamine evokes contractions of longitudinal muscle–myenteric plexus preparations from guinea-pig small intestine (Barker & Ebersole, 1982; Zavecz & Yellin, 1982) and evokes increases in chloride secretion by the guinea-pig small intestinal mucosa (Cooke, Nemeth & Wood, 1984). Both of these actions are partially sensitive to tetrodotoxin and have been interpreted as excitatory actions of histamine on enteric neurones. [^{3}H]histamine is taken up within the gut wall and is released by electrical field stimulation (Håkanson, Wahlestedt, Westlin, Vallgren & Sundler, 1983). This release is abolished by tetrodotoxin and requires Ca^{2+} which suggests that uptake and release are by neurones.

The aim of this study was to investigate directly with intracellular recording methods the actions of histamine on electrical properties of enteric ganglion cells. Preliminary reports of the study have been communicated elsewhere (Wood & Nemeth, 1983; Nemeth & Wood, 1983).

METHODS

Segments of intestine were obtained from the ileum 10–20 cm orad to the ileocaecal junction of adult guinea-pigs (250–800 g) that had been stunned by a blow to the head and exsanguinated. Flat preparations of longitudinal muscle with myenteric plexus attached were prepared, mounted in a superfusion chamber and observed with an interference contrast microscope as described in an earlier report (Wood & Mayer, 1978*a*). Conventional intracellular recording methods were used (Wood & Mayer, 1978*a*). Synaptic input to the ganglion cells was activated by electrical shocks (200 μs duration) applied to the ganglia or interganglionic connectives with electrodes made from Teflon-insulated Pt wire (20 μm diam.) and a Grass S-88 square-wave stimulator. Most of the records were reproduced on a strip-chart recorder (Gould Inst.) from data recorded earlier on magnetic tape, and the amplitudes of the action potentials as they appear in the illustrations are attenuated by the limited frequency response of the recorder.

The tissues were maintained in Krebs solution at 37 °C and gassed with 95% O_2–5% CO_2. Composition of the solution was (mM): NaCl, 120·9; KCl, 5·9; $MgCl_2$, 1·2; NaH_2PO_4, 1·2; $NaHCO_3$, 14·4; $CaCl_2$, 2·5; glucose, 11·5. In some protocols, Mg^{2+} was elevated to 16 mM and Ca^{2+} was reduced to 1·25 mM in order to block synaptic transmission. In these experiments, HEPES was substituted for the bicarbonate–phosphate buffer system and constant osmolarity was maintained by adjusting the NaCl concentration. The liquid junction potentials of the micro-electrodes never varied by more than 4 mV in the altered solutions and there were no consistently measurable changes in the electrode resistances.

Histamine and other substances were either applied by addition to the superfusion solution or by microejection from fine-tipped pipettes (tip diam. 10–20 μm) with nitrogen pulses of controlled pressure and duration. Concentrations of chemical agents in the pipettes were three to four orders of magnitude greater than the lowest effective concentration applied in the superfusion solution.

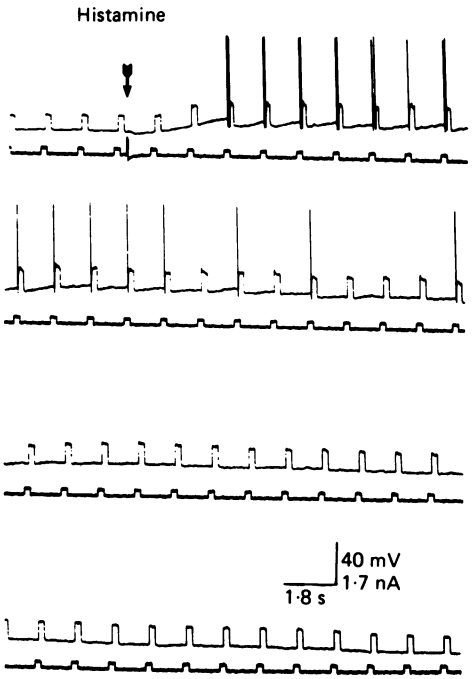

Fig. 1. The effects of histamine on electrical behaviour of an AH/type 2 myenteric neurone. The arrow indicates application of a 50 ms pulse of 0·1 mM-histamine. The lower trace shows repetitive intrasomal injection of constant-current depolarizing pulses. The upper trace of transmembrane voltage shows membrane depolarization and increased frequency of spike discharge during depolarizing current pulses after application of histamine. Traces are continuous.

