Exp Brain Res (1995) 105:18–24 © Springer-Verlag 1995

RESEARCH ARTICLE

Jian-Jun Wang · Mayank B. Dutia

Effects of histamine and betahistine on rat medial vestibular nucleus neurones: possible mechanism of action of anti-histaminergic drugs in vertigo and motion sickness

Received: 7 December 1994 / Accepted: 13 March 1995

Abstract The tonic discharge of 71 medial vestibular nucleus (MVN) neurones was recorded in slices of the dorsal brainstem of young adult rats. Bath application of histamine caused a dose-related excitation in 59 of the 71 cells (83%), the remaining 12 (17%) being unresponsive. Dimaprit, a selective H_2 agonist, also caused excitation in all 20 cells tested. The histamine-induced excitation and the response to dimaprit were antagonised by the selective H_2 antagonist ranitidine, confirming that the H_2 subtype of histamine receptor is involved in mediating the effects of histamine on these cells. Triprolidine, a selective H_1 antagonist, also antagonised the excitation caused by histamine, at a concentration (0.3 μM) which left the H_2 receptor-mediated response to dimaprit unchanged. Thus the excitatory effects of histamine on MVN cells in the rat involve two components mediated through H_1 and H_2 receptor-linked mechanisms, respectively. Betahistine, a weak H_1 agonist and H_3 antagonist, had little excitatory action when applied on its own, but significantly reduced the excitation caused by histamine when the two drugs were applied together. The effects of betahistine were consistent with a partial-agonist action at H_1 receptors on MVN cells, reducing the excitatory responses to histamine presumably by occupying these receptor sites in competition with the exogenously applied neurotransmitter. This partial-agonist action of betahistine may be an important part of its mechanism of action in the symptomatic treatment of vertigo and motion sickness, since it is likely to occur not only in the MVN but also in many brain regions, including the thalamus and cortex, which express H_1 receptors and which are innervated by the hypothalamic histaminergic system. Thus the effectiveness of betahistine and other anti-H_1 drugs against motion sickness may be explained by their action in reducing the effects of the excess histamine release induced in such conditions in various brain areas, including the MVN.

Key words Medial vestibular nucleus · Histamine · Betahistine · Vertigo · Motion sickness · Rat

J.-J. Wang[1] · M. B. Dutia (✉)
Department of Physiology, Medical School,
Teviot Place, Edinburgh EH8 9AG, UK;
Fax no.: +44–131–650 6527

Present address:
[1] Department of Biology, Nanjing University, Nanjing, China

Introduction

Double-axis rotation, which causes behavioural symptoms associated with motion sickness in the rat, also causes an elevation of histamine levels in the hypothalamus and medulla (Takeda et al. 1986, 1989, 1993). A similar increase in histamine release occurs with unilateral stimulation of the vestibular receptors (Horii et al. 1993). These findings suggest that the hypothalamic histaminergic system, which has highly divergent projections to almost all brain areas including the brainstem (Panula et al. 1989; Schwartz et al. 1991), may be activated both by central sensory conflicts as in motion sickness, and by disturbances of the afferent inflow from the peripheral vestibular receptors as in vestibular neuritis, Meniere's disease or after unilateral vestibular de-afferentation (Brandt 1991; Horii et al. 1993). This may be a normal physiological response to the stress associated with such conditions, comparable for example to stress induced by restraint which also causes increased histamine release (see, e.g. Fleckenstein et al. 1994). While the histaminergic system is implicated in regulating a wide range of functions, including sleep and arousal (Schwartz et al. 1991), its specific effects on the processing of vestibular information through its actions on vestibular nucleus neurones and the possible mechanisms of action of anti-histaminergic drugs which are effective against vertigo and motion sickness in man, are unclear.

