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Some studies of the action of betahistine at H1 and H2 receptors for histamine

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Abstract

Betahistine produced a concentration-dependent contraction of the guinea-pig ileum and was about 27 times less active than histamine in this respect. Betahistine induced desensitization of contractile responses to histamine in the guinea-pig ileum. The H1 histamine receptor antagonist mepyramine was a competitive antagonist of the action of betahistine on the guinea-pig ileum.

Betahistine caused relaxation of the rat uterus contracted by acetylcholine, and this action of betahistine was blocked by the H2 receptor antagonist cimetidine. Betahistine had a concentration-dependent positive chronotropic action on isolated guinea-pig atria, and in this respect was tenfold less potent than histamine. The action of betahistine on the atria was blocked by the H2 receptor antagonist YM11170. Betahistine caused a concentration-related contraction of the isolated lung parenchymal strip of the guinea-pig, and YM11170 potentiated this effect.

Betahistine failed to release histamine from rat peritoneal mast cells at concentrations up to 100 μM and it did not prevent histamine release induced by either substance P or anti-IgE.

Betahistine produced a dose-related flare and wheal reaction when injected intradermally into human skin.

It is concluded that betahistine has agonist activity at both H1 and H2 receptors for histamine.

Introduction

There is evidence that betahistine (2-[2′-methyl amino ethyl pyridine]) is of value in the treatment of Meniere's disease [1]. Meniere's disease is a triad of symptoms including vertigo, deafness and tinnitus which presents with recurrent attacks. It has been suggested that a pathological basis of Meniere's disease is sclerosis of capillary networks in the stria vascularis. The rationale for treating this condition with betahistine is the production of vasodilatation and increased circulation in the stria vascularis. MARTINEZ [2] has studied the effect of betahistine on the circulation of the inner ear and reported that it increases blood flow. Similar findings have been made by SUGA & SNOW [3]. In another study [4], betahistine was found to increase blood flow in the basilar artery of dogs, and it has largely been assumed that the vasodilator action of betahistine is mediated through histamine receptors in the smooth muscle of the vascular wall. However, most studies with betahistine have preceded the discovery of H2 receptor antagonists and so it is not clear whether its vasodilator action may be mediated through H1 or H2 receptors. Histamine itself causes vasodilatation in the external and internal carotid vasculature of monkeys [5] and, in man, it has been shown that temporal arteries are dilated by an H2 receptor-mediated action of histamine [6]. The evidence cited above that betahistine causes vasodilatation in cerebral vasculature raises the question as to whether this is an H2 receptor action.

Curwain, Holton & Spencer [7] have shown that betahistine stimulates gastric acid secretion in dogs. Histamine stimulation of acid secretion is an H2 histamine receptor effect, and so we have studied the action of betahistine in a number of experimental models to determine the extent of its action at H2 histamine receptors.

Methods

Rat Uterus

Virgin Sprague Dawley rats weighing 125–190 g were primed approximately 12 hours prior to the experiment by injection of stilboestrol 0.1 mg/kg s.c. At the time of the experiment the rat was killed by stunning and section of the carotid arteries. The abdominal cavity was opened by a midline incision and the two horns of the uterus were dissected free. One horn was suspended in a 5 ml organ bath and maintained at 35°C in DeJalon solution gassed with 95% oxygen, 5% carbon dioxide. The preparation was allowed to rest for approximately 20 minutes before the commencement of the experiment. Contractions of the uterus were recorded isotonically by a photo-electric transducer connected to a

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Servoscribe pen recorder. A tension of 0.5 g wt was applied to the tissue. The cycle time for the application of agonists to the uterus consisted of 45 sec of contact with the agonist, followed by 2 washes with DeJalon solution taking 2.5 min and then a rest of 2 min before the next addition of agonist.