Concentrations attained at the receptors were impossible to determine when the microejection method was used because the tips of the pipettes were positioned 20–50 μm from the impaled neurone and the 1 ml volume of the tissue chamber was perfused at a rate of 10–14 ml/min. Relative changes in concentration of drug at the tissue were achieved by varying the duration of the pressure ejection pulse. Amount of substance released from the pipette was a linear function of duration of the pulse over the range of durations used. All substances in the pipettes were freshly prepared and dissolved in Krebs solution.

Drugs used were tetrodotoxin, cimetidine, pyrilamine maleate, diphenhydramine HCl, 5-hydroxytryptamine creatinine sulphate (5-HT), acetylcholine chloride (ACh) and histamine dihydrochloride (Sigma Chemical Co.); methysergide maleate (Sandoz Pharmaceuticals); dimaprit and 2-methylhistamine dihydrochloride (Smith, Kline and French Laboratories); substance P (Peninsula Laboratories).

RESULTS

The results were obtained from impalements of 150 neurones in preparations from sixty-one guinea-pigs. These impalements were maintained for periods of 15 min to several hours in cells with stable resting potentials. Seventy of the neurones were

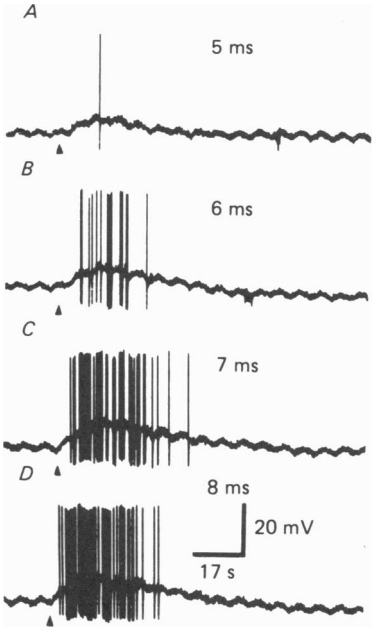

Fig. 2. The relation between duration of histamine ejection pulse and intensity of response. *A*, 5 ms pulse; *B*, 6 ms; *C*, 7 ms; *D*, 8 ms. The microejection pipette contained 1 mM-histamine; triangles indicate times of histamine applications.

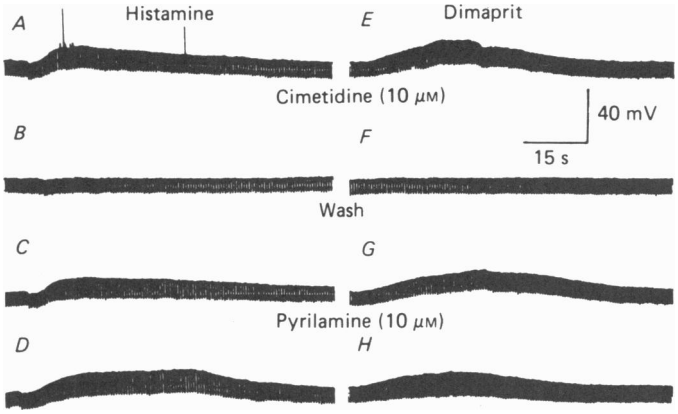

Fig. 3. Effects of histamine and dimaprit on electrical behaviour of a myenteric neurone. *A*, response to pulse of histamine. *E*, response to pulse of dimaprit. *B*, *F*, cimetidine blocked the action of histamine and dimaprit. *C*, *G*, the blocking action of cimetidine was reversed after removal of the drug from the superfusion solution. *D*, *H*, pyrilamine did not affect the action of histamine or dimaprit. The duration of focal pulses of histamine and dimaprit was 650 ms for all records. The concentration of histamine or dimaprit in the micropipettes was 0·1 mM. Increases in input resistance were reflected by increases in the amplitude of electrotonic potentials resulting from repetitive intrasomal injection of constant-current (254 pA) hyperpolarizing pulses.

