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Effects of histamine on the guinea-pig stomach: excitation of smooth muscle and inhibition of transmitter release

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1 The effects of histamine on electrical responses of smooth muscle cells of the guinea-pig stomach were studied.

2 In the fundus, histamine (above 10^{-6} M) depolarized the membrane and decreased the membrane resistance. In the antrum, the slow waves were enhanced by histamine, without change in the resting membrane potential or membrane resistance (10^{-7}–10^{-6} M), or with depolarization of the membrane (above 10^{-5} M).

3 When the effects of histamine on neuromuscular transmission were estimated from changes in the amplitude of junction potentials, the amine (above 10^{-7} M) inhibited the excitatory junction potential (e.j.p.) recorded in the fundus. Inhibitory junction potentials (i.j.p.) recorded in the antrum and atropine-treated fundus were also inhibited by histamine.

4 Repolarization of the histamine-induced depolarization to the resting potential level did not restore the amplitude of the e.j.p. to the control value.

5 These actions of histamine on the smooth muscle cells and on junction potentials were inhibited by either mepyramine or cimetidine, agents which block the H_1- and H_2-receptor, respectively.

6 It is concluded that in the guinea-pig stomach, histamine exerts a direct excitatory effect on the smooth muscle cells and has inhibitory actions on cholinergic excitatory and non-adrenergic, non-cholinergic inhibitory transmission.

Introduction

Histamine is involved in many patho-physiological phenomena such as allergic reactions, inflammation and gastric ulceration (Beaven, 1978). These actions are mainly mediated by H_1- and H_2-receptors (Black *et al.*, 1972), although an additional histamine receptor has also been postulated in tracheal smooth muscle cells (Fleisch & Calking, 1976).

The gastric mucosa is rich in mast cells, and histamine is liberated from this cell type by acetylcholine (ACh) released from vagal nerves or by gastrin (Vizi *et al.*, 1973; Szurszewski, 1976; Stewart & Thomas, 1980). This endogenous histamine stimulates the release of gastric acid through activation of H_2-receptors (Black *et al.*, 1972; Hirschowitz, 1979), and also enhances gastric motility via H_1-receptor activation (Fujii *et al.*, 1981). H_1-receptors located at postganglionic autonomic nerve endings facilitate transmitter release, a process which can be inhibited via H_2-receptors (Hirschowitz, 1979).

There are regional differences in the electrical and mechanical properties of gastric smooth muscle cells. The antrum generates myogenic oscillatory potentials (slow waves) and phasic contractions, while the fundus is electrically and mechanically quiescent (Tomita, 1981). The electrical responses of stomach smooth muscle cells to intramural nerve stimulation are complex and cholinergic excitatory junction potentials (e.j.p.), adrenergic inhibitory junction potentials (i.j.p.), non-adrenergic, non-cholinergic e.j.ps and non-adrenergic, non-cholinergic i.j.ps have all been described (Holman, 1970; Kuriyama, 1970; Tomita, 1981). In the guinea-pig stomach, a cholinergic e.j.p. can be recorded in the fundus with a non-adrenergic, non-cholinergic i.j.p. both in the antrum and in the atropinized fundus (Komori & Suzuki, 1986).

In the present study we have investigated the effects of histamine on the smooth muscle cells and on neuromuscular transmission in the circular muscle of the guinea-pig stomach. Experiments were carried out by recording the electrical responses of smooth muscle cells with intracellular microelectrodes. The effects of histamine on neuromuscular transmission were

estimated from changes in the amplitude of junction potentials recorded from the smooth muscle cells.

Methods

Albino guinea-pigs of either sex, weighing 200–250 g, were stunned and bled. The stomach was isolated and cut in the longitudinal direction along the small curvature. The contents of the stomach and the mucosal layer were removed from the muscle layers under Krebs solution at room temperature. Strips of circular muscle (1.5 mm wide, 1.5–2.0 cm long) were isolated together with the longitudinal layer, and mounted in an experimental chamber with tiny pins. The chamber (volume about 2 ml) was made from Lucite plate, and the tissues were superfused with warmed (35°C) Krebs solution, at a flow rate of 2–3 ml min^{-1}.

Electrical responses of smooth muscle cells were recorded by means of glass capillary microelectrodes of tip resistance 40–80 MΩ and filled with 3 M KCl. Smooth muscle tissues were stimulated by the partition stimulating method (Abe & Tomita, 1968), to produce electrotonic potentials. To evoke junction potentials, field stimulation was applied transmurally via a pair of silver wires (0.5 mm diameter) placed on either side of the tissue. Electrical current pulses of 0.03–0.1 ms duration and 10–50 V intensity were applied through these wires, using an electric stimulator (Nihon Kohden SEN-7130). The electrical responses of smooth muscle cells were displayed on a pen-writing recorder (Nihon Kohden RJG4024).