Immunohistochemical studies have demonstrated a moderate density of histamine-containing fibres within the medial vestibular nucleus (MVN), particularly in its caudal region (Steinbusch 1991), which contains neurones that project directly to the nucleus tractus solitarius and which may be involved in initiating an emetic re-

sponse to abnormal vestibular experience (Balaban and Beryozkin 1994). Ligand-binding studies have demonstrated the presence of H_1 receptors in the MVN (Bouthenet et al. 1988), and northern blot analysis using a hybridization probe derived from an H_2 receptor gene has revealed high levels of messenger ribonucleic acid (mRNA) encoding this subtype of receptor in the brainstem, presumably including the MVN (Ruat et al. 1991). Several recent studies have examined the effects of histamine and related compounds on MVN neurones in brainstem slices in vitro (Phelan et al. 1990; Inverarity et al. 1993; Serafin et al. 1993). Although Phelan et al. (1990) observed excitation, inhibition and biphasic responses elicited by histamine, subsequent studies have only reported excitatory effects on MVN cells. Cimetidine, an H_2 receptor antagonist, was shown by Phelan et al. (1990) and by Serafin et al. (1993) to antagonise the excitatory effects of histamine on rat and guinea pig MVN cells, respectively. Serafin et al. (1993) concluded that the post-synaptic effects of histamine were mediated exclusively by H_2 receptors, since mepyramine, an H_1 antagonist, failed to antagonise the excitatory (depolarising) effect of histamine; and they suggested that the H_1 receptors which were demonstrated immunohistologically in the MVN were likely to be associated with non-neural elements. By contrast, Inverarity et al. (1993) observed that both mepyramine and ranitidine, an H_2 receptor antagonist, antagonised the responses of rat MVN neurones to histamine and concluded that both H_1 and H_2 receptors were involved.

The role of the H_1 subtype of histamine receptor in the vestibular nuclei is of some interest, since betahistine, which is widely used in the symptomatic treatment of vestibular syndromes in man (Fisher 1991), is known to be a weak agonist acting at H_1 rather than H_2 receptors (Arrang et al. 1985b). However, the central mechanism of action of betahistine in this context is not readily apparent, since its agonist action at H_1 receptors and its moderate antagonist action at presynaptic H_3 auto-receptors may be expected to mimic and potentiate the endogenous release of histamine within the brain. In this study we extended the preliminary experiments of Inverarity et al. (1993) to specifically investigate the role of H_1 receptor subtype in the rat MVN, using the potent, selective H_1 antagonist triprolidine in combination with dimaprit, a selective H_2 receptor agonist, and ranitidine, a potent H_2 receptor antagonist (for a review see Hill 1990). We also examined the effects of betahistine on MVN neurones, and our findings indicate that this substance acts as a partial agonist at H_1 receptors on MVN cells, reducing their sensitivity to histamine. Modulation of the excitability of MVN neurones may therefore be an integral part of the physiological function of the hypothalamic histaminergic system during abnormal vestibular stimulation. Our results also suggest that the MVN is one of the central sites of action of anti-histaminergic drugs that are effective against vertigo and motion sickness in man.

Materials and methods

The experiments were carried out on slices of the dorsal brainstem of the rat, prepared as described in detail previously (Dutia et al. 1992; Johnston et al. 1993, 1994). Briefly, Sprague-Dawley rats weighing 150-200 g were anaesthetised with 3% halothane in oxygen and decapitated. The brainstem extending from the obex to the superior colliculi was rapidly removed into ice-cold medium and cemented, fourth ventricle uppermost, onto the stage of a Vibroslice (Campden Instruments, London). Slices containing the MVN (350–400 μM thick) were cut in the horizontal plane, approximately parallel to the floor of the fourth ventricle. The slices were incubated at 33±0.2°C in a recording chamber perfused with artificial cerebrospinal fluid (aCSF; composition: NaCl 124 mM, KCl 5 mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.3 mM, $CaCl_2$ 2.4 mM, $NaHCO_3$ 26.0 mM, *d*-glucose 10.0 mM, equilibrated with 95% O_2 and 5% CO_2) at a rate of 1.5 ml/min. The spontaneous tonic activity of MVN cells was recorded extracellularly using conventional glass microelectrodes filled with 2M NaCl (impedances 20–70 MΩ). The tonic discharge rate was monitored on line using a CED 1401 interface connected to a microcomputer. Agonists (histamine, dimaprit, *N*-alpha-methyl histamine (NAMH) and *R*-alpha-methyl histamine (RAMH), obtained from Research Biochemicals, Semat, UK) were added to the perfusing aCSF for test periods of 60 s. Antagonists (triprolidine, ranitidine and mepyramine, also obtained from Semat, UK) were equilibrated with the tissue for periods of at least 10 min, before test pulses of agonists were again applied in the presence of antagonist. In several experiments doses of 10–100 μM 5-hydroxytryptamine were also applied in the presence of the histamine antagonists, to confirm that non-specific effects on the cell membrane excitability did not occur. Betahistine (obtained from Sigma, UK) was added to the aCSF for test pulses of 60 s either on its own or together with histamine over a range of concentrations. These experiments were done in compliance with the UK legislation on the use of laboratory animals.