Guinea-pig ileum

Male Hartley guinea-pigs weighing 300–500 g were killed by stunning and exsanguination. The abdominal cavity was opened by a midline incision and the terminal ileum dissected out and washed through with Tyrode solution. A section of approximately 1–2 cm was mounted in an organ bath containing Tyrode solution at 37°C, gassed with oxygen 95%, carbon dioxide 5%. The tissue was allowed to rest for approximately 1 hour with repeated washing in Tyrode solution before the experimental protocol was commenced. The tension placed on the tissue was 0.5 g wt. Contractions of the ileum were recorded isotonically using a photo-electric transducer connected to a potentiometric chart recorder.

Guinea-pig artria

Male Hartley guinea-pigs weighing 200–300 g were killed by stunning and exsanguination. The thoracic cavity was opened and the heart and lungs were dissected free. An isolated atrial preparation was prepared as previously described [8]. The tissue was bathed in McEwan solution gassed with 95% oxygen, 5% carbon dioxide. Contractions were recorded isometrically, and the average atrial rate was recorded on a ratemeter.

Histamine release

The effects of betahistine on histamine release were determined using a preparation of rat peritoneal mast cells prepared as described previously [9]. Sprague Dawley rats weighing between 150 and 250 g were used for these experiments. The rats were killed by cervical dislocation following anaesthesia with nitrous oxide, and the peritoneal cavity washed out with 5 mls of heparinised saline (heparin 25 U/ml; NaCl 154 mM) through a midline incision in order to obtain peritoneal cells for the experiment. Histamine release from the cells in response to various agents including betahistine were expressed as a percentage of the total histamine content of the cells. For these experiments, peritoneal cells were incubated in HEPES-Tyrode solution.

Human skin

Betahistine was compared with histamine for its ability to produce wheal and flare reactions in human skin by the method described previously [10]. Histamine or betahistine was injected intradermally into the volar surface of the human forearm of healthy adult volunteers. The volume of injection was 25 μl and the flare response was measured 3 min after injection and the wheal response 12 min after injection: these being the times at which the respective responses reached maximum. Volunteers for this experiment were taking no medication at the time of, or in the two weeks prior to, the experiments.

Guinea-pig parenchymal lung strip

Male Hartley guinea-pigs weighing 200–300 g were killed by stunning and exsanguination. The thoracic cavity was opened by a midline incision and the heart and lungs dissected free and placed in Tyrode solution. Strips of parenchymal tissue were cut from the periphery of the lungs. The size of the strips was approximately 1–1.5 cm in length and 3–4 mm in width. The strips were mounted in a 2 ml organ bath containing Tyrode solution maintained at 37°C and gassed with oxygen 95% and carbon dioxide 5%. Contractions of the tissue were recorded isotonically using a photo-electric transducer. The tension placed on the tissue was approximately 0.5 g.wt. The tissue was allowed to rest for approximately 1 hour before the experimental protocol commenced and during this time the bathing fluid was changed every 10 min.

Materials

The sources of materials used in this study were as follows:

Cimetidine – Smith, Kline & French Research Ltd, U.K.; 3-[[[2-[diaminomethylene)-amino]-4-thiazolyl] methyl]thio]-N2-sulfamoyl-propionamidine (YM11170)-Hoechst (UK) Ltd; Betahistine – Duphar Laboratories Ltd, U.K.; substance P – Peninsula Laboratories Europe; goat anti (rat IgE) – Miles Laboratories Ltd, U.K.; histamine acid phosphate and acethylcholine iodide, B.D.H. England; mepyramine – May & Baker Ltd, U.K.; stilboestrol – WB Pharmaceuticals, U.K.

All other chemicals and reagents were of 'Analar' or equivalent quality.

Results

Rat uterus

Neither histamine nor betahistine at concentrations up to 10 μM produced any contraction of this preparation. To examine the possible smooth muscle relaxing effect of histamine and betahistine the uterus was contracted with acetylcholine. Concentration-dependent contraction of the uterus to acetylcholine was obtained in the concentration range 0.5–5 μM. Figure 1 shows that histamine produced a dose-dependent inhibition of the contraction of the rat uterus induced by acetylcholine, 2 μM, and Figure 2 shows the effect of histamine and betahistine at fixed concentrations of 1 and 10 μM respectively on the acetylcholine dose-response curve on the uterus. Both histamine and betahistine produced small but significant rightward shifts of the acetylcholine dose-response curve on the rat uterus. The antagonism by betahistine of the contraction of the uterus induced by acetylcholine could be reversed by the H2 histamine receptor antagonist cimetidine (Figure 3).