The ionic composition of the Krebs solution was as follows (mM): Na^+ 137.4, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.5, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, Cl^- 134, glucose 11.5. The solution was gassed with 95% O_2, 5% CO_2, and the pH of the solution was maintained at 7.2–7.4.

Drugs used were atropine sulphate (Sigma), cimetidine (Fujisawa, Tokyo), histamine hydrochloride (Sigma) and mepyramine maleate (Sigma).

The experimental values obtained were expressed as means ± s.d.mean (n = number of observations). Statistical significance was tested by use of Student's t test, and probabilities less than 5% ($P < 0.05$) were considered significant.

Results

Effects of histamine on smooth muscle cells

Electrical responses of the smooth muscle cell membrane during application of histamine were recorded in the fundus and the antrum. As shown in Figure 1a, histamine (10^{-6} M) produced sustained depolarization of the membrane in smooth muscle cells of the fundus. In the antrum, histamine (5×10^{-6} M) increased the amplitude of slow waves with a slight depolarization of the membrane (1–3 mV, Figure 1b). Mepyramine (10^{-7} M) inhibited these excitatory actions of histamine in both regions.

Figure 2 shows the concentration-response relationship of the histamine-induced depolarization in the fundus and the antrum. The resting membrane potential of smooth muscle cells was higher in the antrum (65–70 mV, mean value -67.5 ± 1.9 mV, $n = 20$) than in the fundus (46–55 mV, mean value -51.2 ± 19, $n = 24$). In the fundus, histamine depolarized the membrane in concentrations above 10^{-6} M, while in the antrum higher concentrations of histamine (above 10^{-5} M) were required to depolarize the membrane.

Figure 2 also shows the inhibitory action of mepyramine (10^{-7} M) or cimetidine (10^{-7} M) on the depolarizing action of histamine. Mepyramine was more effective than cimetidine in inhibiting the histamine-induced depolarization. The resting membrane potential was not altered by mepyramine or cimetidine, in both the fundus and the antrum.

The amplitude of slow waves was increased by histamine (above 10^{-7} M), and these effects were inhibited by mepyramine (10^{-7} M) or cimetidine (10^{-7} M). The former showed stronger inhibitory effects than the latter, for the slow wave amplitude in the presence of 10^{-4} M histamine 1.94 ± 0.32 ($n = 10$) and this was reduced to 0.95 ± 0.15 ($n = 7$) and 1.26 ± 0.14 ($n \pm 7$) by mepyramine and cimetidine, respectively. A significant difference between the effects of these two antagonists was detected when histamine was used in concentrations of 10^{-5} M or greater (Figure 3).

The effects of histamine on the membrane conductances of smooth muscle cells were estimated from changes in the amplitude of electrotonic potentials produced by the partition stimulation method (Abe & Tomita, 1968). The electrical length constant of the smooth muscle tissues of the guinea-pig stomach is about 1.4 mm (Kuriyama *et al.*, 1970), therefore the electrotonic potentials were recorded in close proximity to the stimulating electrodes (less than 0.2 mm), to allow histamine-induced changes in membrane resistance to be estimated from changes in the amplitude of the electrotonic potentials (Hodgkin & Rushton, 1946).

Figure 4 shows the fluctuations of the electrotonic potential produced by alternate application of inward and outward current pulses before and during exposure to histamine (10^{-6} M) in the fundus and antrum. In the fundus, histamine depolarized the membrane and decreased the amplitude of electrotonic potentials to $85.0 \pm 3.1\%$ ($n = 6$) of the control, while in the antrum, histamine enhanced the amplitude of slow waves, with no detectable change in the membrane