classified as AH/type 2 neurones, forty-nine were S/type 1 neurones (Hirst, Holman & Spence, 1974; Nishi & North, 1973; Wood, 1981), and thirty-one were either types 3 or 4. Type 3 neurones had low input resistance similar to AH/type 2 neurones, but they did not discharge spikes when depolarized by intracellularly injected current pulses. These cells had prominent nicotinic cholinergic synaptic potentials that never triggered spikes and, unlike AH/type 2 cells, elevated Mg^{2+} or Mn^{2+} did not affect the cells (Grafe, Mayer & Wood, 1980). Type 4 cells had relatively high resting potentials, did not discharge spikes in response to depolarizing stimuli, never showed synaptic potentials, and could have been enteric glial elements.

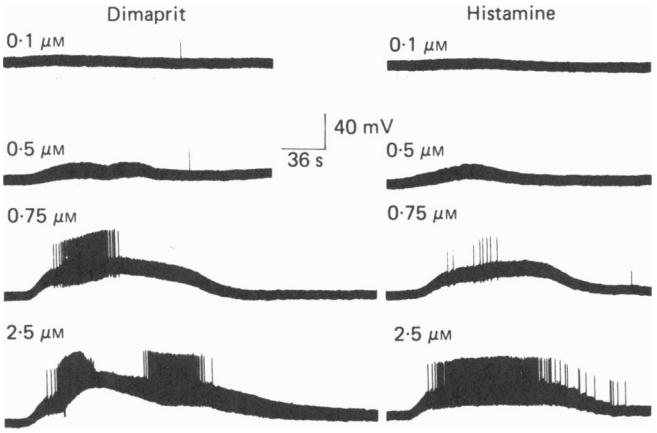

Fig. 4. The effects of graded doses of histamine and dimaprit. The responses to histamine and dimaprit were dose-dependent depolarization, increased resistance, and repetitive spike discharge. Constant-current rectangular hyperpolarizing pulses were injected repetitively into the cell body. An increase in the width of the voltage trace reflected an increase in the input resistance of the cell. All records are from the same cell; the duration of each exposure to histamine was 1 min.

Actions of histamine

Application of histamine either by focal microejection or by addition to the superfusion solution evoked a depolarization of the neuronal membranes of sixty-two of seventy AH/type 2 neurones, in twenty-five of forty-nine S/type 1 neurones and in five of thirty-one type 4 neurones (Figs. 1, 2, 3 and 4). The magnitudes of the depolarizing responses were a direct function of the concentration of histamine in the superfusion solution over a concentration range of 0·1–5 μM (Figs. 4 and 5) or of the duration of the microejection pressure pulse (Fig. 2). The depolarizing responses were associated with an increase in the input resistance of the cells and with enhanced membrane excitability that was prolonged for several seconds after short duration (15–500 ms) applications of histamine.

Increases in input resistance during the depolarizing responses to histamine were reflected in all cells by an increase in the amplitude of electrotonic potentials evoked by intrasomatic injection of hyperpolarizing current pulses (Figs. 3 and 4) and by increased slope of ohmic current–voltage plots (Fig. 6). Increases in input resistance

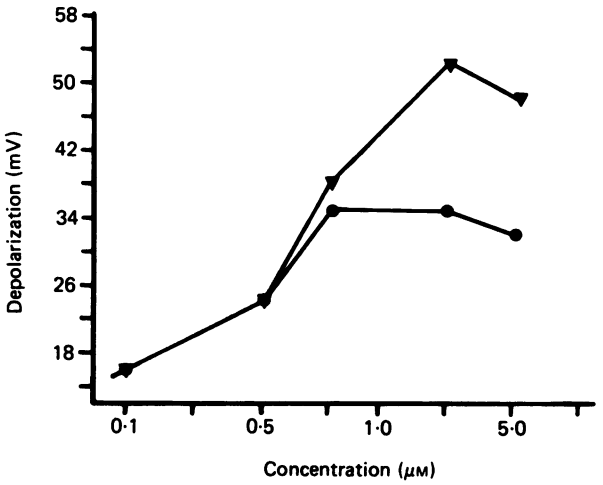

Fig. 5. Comparison of dose–response relations between histamine (●) and dimaprit (▼) for depolarization of the same myenteric neurone. Graphs were drawn from the data of Fig. 4.