Results

The spontaneous tonic discharge of 71 MVN cells was recorded in 33 slice preparations. Of these, 59 cells (83%) were excited by histamine (1–100 μM) added to the perfusing medium. The remaining 12 cells (17%) were not responsive to histamine (tested with doses up to 300 μM), and these cells were not studied further.

H_2 receptors

Dimaprit, a highly selective agonist acting at the H_2 subtype of histamine receptor, also excited MVN cells responsive to histamine (n=20; Figs. 1, 2). However histamine caused a greater excitation and was effective at lower concentrations than dimaprit in all the cells tested. The excitatory effects of histamine and dimaprit were antagonised by ranitidine, a highly selective H_2 receptor antagonist (Figs. 1, 2C; n=12). This result is in agreement with the findings of Phelan et al. (1990), Inverarity et al. (1993) and Serafin et al. (1993) and confirms that in the rat, as in the guinea pig, the H_2 receptor subtype is involved in mediating the excitatory actions of histamine on MVN neurones.

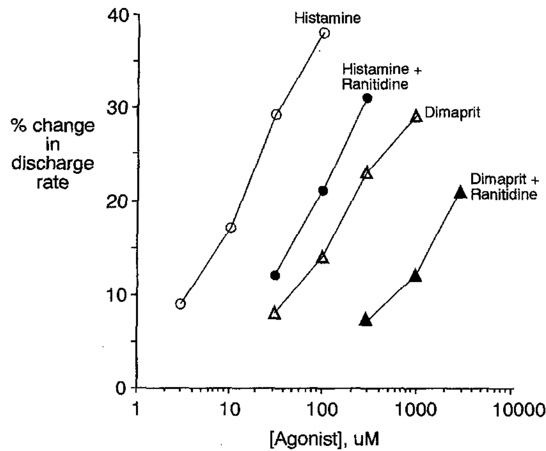


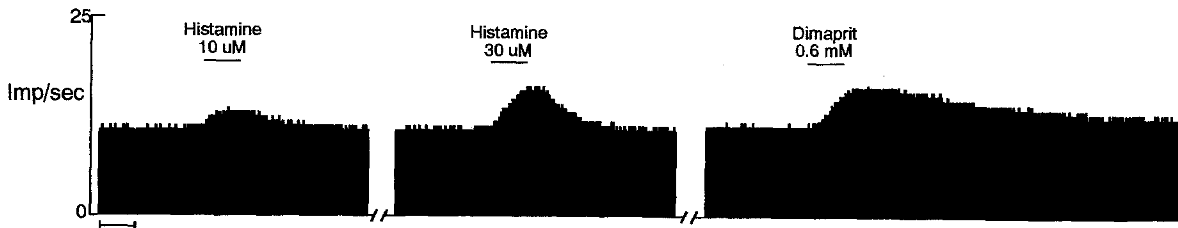
Fig. 1 Dose-response curves showing the effects on the discharge rate of the same medial vestibular nucleus cell of histamine and dimaprit (a selective H_2 receptor agonist), in control medium (*open symbols*) and after equilibration for 15 min with 1 μM ranitidine (an H_2 antagonist; *closed symbols*). Each point in this figure and in Fig. 3 represents the increase in discharge rate, expressed as a percentage of the control discharge rate, in response to a 60-s test pulse of agonist