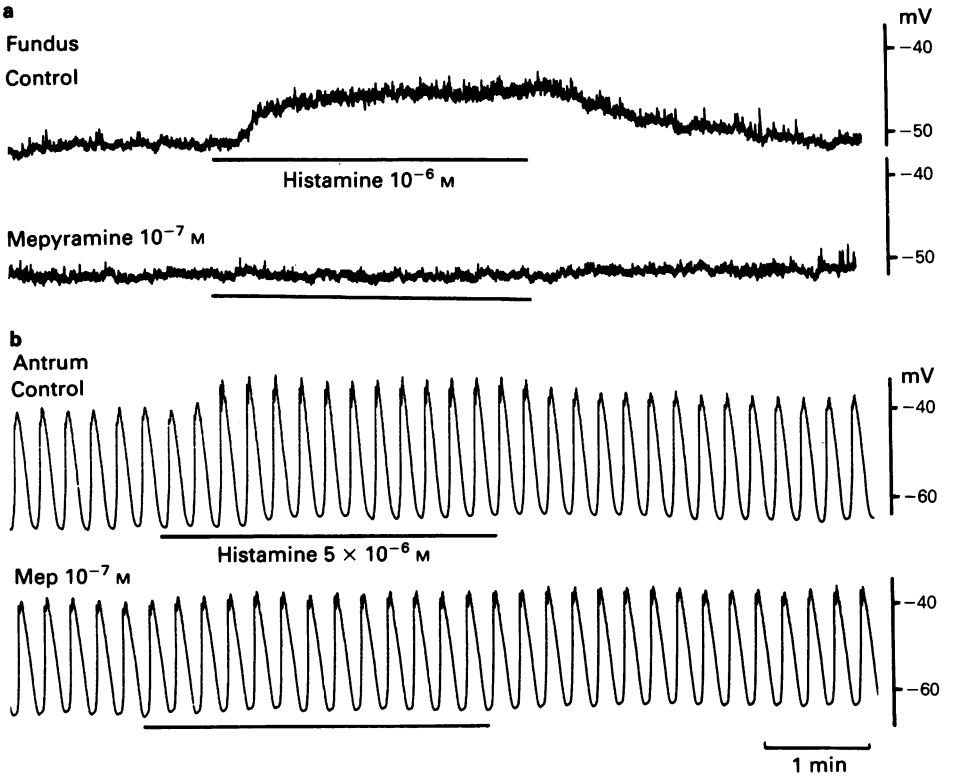

Figure 1 Electrical responses produced by histamine in the fundus (a) and the antrum (b). Histamine (a, 10^{-6} M; b, 5×10^{-6} M) was applied at a bar under each record, before (upper record) or after application of mepyramine (10^{-7} M, lower record). In both (a) and (b) the two recordings were taken from the same cell.

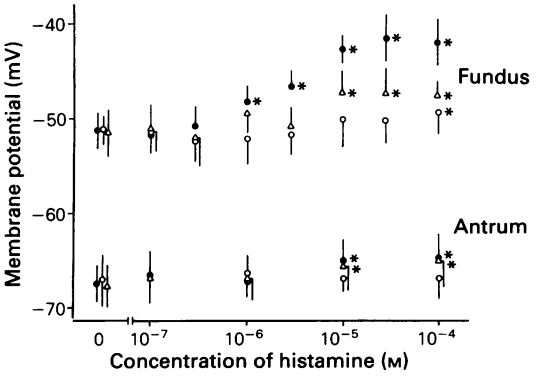

Figure 2 Histamine-induced depolarization of smooth muscle membrane of the fundus and the antrum; (●) control; (○) in the presence of 10^{-7} M mepyramine; (△) in the presence of 10^{-7} M cimetidine. Mean results are shown ($n = 8-25$); vertical lines show s.d.
* Significantly different from the membrane potential before application of histamine ($P < 0.05$).

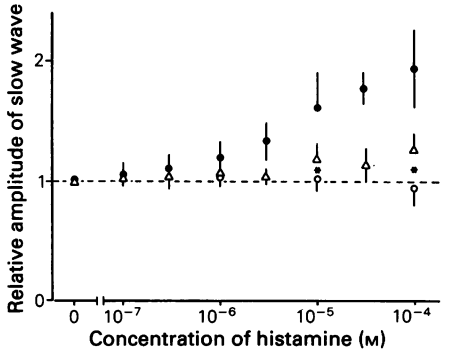

Figure 3 Effects of histamine on the amplitude of slow waves recorded in the antrum smooth muscle, in the absence (●, control) or presence of 10^{-7} M mepyramine (○) or 10^{-7} M cimetidine (△). Slow wave amplitude is expressed relative to that before application of histamine. Mean of $n = 7-10$; vertical lines show s.d. * Slow wave amplitude in the presence of mepyramine significantly different from that observed in the presence of cimetidine.