Guinea-pig ileum

Both histamine and betahistine produced concentration-dependent contractions of the guinea-pig ileum (Figure 4). The EC_{50} for histamine was found to 0.1 μM and that for betahistine 2.7 μM. Histamine is, therefore, 27 times more potent than betahistine in producing 50% of the maximum contraction of the guinea-pig ileum.

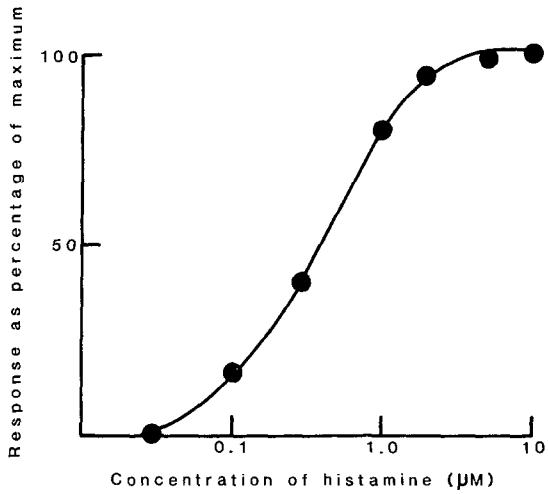

Figure 1
Concentration-response curve for histamine-induced relaxation of the isolated rat uterus. The uterus was caused to contract with acetylcholine, 2 μM, and histamine, at the concentrations indicated, was added to produce relaxation of the acetylcholine-induced contraction. The relaxation induced by each concentration of histamine has been expressed as a percentage of the maximum relaxation of the contracted uterus that could be obtained with histamine. Data is from a single experiment.

The H1 histamine receptor antagonist mepyramine produced a concentration-dependent rightward shift of the betahistine dose-response curve on the guinea-pig ileum (data not shown). The pA_2 value for mepyramine calculated from a Schild plot of this data was found to be 10.1.

It has been established for many years that histamine produces desensitization of guinea-pig ileum [11] and this has been used as a criterion for the identification of histamine in tissue fluids. Desensitization of the smooth muscle of the guinea-pig ileum to histamine also resulted in desensitization of the tissue towards betahistine. The procedure for studying desensitization of the guinea-pig ileum has previously been described [12] but briefly, recovery of the response to an agonist following exposure to high concentrations of desensitizing agent was monitored by measuring the responses to the agonist at various time intervals. Post-desensitization dose-ratios were calculated from log dose-response curves established at the beginning of the experiment. The fraction of receptors remaining in the desensitized state (Pd) was calculated from the model proposed by RANG and RITTER [13]. The high concentration of agonist used for desensitization has been expressed as multiples of its EC_{50} value. Figure 5a shows that histamine desensitized the tissue: the recovery of the response to histamine after desensitization being faster for the lower desensitizing dose. Similarly a high dose of betahistine resulted in desensitization towards itself (Figure 5b). Figure 5c shows that a high dose of histamine desensitized the tissue to the action of betahistine: the rate of recovery of the response to betahistine being inversely proportional to the initial desensitizing dose of histamine. Figure 5d likewise shows that a high dose of betahistine desensitized the tissue to the action of histamine.

Guinea-pig atria

Both histamine and betahistine produced a concentration-dependent positive chronotropic