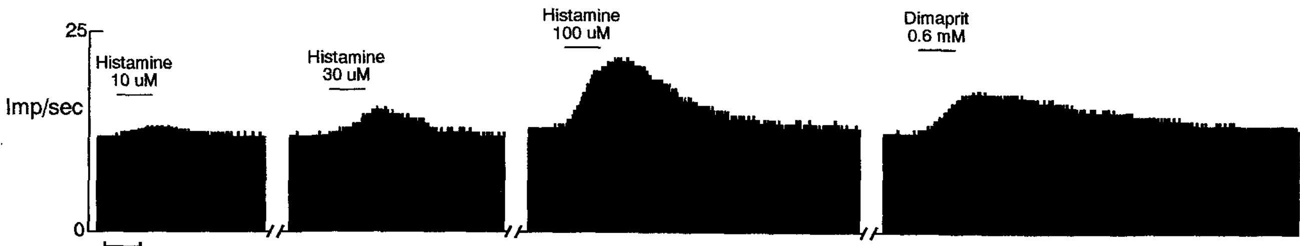
Fig. 2A–C Rate histograms showing medial vestibular nucleus the effects of histamine and dimaprit on the spontaneous discharge rate of a cell. The *bars above the data* indicate the 60-s period for which the agonists were applied. **A** Responses in normal artificial cerebrospinal fluid (aCSF). **B** Responses after equilibration with 0.3 μM triprolidine (an H_1 antagonist) for 15 min. **C** Responses after equilibration with aCSF containing 0.3 μM triprolidine and 0.6 μM ranitidine. Bin width 3 s

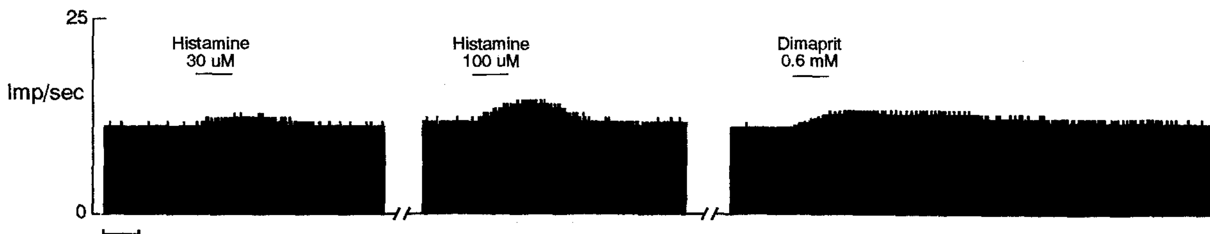
H_1 receptors

NAMH, an H_1 agonist, was tested on eight MVN cells which were responsive to histamine. NAMH mimicked the excitatory effects of histamine in all the cells tested. However, H_2 receptor antagonist ranitidine was also effective in antagonising this excitatory response to NAMH, indicating that NAMH was not acting selectively through H_1 receptors on these cells. For this reason the excitatory effects of NAMH were not studied in any detail.

In 15 MVN cells which were responsive to histamine, the effects of the selective H_1 antagonist triprolidine (0.3 μM) were examined. In each case triprolidine was effective in reducing the excitatory responses to exogenous histamine. Since NAMH had proved to be unsuitable as a selective agonist for H_1 receptors, it was necessary to exclude the possibility that effects of triprolidine were due to non-selective interactions with H_2 receptors. To this end the effects of triprolidine on the excitatory responses to histamine were determined, while the response of the same cell to the selective H_2 agonist dimaprit was used as a control. One such experiment is illustrated in Fig. 2. The control responses to histamine and dimaprit in normal medium are shown in Fig. 2A. The responses shown in Fig. 2B were obtained after the slice had been equilibrated with 0.3 μM triprolidine for 15 min. The responses to exogenous histamine were selectively antagonised by the H_1 antagonist (Fig. 2B, left and middle panels), while the excitation caused selec-