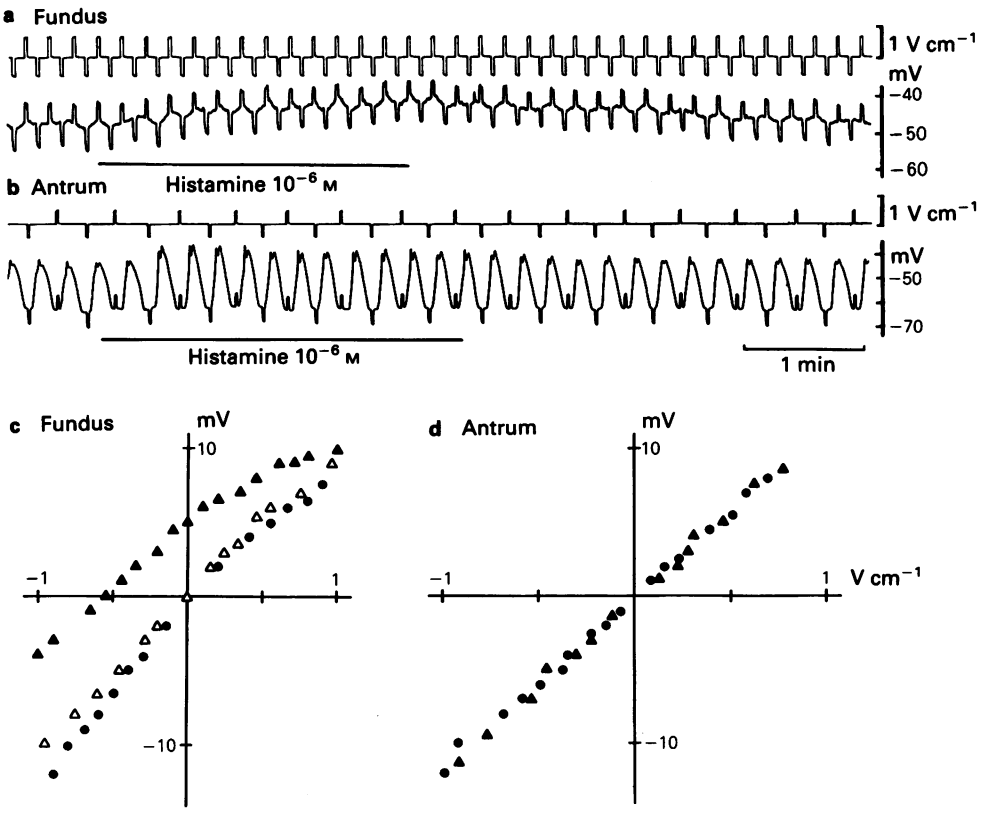

Figure 4 Effects of histamine on electrotonic potential measured by the partition stimulating method. Atropine (10^{-6} M) was present throughout. Electrotonic potentials produced by alternate application of inward and outward current pulses (a, 1.5 s; b, 1 s) were recorded from smooth muscle cells of the fundus (a) or the antrum (b), during application of 10^{-6} M histamine. Upper trace, current monitor in which intensity of current is expressed as V cm^{-1}; lower trace, membrane potential change. The current-voltage relationship obtained from the fundus (c) and the antrum (d), before (●, control) or after application of 10^{-6} M histamine (▲) or after the membrane was repolarized to the resting potential level by inward current in the presence of histamine (△). All points in (c) and (d) were obtained from different single cells.

potential and the electrotonic potential.

When the current-voltage relationships were compared before and during exposure to histamine, the slope of the relationship was shallower in the presence of histamine (in the fundus) or was not different (in the antrum) (Figure 4c and d). The less negative membrane potential observed in the presence of histamine was returned to the pre-histamine level by applying inward current to eliminate possible effects of depolarization on the electrotonic potential. When the current-voltage relationship was determined at this new membrane potential, this relationship was still shallower than in the absence of histamine (Figure 4c). In 6 experiments, the slope of the relationship was decreased to 86.0 ± 5.0% of the control by histamine, thus indicating that the histamine-induced depolarization was associated with a decrease in membrane resistance.

Effects of histamine on junction potentials

In the upper part of the stomach (fundus and corpus), field stimulation applied transmurally using brief current pulses (0.05–0.1 ms duration, 10–50 V intensity) evoked an excitatory junction potential (e.j.p.), while in the lower regions (antrum and pylorus), field stimulation evoked an inhibitory junction potential (i.j.p., Komori & Suzuki, 1986).