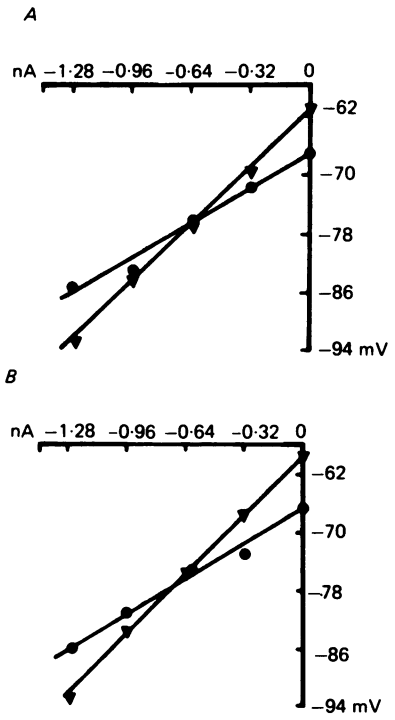

Fig. 6. Current–voltage relations in the presence and absence of histamine. *A*, current–voltage relation for hyperpolarizing current pulses injected before (●) and at the peak of the response to histamine (▼). *B*, current–voltage relation for current pulses injected before (●) and at the peak of the response to dimaprit (▼).

were most prominent in AH/type 2 neurones and ranged between 30 and 80 % of the value before histamine exposure. Plots of current–voltage relations obtained before and during the depolarizing responses to histamine intersected each other at a membrane potential between −75 and −80 mV (Fig. 6). This suggested that the reversal potential for the response was within the range of −75 to −80 mV.

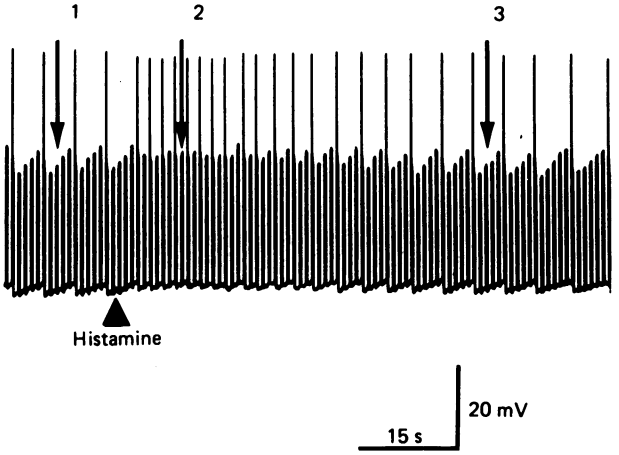

Fig. 7. Histamine suppression of post-spike hyperpolarizing potentials. Constant-current depolarizing pulses were injected repetitively into the neurone and a current pulse periodically evoked a single action potential. Each spike was followed by a prolonged after-hyperpolarization before histamine (arrow 1); the duration and amplitude of the after-hyperpolarization were reduced immediately after a 20 ms pulse of 1 mM-histamine (arrow 2); recovery was apparent at arrow 3.

Enhanced excitability during the depolarizing response to histamine was reflected by a significant increase in the number of action potentials evoked by rectangular pulses of constant current injected intrasomally (Fig. 1). Increased excitability was apparent in some cases as a train of action potentials that appeared at the crests of the histamine-induced depolarizations (Figs. 2 and 10) and also in most cases as discharge of one or two action potentials at the offset of the hyperpolarizing current pulses that were used to assess changes in input resistance (Fig. 8*B*). The enhanced excitability resulted from membrane actions additional to depolarization because none of the three indications of increased excitability occurred during steady depolarization of the membrane by experimental injection of inward current before application of histamine.

Action potentials of the AH/type 2 neurones were followed by characteristic hyperpolarizing after-potentials that lasted for several seconds (Nishi & North, 1973; Hirst *et al.* 1974). Both the amplitude and duration of the hyperpolarizing after-potentials were reduced during the depolarizing responses to histamine (Fig. 7). This effect of histamine was not due to membrane rectification associated with depolarization because suppression of the hyperpolarizing after-potentials still occurred when the histamine-evoked depolarization was prevented by clamping the

membrane potential at the resting value with continuous injection of hyperpolarizing current.