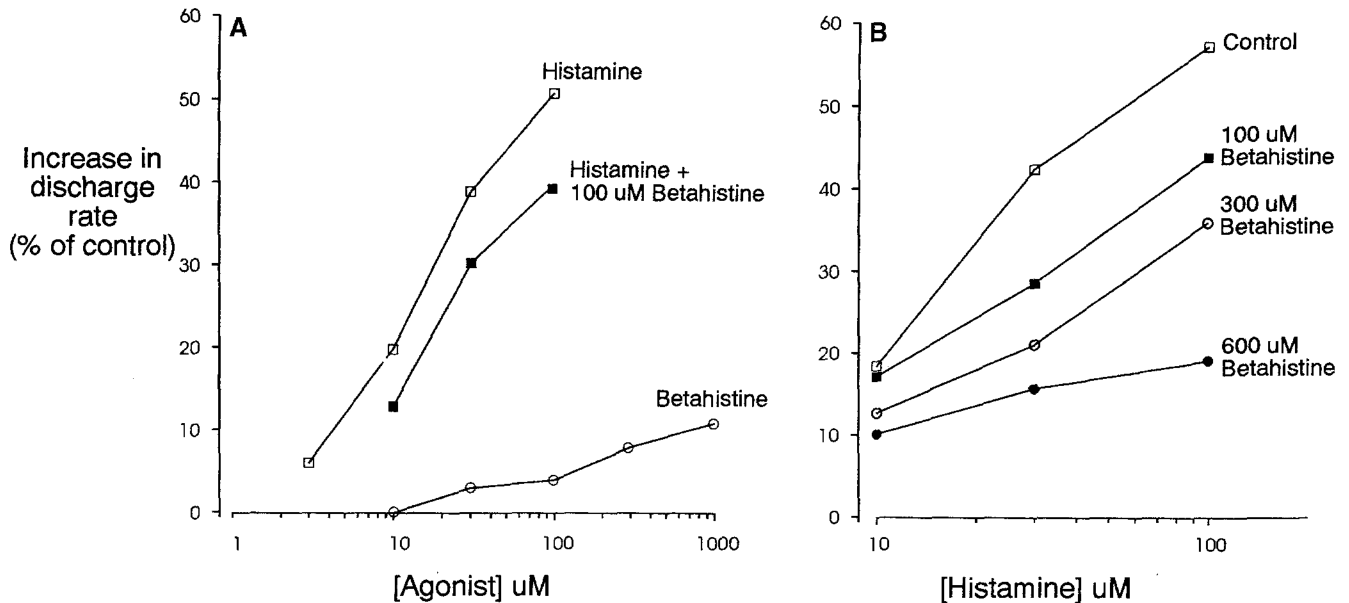


Fig. 3 **A** Dose-response curves showing the effects of histamine and betahistine applied singly (*open symbols*) and together (*filled squares*) on the discharge rate of a medial vestibular nucleus (MVN) cell. **B** Effects of varying the concentration of betahistine on the responses of a different MVN cell to histamine when the two drugs are applied together

tively through H_2 receptors by dimaprit was unchanged (Fig. 2B, rightmost panel). Susequently the remaining histamine-induced excitation and the excitatory response to dimaprit were both antagonised by the H_2 antagonist ranitidine (Fig. 2C).

Similar results, indicating a combined action of exogenous histamine through both H_1 and H_2 receptor-mediated components, were obtained in all nine MVN cells tested in this way. In three further cells, higher concentrations of triprolidine (0.6–1 μM) were found to antagonise the responses to both histamine and dimaprit together, indicating that at these concentrations triprolidine fails to act selectively at the H_1 receptor subtype.

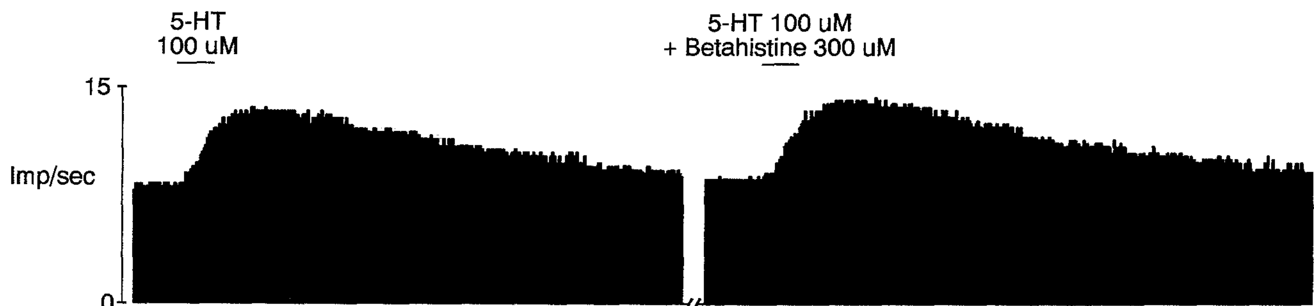
H_3 receptors

In five MVN cells responsive to histamine, the effects of the H_3 receptor agonist RAMH were tested. None of the cells were responsive to RAMH up to doses of 300 μM. The H_3 receptor antagonist thioperamide was also ineffective in antagonising the excitatory responses to histamine, in all eight cells tested. This result agrees with that of Serafin et al. (1993) in the guinea pig, and indicates that presynaptic H_3 autoreceptors, which modulate neurotransmitter release from presynaptic terminals in vivo (Arrang et al. 1983, 1985a), do not significantly affect the excitability of MVN cells in vitro.

