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Comparison of the Effects of Histamine and N^{α}-Methylhistamine on Neuronal Function in the Guinea-pig Oesophagus and Ileum

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Abstract

The effects of histamine and N^{α}-methylhistamine, two components of gastric juice, on vagal and transmural stimulation of the guinea-pig isolated oesophagus were compared with their effects on cholinergic and on non-adrenergic-non-cholinergic (NANC) neuronal responses in the isolated ileum, both tissues having been pretreated with mepyramine (1 μM).

Histamine ($\leq$10 μM) and N^{α}-methylhistamine ($\leq$1 μM) had no significant effect on either vagal or transmural stimulation in the oesophagus. Substance P, which produces a contraction by activation of cholinergic nerves in the oesophagus also was unaffected by histamine. In contrast, the agonists inhibited contractions produced by cholinergic nerve stimulation in the ileum; the inhibition produced by histamine (10 μM) was up to 73 $\pm$ 5%, that by N^{α}-methylhistamine (1 μM), 48 $\pm$ 5%. Histamine also inhibited responses to stimulation of NANC neurons by up to 37 $\pm$ 14%. The effects of histamine and N^{α}-methylhistamine in the ileum were inhibited by clobenpropit (0·1 μM).

These findings suggest that histamine and N^{α}-methylhistamine have no role in the modulation of neuronal function in the oesophagus, in contrast with their effect in the ileum.

Activation of histamine H_3 receptors has been shown to inhibit nerve transmission via cholinergic and non-adrenergic-non cholinergic (NANC) neurons in the gastrointestinal tract (Trzeciakowski 1987; Coruzzi et al 1991; Poli et al 1991; Taylor & Kilpatrick 1992; Vollinga et al 1992) and respiratory system (Ichinose et al 1989; Ichinose & Barnes 1989a) and from sensory nerves in various tissues (Ichinose & Barnes 1989b; Ohkubo et al 1995). Histamine is known to be more potent at H_3 receptors than at either H_1 or H_2 receptors and the histamine metabolite, N^{α}-methylhistamine is even more selective and potent at the H_3 receptor (Leurs et al 1991, 1995). As both agonists are present in gastric juice, which can reflux into the oesophagus, a study was undertaken to compare the effects of the two compounds on excitatory neuronal responses in the guinea-pig oesophagus with their effects on cholinergic and NANC neurons in the guinea-pig ileum, a tissue often used for investigating putative agonists and antagonists at H_3 receptors (Leurs et al 1991; Taylor & Kilpatrick 1992; Rizzo et al 1995).

Vagal and transmural stimulation of the oesophagus have been shown to induce a triphasic response (Kerr et al 1995). The initial contraction was shown to involve striated muscle, because it was inhibited by low concentrations of tubocurarine. The second phase was a result of contraction of smooth muscle and was inhibited by atropine. The response to vagal stimulation was also inhibited by hexamethonium and other ganglion-blocking drugs; transmural stimulation involved post-ganglionic neurons, as this phase of the response was resistant to ganglionic blockade. The third phase of the response involved retrograde activation of sensory neurons with subsequent activation of post-ganglionic cholinergic neurons because both vagal and transmural stimulation gave a response that was abolished by pre-treatment with capsaicin, ω-conotoxin GVIA or atropine and was enhanced by thiorphan or physostigmine. Thus, in the oesophagus it was possible to examine the effect of histamine on responses produced by cholinergic nerves innervating both striated and smooth muscle, and those produced by sensory neurons.

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Materials and Methods

All tissues were placed in modified Krebs-Henseleit solution of composition (g L^{-1}): NaCl 6·8, KCl 0·4, $MgSO_4 \cdot 7H_2O$ 0·14, $CaCl_2$ 0·28 $NaH_2PO_4 \cdot 2H_2O$ 0·18, $NaHCO_3$ 2·1, glucose 2·0; the solution was oxygenated with 95% O_2–5% CO_2 and maintained at 37°C in a 20-mL organ bath. To inhibit the stimulation of histamine H_1 receptors, mepyramine (1 μM) was present in all experiments.

Oesophagus

A 3-cm length of oesophagus, opened out by cutting longitudinally, was prepared as described by Kerr et al (1995). The oesophagus was stimulated via vagal or transmural stimulation at 20 Hz, 0·5-ms pulse-duration at 70 V for 1 s at 1-min intervals. Vagal stimulation was elicited by threading both vagus nerves through a bipolar ring electrode positioned about 0·5 cm from the oesophagus in the organ bath to avoid direct stimulation; transmural stimulation was elicited via a pair of platinum electrodes located on the tissue holder.