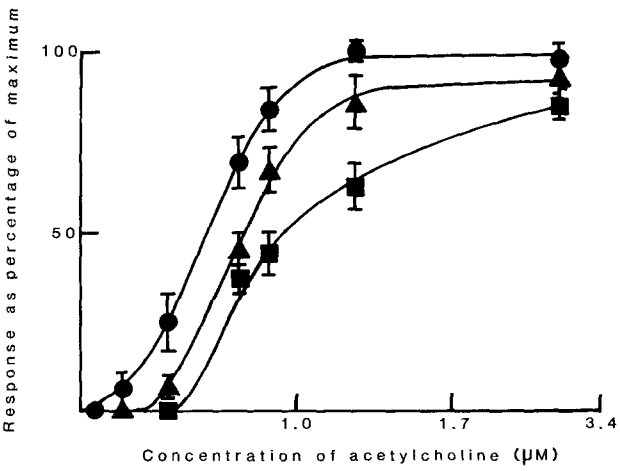

Figure 2
Concentration-response curves for acetylcholine on the isolated rat uterus. The response to acetylcholine is expressed as a percentage of the maximum contraction produced by this agent. ●—● acetylcholine alone; ▲—▲ acetylcholine in the presence of betahistine 10 μM; ■—■ acetylcholine in the presence of histamine 1 μM. Points represent means ±s.e.m. from 3 experiments.

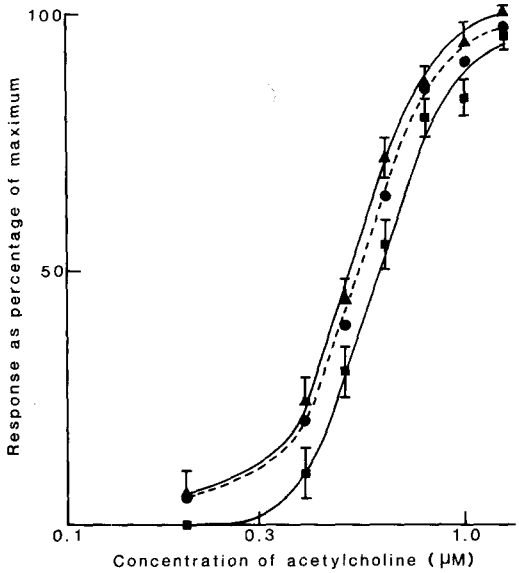

Figure 3.
Concentration-response curves for acetylcholine on the isolated rat uterus. The response to acetylcholine is expressed as a percentage of the maximum response to that agent. ▲—▲ acetylcholine alone; ■—■ acetylcholine in the presence of betahistine 1 μM; ●---● acetylcholine in the presence of betahistine, 1 μM and cimetidine, 100 μM. Points represent means ± s.e.m. from 3 experiments.

effects on the guinea-pig atrial preparation in the concentration ranges 0.5 to 10 and 0.5 to 100 μM respectively. The dose of histamine required to increase the atrial rate by 40% was 1 μM whereas the dose of betahistine required to produce the same effect was 10 μM. Histamine is, therefore, about tenfold more potent than betahistine on the preparation. The positive chronotropic effect of betahistine on this preparation was inhibited by the specific H2 histamine receptor antagonist YM11170 [14] (Figure 6).

Guinea-Pig lung strip

Betahistine produced concentration-dependent contractions of the guinea-pig parenchymal lung strip preparation in the concentration range 1 μM to 400 μM (Figure 7) with an EC_{50} of 30 μM. The histamine H2 receptor antagonist, YM11170, produced a two-fold shift to the left of the betahistine concentration-response curve (Figure 7). The EC_{50} for betahistine in the presence of YM11170 was 14 μM. Thus, blocking of H2 histamine receptors potentiates the effect of betahistine in producing contraction of the guinea-pig parenchymal lung strip preparation.

Histamine release from rat peritoneal mast cells

Table 1 shows that substance P and anti-IgE caused a release of histamine from rat peritoneal mast cells. However, at concentrations up to 100 μM betahistine failed to induce histamine release from rat mast cells. Table 1 also shows that betahistine in concentrations up to 10 μM did not inhibit the histamine release induced by substance P. In similar experiments, betahistine at concentrations up to 10 μM failed to inhibit histamine release induced by anti-IgE.