Effects of betahistine on MVN neurones

The effects of betahistine were tested on eight MVN cells responsive to histamine. As illustrated for one cell in Fig. 3A, betahistine on its own had no effect at low concentrations and a small excitatory effect at high concentrations (300–1000 μM). When histamine and betahistine were applied together, however, the response to histamine was reduced at all the doses tested (Fig. 3A, filled squares). This antagonistic action of betahistine was dose-dependent, as shown for a further MVN cell in Fig. 3B.

Fig. 4 Rate histograms showing the response of a medial vestibular nucleus cell to a test pulse of 100 μM 5-hydroxytryptamine (*5-HT*) alone (*left panel*) and in the presence of 300 μM betahistine (*right panel*). Bin width 3 s



In three of the eight cells tested, betahistine caused a clear reduction both in the peak discharge rate and in the duration of the excitatory response elicited by the standard 60-s pulses of histamine. In the remaining five cells the peak response was less affected, particularly at low concentrations of betahistine, and instead the reduction in the total duration of the response was more conspicuous. The antagonistic effects of betahistine were not due to a non-specific action on the excitability of the cell membrane, since the response of the same cells to 5-hydroxytryptamine was not affected by the simultaneous application of betahistine (Fig. 4). These results therefore indicate that betahistine acts as a partial agonist at histamine receptors on MVN cells, having little excitatory action on its own but antagonising the effects of exogenously applied histamine presumably by competing with the neurotransmitter for receptor sites on the MVN cell membrane.

Discussion

Histamine receptors in the rat MVN

The present results show clearly that the excitatory effects of histamine on MVN cells in the rat involve two components mediated through H_1 and H_2 receptor-linked mechanisms, respectively. While an H_2 receptor-mediated excitatory effect had been demonstrated earlier, evidence for an H_1-mediated component had been contradictory. Inverarity et al. (1993) found that mepyramine was effective in antagonising the excitatory response to histamine and suggested that H_1 receptors were involved, while Serafin et al. (1993) did not observe any antagonistic effects of mepyramine and concluded that the postsynaptic effects of histamine were mediated exclusively through H_2 receptor-linked mechanisms. The present study establishes that H_1 receptors are indeed involved, by excluding the possibility that the findings of Inverarity et al. (1993) were due to a non-specific action of mepyramine on H_2 receptors. It is possible that the absence of any effect of mepyramine in the experiments of Serafin et al. (1993) reflects a species difference between the rat and guinea pig. Significant differences in the regional distribution of brain H_1 and H_2 receptors have been reported between the two species, and the pharmacological characteristics of the receptors also appear to differ in some respects (for reviews see Hill 1990; Schwartz et al. 1991). However, the presence of H_1 receptors has been demonstrated immunohistologically within the MVN in both species, and their functional role in the guinea pig MVN remains to be clarified.