In the fundus, application of histamine (10^{-6} M) decreased the amplitude of the e.j.p. with associated

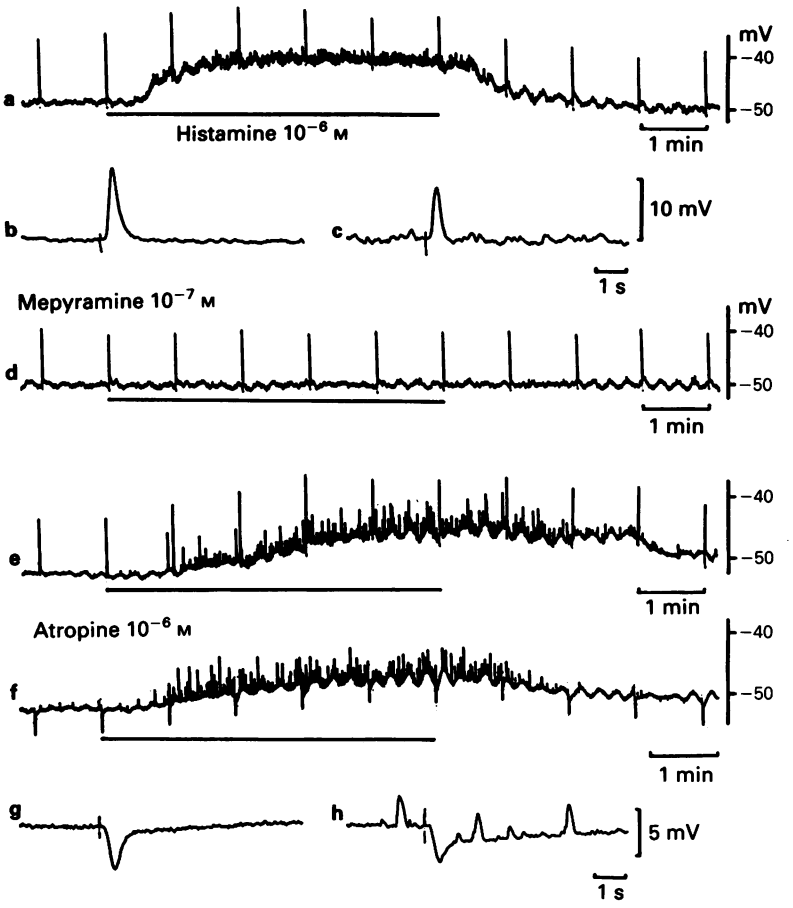

Figure 5 Effects of histamine (10^{-6} M) on the e.j.p. and the i.j.p. evoked in the fundus: (a–d) and (e–h) were recorded from single cells in different tissues. Histamine was applied before (a and e) and after application of 10^{-7} M mepyramine (d) or 10^{-6} M atropine (f). E.j.ps recorded before (b) and after application of histamine (c), and i.j.ps recorded before (g) and after application of histamine (h) are shown with faster time scale.

depolarization of the membrane (Figure 5a). In the presence of mepyramine (10^{-7} M), histamine did not change the membrane potential or the amplitude of the e.j.ps (Figure 5d).

During depolarization of the membrane by histamine, small fluctuations of the membrane potential (0.5 to up to 10 mV in amplitude, 0.1–10 Hz frequency) were often observed (about 30% of the tissues studied). Figure 5e and f shows a typical example of such fluctuations of the membrane potential, in which application of atropine (10^{-6} M) converted the e.j.p. to the i.j.p., with no detectable change in the fluctuating potentials. Thus, these small potential fluctuations may not result from the quantal release of ACh. In the presence of atropine, the amplitude of the i.j.p. was decreased during histamine-induced depolarization.

The concentration-response relationship of the effects of histamine on the e.j.p. and i.j.p. is shown in Figure 6. Histamine (above 10^{-7} M) inhibited the e.j.p. in a concentration-dependent manner, and this inhibition was antagonized by mepyramine (10^{-7} M) or cimetidine (10^{-7} M); mepyramine was more effective than cimetidine in inhibiting these actions of histamine (Figure 6a).

The effects of histamine on the i.j.ps evoked in the fundus were observed in the presence of atropine (10^{-6} M). Histamine (above 10^{-7} M) inhibited the i.j.p. in a concentration-dependent manner, and this histamine action was inhibited completely by

mepyramine (10^{-7} M) or partially by cimetidine (10^{-7} M) (Figure 6b).