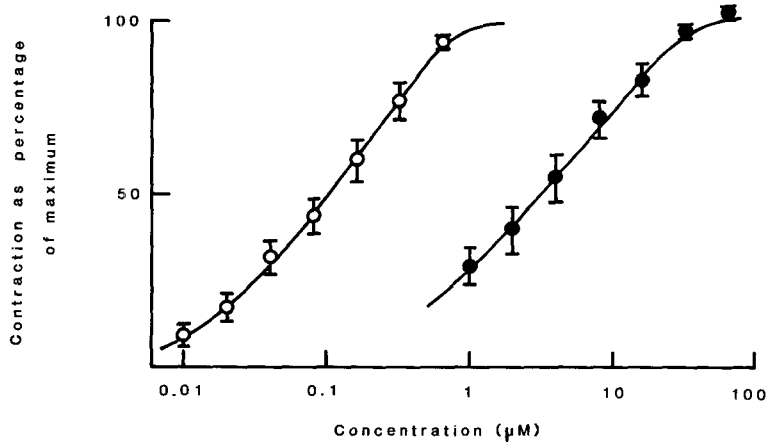

Figure 4
Concentration-response curves for histamine○) and betahistine (●) producing contraction of the isolated guinea-pig ileum. Responses have been expressed as a percentage of the maximum contractile response to histamine. Points are the means ± s.e.m. from 9 experiments.