In four of the AH/type 2 neurones, application of histamine by microejection evoked action potential discharge in the processes of the neurones and this was observed as electrotonic reflexions of the spikes at the recording site in the cell body

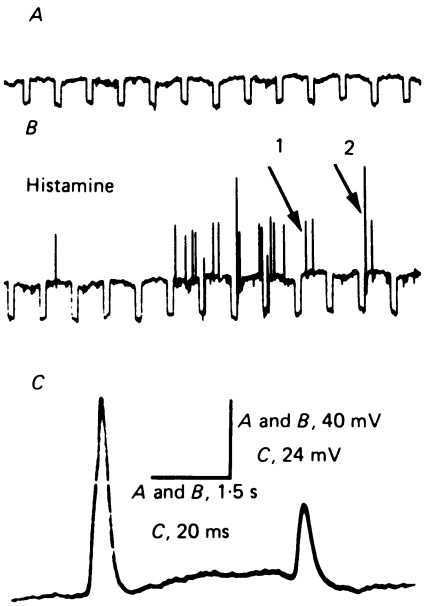

Fig. 8. Histamine-evoked spike discharge at sites remote from the cell body of a myenteric neurone. *A*, electrotonic potentials that resulted from repetitive intrasomal injection of hyperpolarizing constant-current pulses before application of histamine. *B*, record at peak of response to 50 ms pulse of 1 mM-histamine shows electrotonic reflexions of spikes that invaded the soma from one of the cell's neurites (arrow 1). Augmented excitability of cell soma was reflected by somal action potentials at the offset of some of the hyperpolarizing current pulses (arrow 2). *C*, a somal action potential and electrotonic reflexion of a spike from *B* recorded on an expanded time base. Synaptic transmission was blocked by elevated Mg^{2+} and decreased Ca^{2+} during the histamine-evoked response.

(Fig. 8). These potentials were interpreted as action potentials rather than synaptic potentials because they had similar durations to somal action potentials (Fig. 8*C*) and did not change in amplitude when the membranes were hyperpolarized by injected current. This appeared to result from an excitatory action of histamine at spike generation sites away from the soma. The spikes that invaded the cell somas from the processes were not the result of histaminergic activation of synaptic input at the distal neurites because the electrotonic events were still observed after blockade of synaptic transmission in solutions with elevated concentrations of Mg^{2+} and reduction of Ca^{2+} (Fig. 8).

The somal actions of histamine were not the result of synaptic input from other neurones because blockade of synaptic transmission by elevated Mg^{2+} and reduced Ca^{2+} did not prevent the membrane depolarization, increased input resistance and

augmented excitability (Fig. 9). We have already shown that elevated Mg^{2+} and reduced Ca^{2+} act like histamine to depolarize the cell membranes, increase input resistance and augment excitability (Grafe, Mayer & Wood, 1980); and that both slow and fast synaptic transmission in the guinea-pig myenteric plexus were blocked by elevated Mg^{2+} and reduced Ca^{2+} within the time span of histamine application in the present study (Wood & Mayer, 1979*a*, *c*).

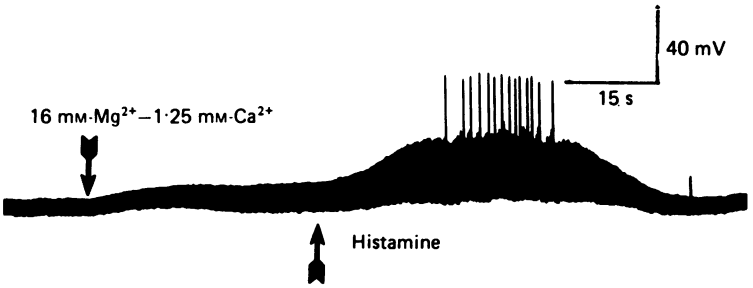

Fig. 9. Histaminergic effects occurred during synaptic blockade by elevated Mg^{2+} and reduced Ca^{2+}. Histamine (0·5 μM) was applied for 1 min in the superfusion solution with elevated Mg^{2+} and reduced Ca^{2+}. The times at which solutions with altered divalent ions or histamine entered the tissue bath are marked by arrows. Constant-current hyperpolarizing pulses were injected into the cell repetitively and an increase in the width of the base line reflects an increase in input resistance.