In agreement with the findings of Kerr et al (1995) the response to vagal or transmural stimulation was abolished by tetrodotoxin (1 μM). The first phase of the response to vagal

stimulation was also inhibited by tubocurarine (30 μM), the second by hexamethonium (100 μM) and both the second and third by atropine (1 μM). In some experiments, tubocurarine (30 μM) was present to eliminate the first response thus enabling better study of the effect of histaminic agonists on the second and third responses.

Ileum

A 3-cm length of ileum was set up on a tissue holder under 2 g weight tension for transmural electrical stimulation by a pair of platinum electrodes, one electrode being positioned in the lumen, the other outside the tissue. For comparison with the oesophagus the ileum was stimulated in two ways, to activate either cholinergic or NANC nerves. Cholinergic nerves were activated by transmural stimulation with single pulses – 0·1 ms pulse duration at 5–10 V every minute (Menkveld & Timmerman 1990). To activate NANC neurons, transmural stimulation was performed at 40 Hz, 0·1 ms duration at 70 V for 1 s every minute. Such stimulation has been shown to produce a biphasic response; the initial phase involved direct stimulation of smooth muscle, because it was resistant to tetrodotoxin, whereas the second phase involved NANC nerves because it was unaffected by atropine and was inhibited by a tachykinin NK_1 receptor antagonist (Taylor & Kilpatrick 1992).

The agonists histamine, N^{α}-methylhistamine, substance P and acetylcholine were added for 2 min. Tissues were initially incubated with antagonists for 30 min before re-testing agonists.

Data evaluation

Data are expressed as means ± s.e.m. The EC50 values, concentrations producing 50% of the inhibitory response elicited by the highest concentration of histamine and its analogue on excitatory responses, were estimated by interpolation from plots of the mean data using the computer program Prism 2·0 (GraphPad Software, San Diego, CA).

Student's *t*-test was used for comparison of means; the criterion for statistical significance was set at $P < 0.05$.

Drugs

The drugs used were acetylcholine chloride, histamine hydrochloride and propranolol hydrochloride (Sigma, Poole, UK), atropine sulphate and tubocurarine hydrochloride (Sigma, St Louis, MO), clobenpropit dihydrobromide and N^{α}-methylhistamine (Tocris Cookson, Bristol, UK), mepyramine maleate (May & Baker, Dagenham, UK), prazosin hydrochloride (Pfizer, UK), SR 140333 (gift from Drs Brelière & Edmonds-Alt, Sanofi Recherche, Montpellier, France), substance P (Auspep, Melbourne, Australia) and tetrodotoxin (ICN, Seven Hills, Australia). Tubocurarine and SR 140333 were dissolved in alcohol before dilution to the final concentration with physiological saline. The volume of solvent used constituted less than 0·06% of the final bath concentration. All other drugs were dissolved in saline.

FIG. 1. Response of the guinea-pig oesophagus to vagal nerve stimulation at 20 Hz, 0·5 ms duration at 70 V for 1 s. Duration of stimulation (–). Scale marker: tension 1 g weight. Time marker: 5 s.

Results

Experiments in the oesophagus

Effect of stimulation. Vagal nerve or transmural stimulation of the guinea-pig oesophagus resulted in a triphasic response (Fig. 1), which was abolished by tetrodotoxin (1 μM, n = 3), in agreement with the findings of Kerr et al (1995).

Effect of histamine. The first phase of the response to vagal nerve stimulation was unaffected by histamine (1 to 30 μM). The second and third phases of the contractile response to vagal nerve stimulation (n = 3) were slightly inhibited by high concentrations (> 10 μM) of histamine and the effect of histamine was reduced by clobenpropit (0·1 μM) as shown in Fig. 2.

Histamine (1 to 30 μM) had no significant effect ($P > 0.05$) on any of the three phases of the contractile responses to transmural electrical stimulation (n = 3), as is shown in Fig. 3.