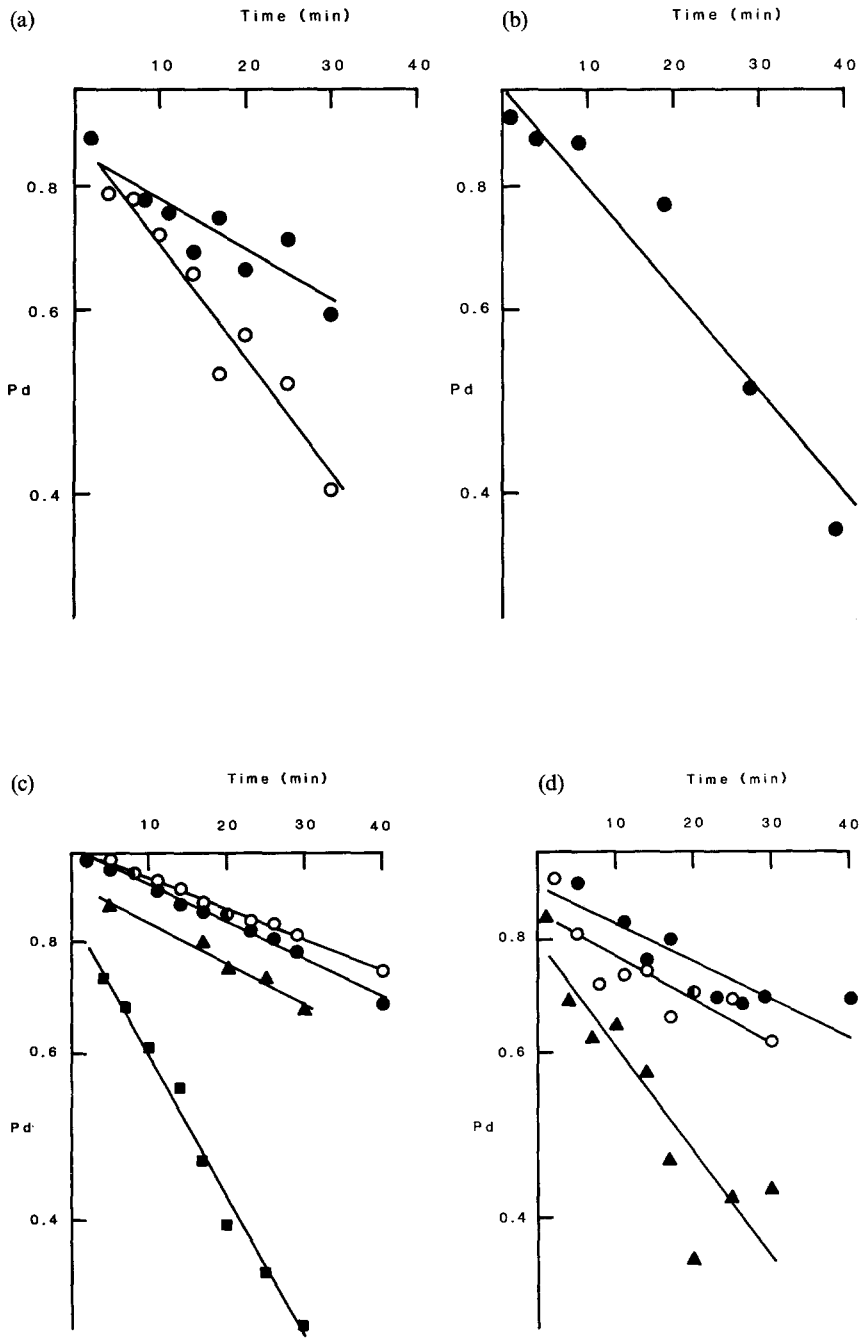

Figure 5
Desentization of receptors in the isolated guinea-pig ileum to histamine and betahistine. Recovery after a desensitizing dose of histamine or betahistine is expressed as a rate of change in the number of receptors remaining in the desensitized state (Pd). Explanation of the calculation of Pd is given in the text. (a) the recovery of the response to histamine following desensitization to histamine (b) the recovery of the response to betahistine following desensitization to betahistine (c) the recovery of the response to betahistine following desensitization to histamine (d) the recovery of the response to histamine following desensitization to betahistine. Different symbols show experiments with different doses of desensitizing agent and the dose of desensitizing agent is given as a multiple of the EC_{50} value for the agent on the preparation. The multiples of EC_{50} were: (a) 153-●; 39-○. (b) 37-●. (c) 1430-○; 2900-●; 153-▲; 45-■. (d) 300-●; 56-○; 25-▲. Each line represents data from a single experiment.

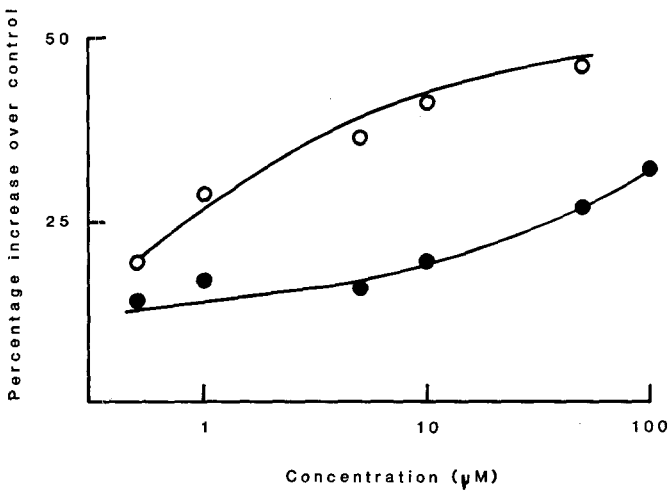

Figure 6
Concentration-response curves for the increase in control beating rate of isolated guinea-pig atria induced by betahistine (○) and betahistine in the presence of YM11170,0.1 μM (●). Changes in control beating rate induced by the drugs have been expressed as percentage increases over the control beating rate in the absence of drug which had a value of 258 ± 4.5 (means ± s.e.m. $n = 31$) beats/min. Each point is the mean of 3 experiments.

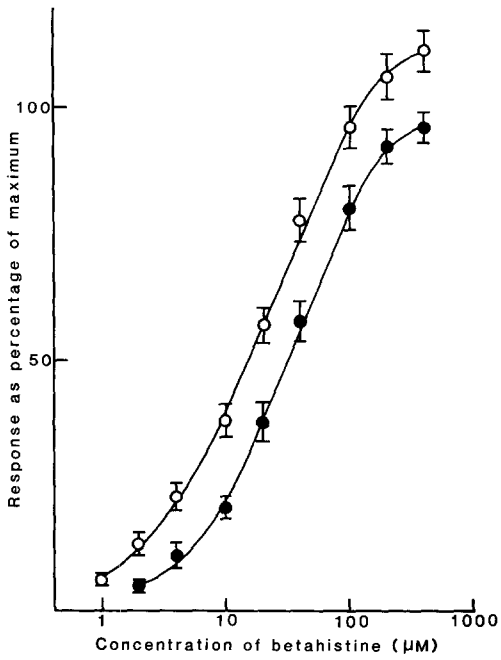

Figure 7
Concentration-response curves for betahistine-induced contraction of the isolated parenchymal lung strip of the guinea-pig. Responses are expressed as percentage of the maximum response to betahistine alone. ●—● betahistine alone; ○-○ betahistine in the presence of the H_2 histamine receptor antagonist YM11170, 1 μM. Data are the means (± s.e.m.) of 5 experiments.