Effects of agonists and antagonists

Dimaprit mimicked the effects of histamine on four of five AH/type 2 neurones in preparations from five animals when applied in the superfusion solution or when microejected onto the neurones. Application of dimaprit depolarized the cell membranes, increased the input resistance and augmented excitability of the neuronal somas (Figs. 3, 4, 5 and 6). Histamine and dimaprit were equally potent in depolarizing the cell membranes at concentrations less than 0·5 μM; whereas, dimaprit evoked larger depolarizations when added to the superfusion solutions in concentrations greater than 0·5 μM (Figs. 4 and 5). Cimetidine (10 μM) blocked the response to dimaprit in all cases. Responses to dimaprit were never affected by pyrilamine or diphenhydramine (10 μM).

The actions of histamine on two of five AH/type 2 neurones and one S/type 1 neurone in six preparations were mimicked by 2-methylhistamine (1 μM in superfusion or 1 mM in micropipette). Pyrilamine (10 μM) blocked the response to 2-methylhistamine in each of the cells.

The actions of histamine were suppressed reversibly by cimetidine in twenty-three of twenty-four AH/type 2 neurones and in four of nine S/type 1 neurones (Fig. 3). Cimetidine (10 μM) in the superfusion solution abolished responses evoked by microejection of histamine from micropipettes containing 0·10 or 1 mM-histamine as well as responses evoked by addition of 10 μM-histamine to the superfusion solutions. The effects of microejection of histamine in pulses as short as 20 ms were often prolonged for periods up to 5 min. When addition of cimetidine to the superfusion

solution was timed to enter the tissue chamber at the peak of the histamine response, the prolonged responses were aborted by the arrival of cimetidine at the tissue. Reversal of the blocking action of cimetidine required 3–5 min after removal from the superfusion solution. Cimetidine (10 μM) alone did not change the resting membrane potential, post-spike hyperpolarizing potentials or the input resistance of the neurones. Cimetidine did not alter the responses of the neurones to microejection of 5-HT, substance P or ACh.

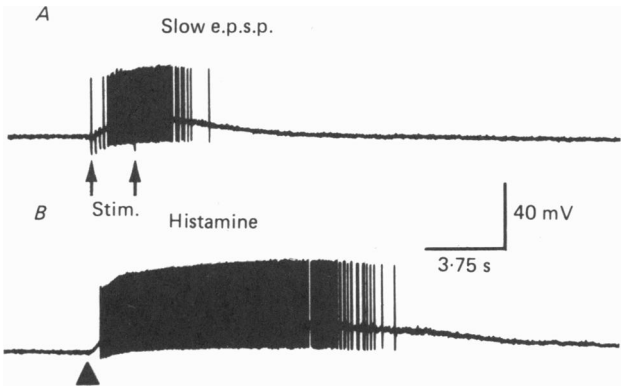

Fig. 10. Action of histamine resembled slow synaptic excitation. *A*, depolarization and repetitive spike discharge during slow e.p.s.p. evoked by electrical stimulation of interganglionic fibre tract. Arrows indicate onset and offset of train of stimulus (stim.) pulses. *B*, response to 15 ms pulse of 1 mM-histamine in the same cell.

Pyrilamine and diphenhydramine (10 μM) did not affect the histamine-induced responses in neurones that were sensitive to the blocking action of cimetidine (Fig. 3), but did reduce the responses to histamine in five of ten cells that were insensitive to cimetidine.

The non-selective antagonist methysergide blocked or greatly reduced the histamine-evoked responses of eight of ten AH/type 2 neurones from ten animals. Methysergide was effective in concentrations of 10 or 25 μM on the application of 0·1 and 0·5 μM-histamine in the superfusion solution and on microejection from micropipettes that contained 0·1 or 1 mM-histamine.