Since the reversal potential of the e.j.p. is estimated to be about −18 mV (Komori & Suzuki, 1986), the histamine-induced inhibition of the e.j.p. may be overestimated due to the concomitant depolarization of the postjunctional membrane. Attempts were thus made to observe the e.j.p. in the presence of histamine, after the depolarized membrane had been displaced to the pre-histamine potential level by applying inward current. As shown in Figure 7, in the absence of histamine, the amplitude of the e.j.p. was 5.4 ± 0.8 mV ($n = 9$). Depolarization of the membrane by about 6 mV using an outward current pulse decreased the

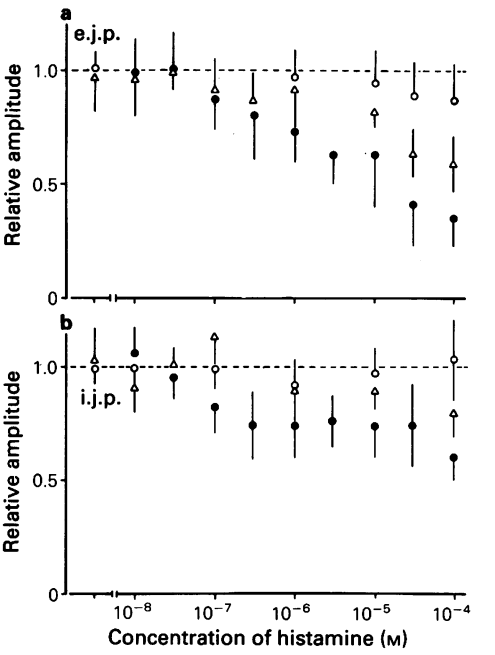

Figure 6 Concentration-response relationship of the effects of histamine on e.j.ps (a) and i.j.ps (b) evoked by single stimuli in the fundus. The amplitude of the e.j.p. or the i.j.p. evoked in the presence of histamine is expressed relative to that evoked before application of histamine: (●) control; (○) in the presence of 10^{-7} M mepyramine; (△) in the presence of 10^{-7} M cimetidine. Mean of $n = 3$–7; vertical lines show s.d.

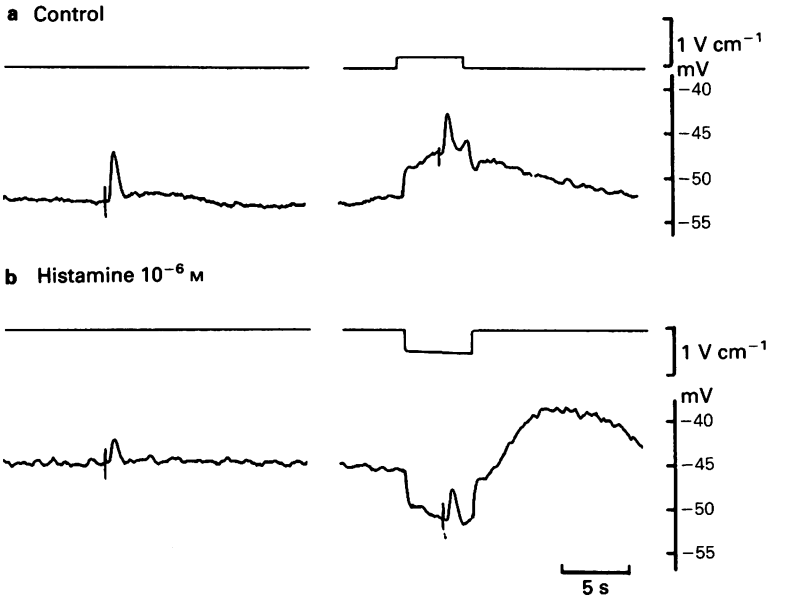

Figure 7 Effects of changing the membrane potential on the e.j.p. evoked by single stimuli (0.1 ms duration, 20 V intensity) in the fundus, before (a, control) and during exposure to 10^{-6} M histamine (b). In (a) the e.j.p. was evoked at the resting potential level (left) or in the depolarized condition produced by an outward current pulse (right) (pulse: 5 s duration). In (b), an e.j.p. was evoked at about 6 mV depolarization produced by 10^{-6} M histamine (left) or after the depolarized membrane was repolarized by about 6 mV with an inward current pulse (right). Note reduced e.j.p. amplitude during electrically-induced depolarization (a) and increased e.j.p. amplitude when histamine-induced depolarization is electrically offset (b).