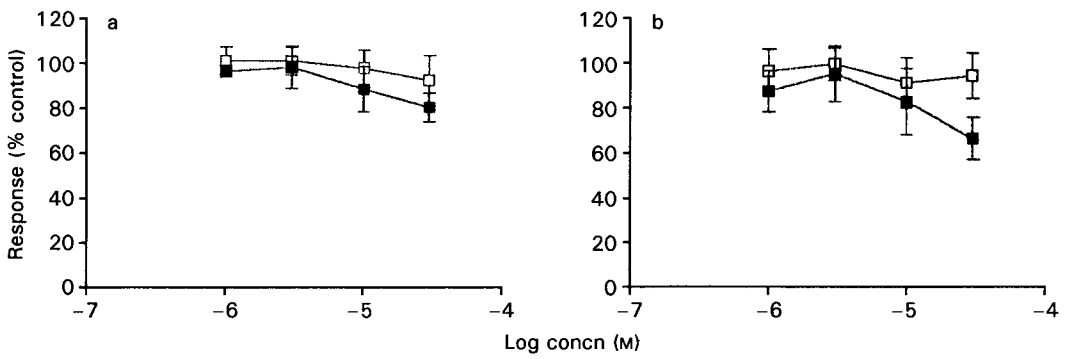

FIG. 2. Concentration–response curve for the effect of histamine on (a) the second phase of vagal nerve stimulation of the oesophagus in the absence (■) and presence (□) of clobenpropit (0·1 μM) and (b) the third phase of vagal nerve stimulation in the absence (■) and presence (□) of clobenpropit (0·1 μM), at 20 Hz, 0·5 ms duration, at 70 V. Abscissa, log molar concentration of histamine; ordinate, percentage of control contractile response to stimulation. Each point is the mean of results from three experiments, with the vertical lines indicating the s.e.m.

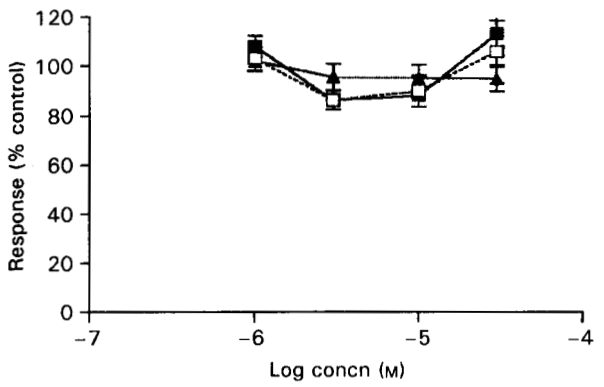

FIG. 3. Concentration–response curve for the effect of histamine on the first (▲) second (□) and third (■) phases of transmural electrical stimulation of the oesophagus. Abscissa, log molar concentration of histamine; ordinate, percentage of control contractile response to stimulation. Each point is the mean of results from three experiments, with the vertical lines indicating the s.e.m.

Effect of N^{α}-methylhistamine. N^{α}-methylhistamine (0·01 to 1 μM) had no effect on the second or third phases of the contractile response to vagal nerve or transmural stimulation (n = 8). The effect of the agonist on the first phase was not investigated as tubocurarine (30 μM) was present in this series of experiments (see Materials and Methods).

Effect of histamine on exogenous substance P. The contraction induced by substance P (1 μM) was mediated indirectly via the release of acetylcholine, because it was abolished by atropine (1 μM, n = 6). Histamine (10 or 100 μM) had no significant effect ($P > 0.05$) on contractions produced by exogenous substance P (1 μM). In four experiments with substance P and histamine 100 μM the control response to substance P alone was 14·3 ± 3·4 g weight tension and in the presence of histamine the response to the tachykinin was 14·0 ± 3·9 g weight tension.

Experiments in the ileum

Effect of stimulation with single and trains of pulses. Contractions elicited by stimulation with single pulses were abolished by the addition of atropine (1 μM, n = 3), indicating cholinergic nerves were being stimulated.

In agreement with Taylor & Kilpatrick (1992), stimulation of the ileum with trains of pulses resulted in a biphasic contractile response, the second phase of which was abolished by tetrodotoxin (1 μM). The NK_1 receptor antagonist, SR 140333 (0·1 μM), caused a significant decrease ($P < 0.05$, paired *t*-test) of 59 ± 2·0% (mean ± s.e.m., n = 3) in the response, whereas in the presence of atropine (1 μM), propranolol (0·3 μM) and prazosin (1 μM) there was a non-significant ($P > 0.05$) increase in the amplitude of the phase to 151 ± 33% of the control response (n = 6). Overall, these findings indicated that the second phase of the response to stimulation with trains of pulses was mediated by activation of NANC nerves.

Cholinergic nerve stimulation of the ileum

Effect of agonists in the absence and presence of clobenpropit. Histamine (0·1 to 10 μM) or N^{α}-methylhistamine (0·01 to 1 μM) caused concentration-dependent inhibition of the contractile response to electrical stimulation (Table 1).