Mechanism of action of betahistine

Our confirmation that the H_1 subtype of histamine receptor is involved in mediating the actions of histamine on MVN cells is important in elucidating the mechanism of action of betahistine, since this drug is known to be a weak agonist at the H_1 receptor and a moderate antagonist at the H_3 presynaptic auto-receptor (Arrang et al. 1985b). While its antagonist action at the H_3 receptor can be expected to potentiate the release of presynaptic histamine in vivo by blocking the auto-inhibitory feedback at histaminergic terminals (Arrang et al. 1983, 1985a), the present results show that its action on MVN cells is to significantly reduce their responsiveness to histamine. This action of betahistine occurs presumably at post-synaptic H_1 receptors, since betahistine lacks any effect at H_2 receptors (Arrang et al. 1985b). The effects of betahistine are thus consistent with a partial-agonist action at these receptors, with betahistine having little excitatory action on its own but reducing the excitatory responses to histamine presumably by occupying H_1 receptor sites in competition with the exogenously applied neurotransmitter. The reduced response of the MVN cells to histamine in the presence of betahistine may be the result of the activation of H_2 receptor-coupled sesond-messenger pathways alone rather than the normal activation of both H_1 and H_2 second-messenger systems together. Thus, simultaneous stimulation of the H_1 and H_2 receptor pathways is known to cause a large amplification of the cellular cAMP response, above that caused by stimulation of the H_2 receptor pathway alone, in a number of cell types (Palacios et al. 1978; Al-Gadi and Hill 1985; Hill 1990; Schwartz et al. 1991). In the present study the reduction in the amplitude and total duration of the histamine-induced excitation in MVN cells in the presence of betahistine is suggestive of such a mechanism. This reduction is presumably more than sufficient to compensate for any potentiation of histamine release caused by the blockade of presynaptic H_3 auto-receptors by betahistine, as would be the case, for example, if the release of histamine was already sufficient to occupy most of the postsynaptic H_2 receptors.

We suggest that this partial-agonist action of betahistine at H_1 receptors may be an important component of its mechanism of action in the symptomatic treatment of vertigo and motion sickness in man. Thus, assuming that vestibular dysfunction in man is correlated with an increase in the activity of the hypothalamic histaminergic system as in the rat behavioural model (Takeda et al. 1993; Horii et al. 1993), and that as a consequence there is an increased release of histamine within the MVN from descending histaminergic hypothalamic fibres, then administration of betahistine would reduce the effects of the excess histamine on MVN cells as we have demonstrated here. Moreover, since H_1 receptors are found distributed in many forebrain regions that are innervated by the hypothalamic histaminergic system including the thalamus and cortex (Panula et al. 1989; Schwartz et al. 1991; Steinbusch 1991), the partial-agonist action of betahistine at these receptors is likely to occur in these regions as well. The effectiveness of betahistine against vertigo and motion sickness may therefore be due to it counteracting the effects of excess histamine release at various sites in the brain, including the MVN. In this, be-

tahistine would have a similar action to diphenhydramine, a selective H_1 blocker which is also effective against motion sickness (Matsuoka et al. 1985). Although the effectiveness against motion sickness of H_1 antagonists has often been attributed to their atropine-like side-effects (e.g. Schwartz et al. 1991), the present results indicate that their direct actions on post-synaptic histamine receptors may be more pertinent than has been recognised so far.

The importance of the additional effects of betahistine on presynaptic H_3 receptors, which are known to modulate not only histamine release from synaptic terminals but also that of other neurotransmitters, has yet to be demonstrated in the MVN. Yabe et al. (1993) have shown that local brainstem superfusion or intraperitoneal injection of thioperamide causes changes in the activity of the vestibulo-ocular and tonic vestibulo-spinal reflex pathways in the guinea pig, indicating that H_3 receptor-mediated effects may occur. The cardiovascular effects of systemic betahistine, which include its effects on the vascular perfusion of the inner ear (e.g. Laurikainen et al. 1993), may be relevant in vestibular disorders of peripheral origin such as Meniere's disease, but are likely to be less important in motion sickness due to abnormal sensory experience or vertigo following unilateral vestibular de-afferentation.

While the present results indicate that the partial-agonist action of betahistine at neuronal H_1 receptors may be important in explaining its effectiveness against vertigo and motion sickness, they also suggest that antagonists of the H_2 subtype of histamine receptor should be similarly effective, since they would also reduce the effects of excess histamine release on MVN and other cells. This prediction may be tested using zolantidine, an H_2 antagonist which differs from cimetidine and ranitidine in that it is able readily to cross the blood-brain barrier (Calcutt et al. 1988). The present results also suggest that the rat may provide a useful model in which to investigate the cellular mechanisms of action of putative anti-vertiginous drugs, since the effects of such agents may be tested at the behavioural as well as the cellular level.

Acknowledgements This work was made possible by support from the Wellcome Trust (grant 018707). Jian-Jun Wang was the holder of a Fellowship from the National Education Commission of China. We thank Donald J. Inverarity for his collaboration in some of these experiments, and Daniel S. McQueen for helpful advice.

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