Relationships to slow synaptic excitation

The actions of histamine closely resembled the characteristic slow synaptic excitation (slow excitatory post-synaptic potential (e.p.s.p.)) in myenteric neurones (Wood & Mayer, 1978*b*; Fig. 10). This raised the question of whether histamine might be a neurotransmitter for the slow e.p.s.p. This possibility was reduced by observations that concentrations of cimetidine, which blocked the actions of histamine, did not affect the stimulus-evoked e.p.s.p.s (Fig. 11). Methysergide always blocks the slow e.p.s.p. in myenteric neurones (Wood & Mayer, 1979*b*). In one of the AH/type 2 neurones of the present study, methysergide did not affect the action of histamine;

yet, it abolished the stimulus-evoked slow e.p.s.p. This was interpreted as additional evidence that histamine was not the transmitter for the slow e.p.s.p.

Interactions between histamine and putative neurotransmitters

Putative neurotransmitter substances for myenteric slow e.p.s.p.s in guinea-pig small intestine are 5-HT (Wood & Mayer, 1978*b*, 1979*b*), substance P (Katayama & North, 1978) and ACh (Morita, North & Tokimasa, 1982). When these substances

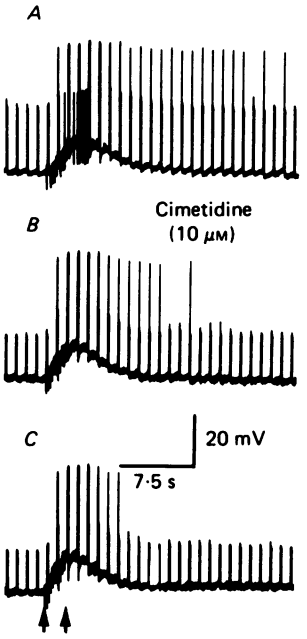

Fig. 11. Cimetidine did not suppress slow synaptic excitation. *A*, control slow e.p.s.p. evoked by electrical stimulation of interganglionic fibre tract consisted of membrane depolarization and increased spike discharge evoked by intracellular injection of constant-current depolarizing pulses. *B*, slow e.p.s.p. evoked in the presence of cimetidine (10 μM). *C*, slow e.p.s.p. after removal of cimetidine from superfusion solution. Arrows indicate application of constant trains of stimulus pulses to interganglionic fibre tract. All records from same cell.

were microejected onto AH/type 2 neurones during the cellular response to histamine, the depolarization and augmentation of excitability evoked by the putative neurotransmitter were either unchanged or were enhanced (Fig. 12). Microejection of 5-HT evoked a greater number of spikes in the presence of histamine (Fig. 12*A* and *B*). Histamine did not change the degree of depolarization, the increase in input resistance or the spike discharge evoked by substance P (Fig. 12*C* and *D*). The depolarizing responses and periods of augmented excitability evoked by ACh were prolonged in the presence of histamine, while there were usually no changes in the degree of increase in input resistance (Fig. 12*E* and *F*).

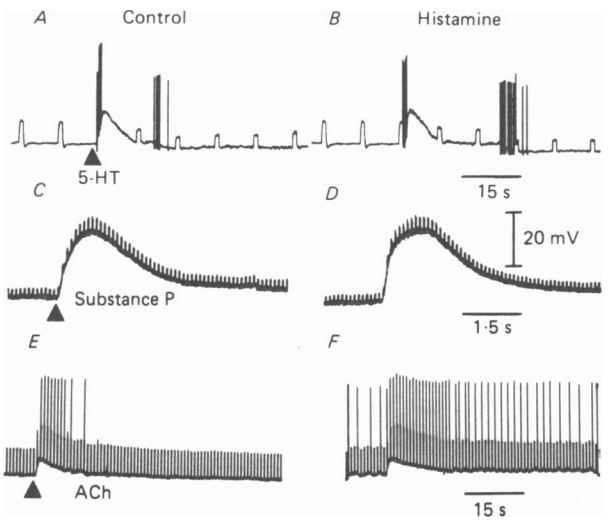

Fig. 12. Interactions between histamine and putative neurotransmitters. *A*, application of a 12 ms pulse of 1 mM-5-HT. *B*, same application of 5-HT in the presence of 50 μM-histamine. *C*, application of a 15 ms pulse of 0·1 mM-substance P. *D*, same application of substance P in the presence of 0·1 μM-histamine. *E*, application of 15 ms pulse of 1 mM-ACh. *F*, same application of ACh in the presence of 1 μM-histamine. Experiments with each neurotransmitter involved a different preparation. Histamine was added to the superfusion solution. Constant-current depolarizing pulses were repetitively injected into the neurone in all of the records. Neurotransmitters were applied by microejection (▲).