Addition of the H_3 receptor antagonist, clobenpropit (0·1 μM) resulted in an initial, non-significant increase (122 ± 13%, n = 4) in the response to electrical stimulation ($P > 0.05$, paired *t*-test). Clobenpropit (0·1 μM) reduced the maximum inhibition of cholinergic nerve stimulation produced by either histamine (10 μM) or N^{α}-methylhistamine (1 μM) and increased the EC50 values of the agonists (Table 1) without significantly ($P > 0.05$) affecting the contractile response produced by exogenous acetylcholine (0·2 or 200 μM).

NANC nerve stimulation

Effect of histamine in the absence and presence of clobenpropit. Histamine (0·1 to 10 μM) inhibited the NANC phase of the contractile response to electrical stimulation with trains of pulses (Table 1).

Clobenpropit (0·1 μM), caused an initial, significant ($P < 0.05$, paired *t*-test) increase in the response to electrical stimulation (373 ± 85%, n = 8) and reduced the maximum inhibition of NANC-nerve stimulation produced by exogenous histamine (10 μM) as well as increasing the EC50 value of the agonist (Table 1).

Discussion

In this study the ability of histamine H_3 receptors to inhibit cholinergic and sensory nerve-mediated contractions in the oesophagus was compared with findings in the ileum, where H_3 receptor activation is known to cause inhibition of both cholinergic (Fjalland & Lundbeck 1979; Trzeciakowski 1987) and NANC nerve-mediated contractions (Menkveld & Timmerman 1990; Taylor & Kilpatrick 1992).

The need to compare the effect of H_3 receptor activation in the two tissues prompted the use of whole ileal segments,

Table 1. The EC50 values for the agonists and percentage inhibition produced by histamine (10 μM) and N^{α}-methylhistamine (1 μM), on cholinergic and NANC nerve-mediated responses of the ileum, in the absence and presence of clobenpropit (0·1 μM).

	Cholinergic			Non-cholinergic, non-adrenergic		
Treatment	EC50 (μM)	Inhibition (%)*	n	EC50 (μM)	Inhibition (%)*	n
Histamine	0·35	73 ± 5	3	0·15	37 ± 14	6
+ clobenpropit	5·0	43 ± 8	3	4·0	24 ± 12	6
N^{α}-methylhistamine	0·03	48 ± 5	4	–†	–	–
+ clobenpropit	> 1	6 ± 5	2	–	–	–

*EC50 values for the agonists in the presence of clobenpropit (0·1 μM) are measured at the percentage corresponding to 50% of the maximum inhibition produced by histamine (10 μM) or N^{α}-methylhistamine (1 μM), respectively, on responses to electrical stimulation, in the presence of mepyramine (1 μM). Percentage inhibition represents mean ± s.e.m. of results from n separate experiments. †Not tested.

despite previous studies which have shown that ileal longitudinal muscle with myenteric plexus produced a more regular contraction and resulted in larger H_3 receptor-mediated inhibition than strips of whole ileum, and that ileum strips were also unsuitable for observation of H_3 receptor-mediated inhibition of the NANC nerve-induced contractile response (Menkveld & Timmerman 1990).

In the ileum histamine was found to inhibit cholinergic nerve-mediated contractions without affecting responses to exogenous acetylcholine, indicating that the inhibition was caused by reduction of acetylcholine release from cholinergic nerves and not physiological antagonism. The amount of inhibition induced by the other H_3 receptor agonist investigated, N^{α}-methylhistamine, was similar to that induced by histamine, but this agonist was about ten times more potent.

Stimulation of the ileum with trains of pulses produced a biphasic contractile response; the first phase was a mixed response involving direct smooth muscle activation and nerve stimulation whereas the second phase was mediated by NANC nerves, because it was abolished by tetrodotoxin but unaffected by the combination of atropine, prazosin and propranolol. The second phase was also inhibited by the NK_1 receptor antagonist SR 140333, supporting the findings of Taylor & Kilpatrick (1992) that the NANC response was inhibited by NK_1 receptor antagonists. Histamine was found to inhibit the NANC-mediated contraction to electrical stimulation with an EC50 value of 0·15 μM. This fell within the range of EC50 values (0·05–0·69 μM) previously obtained on the longitudinal muscle of the ileum, containing myenteric plexus (Menkveld & Timmerman 1990; Taylor & Kilpatrick 1992). The effects of histamine and N^{α}-methylhistamine on contractions of the guinea-pig ileum evoked by electrical stimulation were mediated by histamine H_3 receptors because they were inhibited by the selective antagonist clobenpropit.