Human skin responses

Both histamine, 0.075 to 0.75 n-moles, and betahistine, 2.5 to 25 n-moles, produced dose-dependent flare and wheal reactions in human skin when injected intradermally (Table 2). For the production of a flare of 1400 mm^2 and a wheal of 45 mm^2 betahistine was sixty five times less potent than histamine.

Discussion

Betahistine is of value in the treatment of Meniere's disease but the symptomatic relief produced by the drug in this condition has an unknown mechanism. There is some evidence that Meniere's disease is associated with reduced blood flow in parts of the inner ear and it is, therefore, reasonable to speculate that vasodilator actions of betahistine and the resulting improved circulation in the inner ear are responsible for the improvement seen during treatment with betahistine. In man, histamine produces vasodilatation particularly on the arterial side of the circulation and this effect appears to be mediated in many vessels by both H1 and H2 histamine receptors. In fact, there is evidence from primates that external carotid vessels are dilated through an H2 receptor mechanism [5] while internal carotid arteries are dilated by H1 and H2 receptor mechanisms [5]. In man, histamine-mediated dilatation of temporal

Table 1
Histamine release induced by betahistine from rat peritoneal mast cells, and the effect of betahistine on histamine release induced by substance P. Data are means of 3 experiments ± s.e.m.

Drug and Concentration (μM)	Histamine release (% of total)
Betahistine	
1	0.9 ± 0.4
10	0.1 ± 0
100	0
Substance P	
10	31.4 ± 4.6
Ant – IgE	
1 in 200 dilution	40.7 ± 0.4
Substance P	
5 alone	39.2 ± 6.0
5 + betahistine 0.1	34.7 ± 8.6
5 + betahistine 1	39.0 ± 6.3
5 + betahistine 10	40.6 ± 7.5

Table 2
Betahistine-induced flare and wheal responses in human skin. Each value is the mean of two separate experiments. The areas of flare and wheal responses to a saline control have been subtracted from the responses to histamine and betahistine to yield the value in the table.

Drug and amount injected (n-moles)		Area of flare (mm²)	Area of wheal (mm²)
Histamine	0.075	1283	41
	0.25	1780	71
	0.75	1873	83
Betahistine	2.5	1152	31
	7.5	1442	47
	25.0	960	41

arteries is brought about through the activation of H2 receptors [6]. The results presented in this paper indicate that betahistine exerts H2 as well as H1 actions and hence both of these effects need to be taken into account when considering its mechanism of action in Meniere's disease.

We have shown that betahistine produces contraction of the smooth muscle of the guinea-pig ileum and that this effect is mediated through an H1 receptor since it is antagonised by the selective H1 antagonist mepyramine and the pA_2 value for mepyramine at this receptor was found to be about 10 which is similar to pA_2 values reported for mepyramine in other tissues [15]. The cross-desensitization between histamine and betahistine in this preparation is evidence that the two drugs are acting through a similar mechanism. The contraction of the guinea-pig lung strip induced by betahistine is also evidence of an H1 action of this compound since it is established that H1 histamine agonists contract the guinea-pig lung strip whereas H2 receptor agonists produce relaxation [16, 17]. Evidence that betahistine affects both H2 as well as H1 receptors in the guinea-pig lung was obtained by showing that the selective H2 antagonist, YM11170 produced a shift to the left of the concentration-response curve for betahistine on the guinea-pig lung strip preparation. Blocking H2 receptors with YM11170 would be expected to prevent H2 receptor-mediated relaxation of the lung strip by removing physiological antagonism of the H1 contractile effect of betahistine. Hence, removal of the H2 receptor-mediated smooth muscle relaxant effect results in an increased response of the lung strip to betahistine.