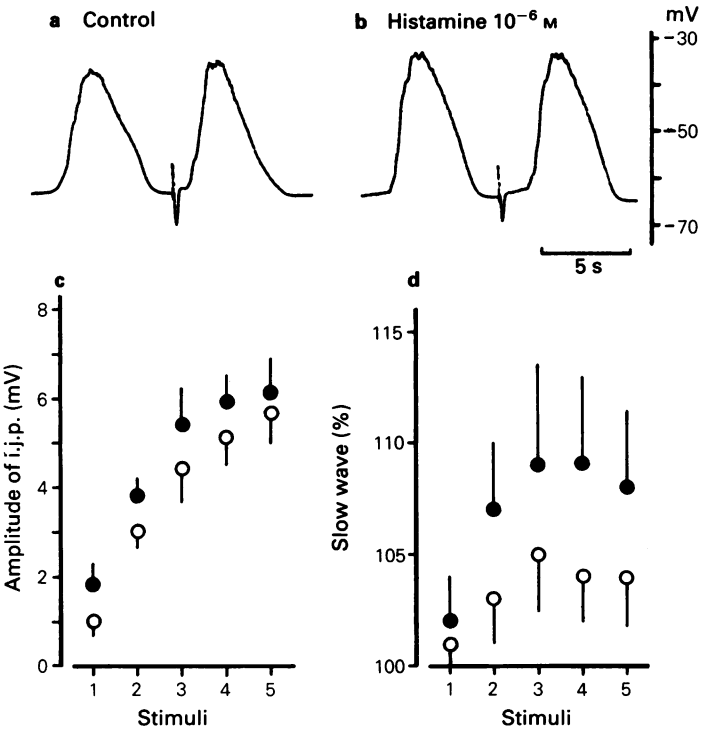

Figure 8 Effects of histamine on the i.j.p. and on the slow waves evoked by field stimulation in the antrum. (a) Control; (b) in the presence of 10^{-6} M histamine. Field stimulation (0.1 ms duration, 30 V intensity) was applied 3 times at 20 Hz frequency. The amplitude of i.j.ps (c) or slow waves evoked after the stimulation (d) is shown as a function of number of stimuli (1–5 at 20 Hz frequency). (●) Control; (○) in the presence of 10^{-6} M histamine. In (d) the amplitude of the slow wave generated after the field stimulation is expressed as a percentage of that before the stimulation. Mean ± s.d. ($n = 5-7$). All the responses were recorded from the same tissue.

amplitude of e.j.p. to 4.0 ± 0.5 mV ($n = 9$). With 10^{-6} M histamine, the membrane was depolarized by about 6 mV and the e.j.p. was decreased to 1.8 ± 0.5 mV ($n = 10$). In this condition repolarization of the membrane to the resting level by inward current pulse (5 s duration) increased the amplitude of e.j.p. to 2.5 ± 0.5 mV ($n = 7$). In 8 preparations, depolarization of the membrane by outward current pulse decreased the e.j.p. amplitude to 78.6 ± 8.1% of the control. Application of histamine (10^{-6} M) decreased the e.j.p. to 55.2 ± 9.9% of the control, and during displacement of the membrane to the resting potential level in the presence of histamine the e.j.p. amplitude was increased to 63.6 ± 9.5% of the control. Thus, depolarization of the postjunctional membrane was one of the factors responsible for the histamine-induced reduction in e.j.p. amplitude.

In the antrum, field stimulation evoked an i.j.p. and then enhanced the subsequently generated slow wave. With repetitive application of field stimulation, the i.j.p. and also the subsequent slow wave were enlarged (Ishikawa *et al.*, 1985). Application of 10^{-6} M histamine increased the amplitude of slow waves, but decreased the amplitude of i.j.ps and also the enhancement of the slow waves induced by field stimulation (Figure 8). These inhibitory effects of histamine on the junction potentials were also observed in the presence of atropine (10^{-6} M).

Discussion

The present experiments have demonstrated that in the guinea-pig stomach, histamine depolarizes the smooth muscle cell membrane and enhances slow wave amplitude. These events occurred in the presence or absence of atropine, indicating that they do not involve a cholinergic component. Such observations contrast with the effects of this amine on other regions in the digestive tract. In the isolated ileum of the

guinea-pig, histamine-induced contractions are inhibited by atropine, suggesting that histamine stimulates intramural cholinergic nerves and as a consequence indirectly contracts the smooth muscle (Harry, 1963). In the guinea-pig oesophagus, histamine produces contractions both by a direct action on the muscle and also indirectly through increased release of ACh (Fujinuma *et al.*, 1985).

We have also shown that in the presence of a histamine-induced depolarization, the amplitude of junction potentials was reduced. In the fundus, there is evidence that the excitatory junction potential (e.j.p.) may be generated by released ACh, with a calculated reversal potential of about −18 mV (Komori & Suzuki, 1986). After conditioned repolarization of the histamine-induced depolarization to the resting potential level, the amplitude of the e.j.p. was still smaller than the control, and this reduction of e.j.p. amplitude was significantly greater than that of the electrotonic potential. Thus, the histamine-induced reduction of e.j.p. amplitude may be due to both the depolarization of the postjunctional membrane and to a reduced release of ACh.