Alone, clobenpropit increased the amplitude of the response to both cholinergic and NANC nerve stimulation, although only the increased amplitude of the response to NANC nerve stimulation was significant. Poli et al (1991) also found that the H_3 receptor antagonists thioperamide and impromidine enhanced electrically-evoked acetylcholine release in the guinea-pig ileum consistent with the suggestion that histamine is released, possibly from mast cells, during electrical stimulation (Sacchi et al 1986).

In contrast with the findings in the ileum, histamine and N^{α}-methylhistamine had no effect on transmural and vagal nerve stimulation in the oesophagus. Histamine is present in gastric juice at concentrations of 2–150 ng mL^{-1} ($\cong$0·02–1·6 μM) (Emmelin & Kahlson 1944; Ivy & Bachrach 1966; Parkin et al 1982) and can enter the oesophagus during gastro-oesophageal reflux, a condition involving the back-flow of stomach contents into the oesophagus. The presence of high concentrations of histamine metabolites is also possible, because the mono- and dimethylated metabolites of histamine have been reported in the gastric juice and tissues of several species, which has led to the suggestion that metabolites of histamine might also function as endogenous ligands of H_3 receptors (Trzeciakowski 1987). It is therefore possible that histamine and N^{α}-methylhistamine could have a role in modulating nerve function in the oesophagus similar to that observed in the ileum. However, a concentration–response curve to histamine or to N^{α}-methylhistamine on electrical stimulation at 20 Hz (the frequency determined to be optimum for the visualization of the third phase) failed to show a significant effect on the second and third phases produced by transmural stimulation and failed to reveal evidence of prejunctional H_3 receptors on NANC endings. This was further supported by investigations involving exogenous substance P, which is thought to release acetylcholine from cholinergic nerves by activation of intramural ganglion cells, because its effect can be abolished by tetrodotoxin or by atropine (Kerr et al 1995). Thus activation by histamine of H_3 receptors on post-ganglionic cholinergic nerve endings would be expected to result in a decrease in substance P-mediated contractions.

The presence of high concentrations of histamine resulted in a small decrease in the second and third phases produced by vagal nerve stimulation, although this was not statistically significant. The inhibitory effect of histamine was more pronounced in the third phase than with the second, suggesting the possibility of H_3 receptors on the axon collateral of the sensory nerve, rather than the pre-ganglionic cholinergic nerve. This might be similar to the situation in the airways of the guinea-pig and man, where H_3 receptors have been suggested to modulate cholinergic neurotransmission in the vagus nerve by acting on pre-ganglionic nerve endings in parasympathetic ganglia and on post-ganglionic nerve endings (Ichinose & Barnes 1989a, b).

The concentration of histamine required to have an effect on vagal stimulation in the oesophagus was about twenty times the EC50 value of histamine which inhibited excitatory responses in the ileum. This suggested the possibility that histamine could not penetrate into the oesophageal tissue as readily as into the ileum. Preliminary experiments performed with hist- amine acting at H_1 receptors, in the absence of mepyramine, showed that the agonist could contract the oesophagus only at concentrations ranging from 30 to 100 μM.

The findings of this study suggest that although H_3 receptors might play a modulating role in excitatory neurotransmission in the intestine, there was no evidence to support the existence of functional H_3 receptors in the oesophagus. This might in fact be beneficial in the maintenance of oesophageal motility and in the propulsion of refluxed gastric juice back to the stomach.

Gastric juice comprises many components, including pepsin, acid and histamine. Gastric acid, which is part of the refluxed contents and has a major role in oesophageal mucosal injury (Vaezi et al 1995), can lead to pain because of its ability to release tachykinins from sensory nerves via stimulation of capsaicin receptors (Geppetti et al 1991; Satoh et al 1993). Any decrease in the release of tachykinins as a result of the activation of the H_3 receptor would mask the symptoms of gastro-oesophageal reflux, which could lead to further complications. Furthermore, activation of H_3 receptors on cholinergic nerves would cause a decrease in oesophageal motility, which would result in an increased contact time between the refluxed contents and the oesophagus. This situation would be detrimental, as it is important that refluxed material be evacuated as quickly as possible to avoid tissue damage (Galmiche & Janssens 1995).

In conclusion, the findings of this study suggest that activation of neuronal H_3 receptors by histamine and N^{α}-methylhistamine is unlikely in the oesophagus during reflux, given the concentrations of histamine and its metabolites known to occur in gastric juice. This might be contrasted with the ileum, where activation of the receptor might modulate both cholinergic and NANC neurotransmission.

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