The rat uterus is one of the classical preparations for examining H2 histamine receptors. The data presented in this paper show that histamine and betahistine produce relaxation of rat uterus precontracted with acetylcholine, this relaxation being manifest as a rightward shift of the acetylcholine concentration-response curve in the presence of either betahistine or histamine.

Relaxation of the rat uterus by betahistine is reversed by the specific H2 receptor antagonist cimetidine, indicating that the relaxant effect of betahistine on the rat uterus is mediated by an H2 receptor.

Isolated guinea-pig atria provide another preparation for examining the effects of H2 histamine receptor agonists, and betahistine has been shown to have a positive chronotropic action on the atrial preparation which was blocked by the potent, selective H2 receptor antagonist, YM11170. Hence this is further evidence for H2 receptor agonist activity of betahistine.

Another well-characterized preparation in which H2 receptors mediate an effect is gastric secretion from the stomach. There are conflicting reports about the activity of betahistine on gastric acid secretion. CURWAIN et al. [7] demonstrated that betahistine increased both gastric mucosal blood flow and gastric acid secretion from the Heidenhein pouch of the dog. In contrast, COCHRAN et al. [18] failed to demonstrate an increase in gastric acid secretion induced by betahistine in man. In the experiments of COCHRAN et al. [18] the concentration of betahistine was high and produced headache and flushing in five of the six subjects and hence it is possible that the H1 side-effects limited the dose that could be given in these experiments. If betahistine has less potency at H2 receptors than histamine, the dose reached in these studies was probably insufficient to activate the H2 receptors mediating gastric acid secretion.

In a previous study [19] betahistine was shown to release histamine from isolated guinea-pig atria. However, we were unable to induce histamine release from rat peritoneal mast cells with betahistine at concentrations up to 100 μM. In the studies of LIGHT and HUGHES [19] the concentrations of betahistine which induced histamine release from the guinea-pig tissue were between 360 μM and 1.47 mM which are very high concentrations and a cytotoxic effect of the drug cannot be ruled out. In fact, in the same study, compound 48/80 released histamine but again at concentrations which would normally be considered to be cytotoxic. It should be pointed out, however, that mast cells from different species and different sources within a species show heterogeneous responses to histamine releasing agents [20]. We used rat peritoneal mast cells in this study because they have been shown to be a good model for the actions of histamine releasing agents in human skin [10].

We have also demonstrated that betahistine produces a wheal and flare reaction in human skin. This probably represents an H1 receptor action since it has previously been shown that the wheal-and-flare inducing effect of histamine in human skin is inhibited by H1 receptor antagonists but not by H2 receptor antagonists [10]. Furthermore, it probably represents a direct effect of betahistine rather than an indirect action through histamine release since we were unable to demonstrate histamine release *in vitro* in response to betahistine (Table 1).

A recent study by ARRANG et al. [21] has shown that betahistine displaces [^{3}H]-mepyramine binding to H1 receptors in guinea-pig brain. Thus, there is evidence from the data presented in this paper and a variety of other studies that betahistine exerts agonist actions at H1 receptors. We have now presented evidence to show that betahistine also exerts agonist action at H2 histamine receptors. From the studies on guinea-pig atria, betahistine appears to be about ten times less potent than histamine at H2 receptors whereas data from human skin and guinea-pig ileum indicate that betahistine is about 30 to 60 times less potent that histamine at H1 receptors. It seems, therefore, that whilst betahistine has significant H1 effects, it is more potent at H2 receptors. The combined H1 and H2 agonist actions of betahistine may be of importance in its therapeutic effect in Meniere's syndrome, although to test this hypothesis it would be necessary to study the action of H1 and H2 antagonists on the response to betahistine of *human* cochlear blood vessels. There is evidence in experimental animals that betahistine increases cochlear and basilar blood flow but apparently no analysis of the H1 and H2 components of this [2–4].

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