Histamine reduced the amplitude of the i.j.ps evoked in the antrum and also in the atropinized fundus; the latter but not the former effect was accompanied by depolarization of the smooth muscle cell membrane. The i.j.ps evoked in the antrum and in the atropinized fundus have the same property, i.e., they are non-adrenergic, non-cholinergic in nature, and their reversal potential is more negative than the resting membrane potential (−80 to −90 mV, Ito & Kuriyama, 1975; Komori & Suzuki, 1986). Therefore, the decrease in amplitude of the i.j.p. by histamine may be due to a reduction in the amount of transmitter released from the non-adrenergic, non-cholinergic nerves.

The results of the present study have therefore shown that the release of transmitter substances responsible for generating the e.j.p. or i.j.p. was inhibited by histamine. When the inhibitory effects on the e.j.p. were compared with those on the i.j.p., histamine inhibited the e.j.p. more than the i.j.p. (Figure 6). Due to depolarization of the postjunctional membrane, the actions of histamine on the e.j.p. may be over-estimated while those on the i.j.p. may be under-estimated.

There is general agreement that histamine mediates its effects via H_1- and H_2-receptors and that mepyramine and cimetidine, respectively, are selective antagonists of these receptors (Black *et al.*, 1972; Brimblecombe *et al.*, 1975; Hirschowitz, 1979). The distribution of these receptor subtypes is not homogeneous. For example, in the bovine and rat isolated stomach, histamine contracts or relaxes these tissues through activation of H_1- or H_2-receptors, respectively (Ercan & Türker, 1977; Ohga & Taneike, 1978). Histamine receptors responsible for contraction of the isolated guinea-pig oesophagus are mainly of the H_1-receptor type with H_2-receptors having a negligible role (Fujinuma *et al.*, 1985). In cardiovascular systems, histamine inhibits release of noradrenaline through activation of H_2-receptors located at nerve terminals (McGrath & Shepherd, 1976; Lokhandwala, 1978; Suzuki & Kou, 1983). Isolated vascular smooth muscles are depolarized and contracted by activation of H_1-receptors and are hyperpolarized and relaxed by H_2-receptor activation (Suzuki & Casteels, 1979; Casteels & Suzuki, 1980).

In the present study, the pre- and post-junctional actions of histamine were blocked by mepyramine. These results are similar to those obtained from the guinea-pig oesophagus (Fujinuma *et al.*, 1985). However in the guinea-pig stomach, the actions of histamine were also antagonized by cimetidine, although its effectiveness was less than that of mepyramine. Thus, it was impossible, from the actions of mepyramine and cimetidine to identify clearly the receptor involved. It remains to be determined whether there are histamine receptors other than the H_1 and H_2-subtypes in the guinea-pig stomach (i.e., an H_3-receptor, Fleisch & Calking, 1976; Eyre & Chand, 1979) or whether H_1- and H_2-receptors co-exist in this organ and mediate similar effects.

In the fundus, small fluctuations of the membrane potential were produced during depolarization by histamine. These fluctuations were resistant to atropine and therefore not due to quantal release of ACh from cholinergic nerves. Osa & Kuriyama (1970) reported that in the guinea-pig fundus, sustained depolarization of the membrane induced oscillations or action potential generation in smooth muscle cells which were quiescent at rest. Although the nature of this membrane potential fluctuation during histamine-induced depolarization is obscure, such oscillations may be a fundamental property of the fundus smooth muscle cell membrane.

The concentration of histamine required to depolarize the membrane was lower in the fundus than in the antrum. Similar observations have been made for ACh and these differences were interpreted by assuming a higher permeability to sodium ions in the fundus than in the antrum (Komori & Suzuki, 1986). The histamine-induced depolarization was associated with increase in ionic conductance of the smooth muscle membrane. This suggests the possible involvement of an increase in sodium or chloride permeability, because in the gastro-intestinal tract the equilibrium potential for these two ions is more positive than the resting membrane potential (Casteels, 1970). These differences in the ability of histamine to depolarize the membrane may not be due to differences in receptor sensitivity because in the antrum, 10^{-6} M histamine was sufficient to enhance

the amplitude of slow waves.

It is concluded that in the guinea-pig stomach, histamine produces excitatory effects on smooth muscle cells, typified by a depolarization of the membrane (fundus) or by an increase in slow wave amplitude (antrum). Furthermore, this amine also exerts inhibitory actions and these may be associated with decreased release of transmitter substances from the cholinergic and the non-adrenergic, non-cholinergic nerves. These actions of histamine are mediated by receptors sensitive to both mepyramine and cimetidine.

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