DISCUSSION

Histamine increased the excitability of the myenteric neurones. This supports earlier suggestions that some of the effects of histamine on contractile activity of the intestinal musculature and mucosal secretion in organ bath experiments reflect an action of histamine on enteric neurones (Barker & Ebersole, 1982; Zavecz & Yellin, 1982; Cooke, Nemeth & Wood, 1984).

The excitatory actions of histamine occurred both at the neuronal cell body and at sites remote from the cell body. The remote sites of spike initiation could have been either the initial segments of the neurites or more distal locations on the neuronal processes. Extrasomal sites of spike initiation were described by Wood & Mayer (1978*a*) and interpreted as evidence of topographic heterogeneity in myenteric neurones (Wood, 1983).

The neuronal actions of histamine seemed to involve both H_1 and H_2 receptors, with H_2 activity predominating. Cimetidine, the H_2 antagonist, was the most effective blocking agent, and the selective H_2 agonist, dimaprit, was more often active than 2-methylhistamine, which is a selective H_1 agonist (Beaven, 1978; Black, Duncan, Durant, Ganellin & Parsons, 1972). The blocking action of cimetidine was selective for histamine without any effects on the actions of substance P, 5-HT, or ACh, all of which have similar actions to histamine on myenteric neurones (Katayama & North, 1978; Wood & Mayer, 1978*b*; Morita *et al.* 1982). The H_1 antagonists,

pyrilamine and diphenhydramine, were effective on a much smaller proportion of neurones than cimetidine. These results suggest that receptors with H_1 and H_2 properties exist on neural elements in the myenteric plexus; however, the results are inconclusive as to whether the two receptor subtypes coexist on some of the neurones and whether some of the responses to histamine are mediated by receptors with properties intermediate between the H_1 and H_2 subtypes.

The actions of histamine on the electrical behaviour of the myenteric neurones were reminiscent of the changes that occur during activation of the slow excitatory synaptic inputs to these cells (Wood & Mayer, 1978*b*, 1979*b*). These actions also closely resembled those of substance P, 5-HT and ACh, all of which are putative neurotransmitters for the slow e.p.s.p. (Katayama & North, 1978; Wood & Mayer, 1978*b*, 1979*b*; Morita *et al.* 1982). Nevertheless, our results did not implicate histamine as an enteric neurotransmitter.

The physiological and pathophysiological significance of the neuronal actions of histamine in enteric nervous control of the intestinal effector systems is uncertain. There are significant stores of histamine in mast cells located at the periganglionic sheaths in the myenteric plexus in the guinea-pig small intestine, and this histamine can be released during anaphylaxis *in vitro* and presumably *in vivo* (Dale & Zilletti, 1970). Putative messenger substances in the gastrointestinal tract such as substance P, neurotensin and somatostatin are known to release histamine from mast cells (Johnson & Erdos, 1973; Oishi, Ishiko, Inagaki & Takaori, 1983; Renner, 1982; Skofitsch, Donnerer, Petronijevic, Saria & Lembeck, 1983; Theoharides & Douglas, 1981). These substances are sometimes elevated in the blood (Powell, Cannon, Skrabanek & Kirrane, 1978) and an unresolved question is whether release of histamine by these substances could significantly influence enteric neuronal function. Degranulation of mast cells caused by antidromic stimulation of cutaneous nerves (Kiernan, 1972) and ultrastructural evidence for innervation of mast cells in the intestine (Newson, Dahlstrom, Enerback & Ahlman, 1983) suggest that nerve-mediated release of histamine could occur and influence enteric nervous function. Our observation that histamine enhances enteric neuronal excitability supports the possibility that release of histamine by antigens, circulating messenger substances or direct innervation of the mast cells could be sensitizing factors that alter intestinal function.

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