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Inhibition of sympathetic hypertensive responses in the guinea-pig by prejunctional histamine H_3-receptors

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1 The effect of (**R**)-α-methylhistamine, a selective H_3-histamine receptor agonist, was examined on the neurogenic hypertension and tachycardia that is induced by stimulation of areas in the medulla oblongata of guinea-pigs. Electrical medullary stimulation (32 Hz, 3–5 s trains, 0.5–1.0 ms square pulse, 25–400 μA) produced intensity-dependent increases in blood pressure and a more variable tachycardia.

2 (**R**)-α-methylhistamine inhibited the hypertension and tachycardia due to submaximal CNS stimulation. The inhibition of hypertension by (**R**)-α-methylhistamine was dose-dependent (10–300 μg kg^{-1}, i.v.) and was not seen at high intensities of stimulation.

3 (**R**)-α-methylhistamine (300 μg kg^{-1}, i.v.) did not attenuate the pressor response to adrenaline (1 and 3 μg kg^{-1}, i.v.), indicating that the effect of (**R**)-α-methylhistamine was not mediated by a postjunctional action on smooth muscle.

4 The inhibition of CNS-induced hypertension by (**R**)-α-methylhistamine (300 μg kg^{-1}, i.v.) was blocked by the H_3 antagonists, thioperamide (ID_{50} = 0.39 mg kg^{-1}, i.v.), impromidine (ID_{50} = 0.22 mg kg^{-1}, i.v.) and burimamide (ID_{50} = 6 mg kg^{-1}, i.v.). The rank order potency of these antagonists is consistent with activity at the H_{3B} receptor subtype. Chlorpheniramine (30 μg kg^{-1}, i.v.) and cimetidine (3 mg kg^{-1}, i.v.) did not antagonize the inhibition of CNS-hypertension by (**R**)-α-methylhistamine.

5 These results suggest that (**R**)-α-methylhistamine inhibits sympathetic hypertensive responses in guinea-pigs by activation of prejunctional H_3-receptors, possibly located on postganglionic nerve terminals. Furthermore, on the basis of the rank order potency to different H_3-antagonists, it appears that the H_{3B}-receptor subtype is involved with H_3-receptor responses on vascular sympathetic nerves.

Keywords: Histamine H_3-receptors; (**R**)-α-methylhistamine; presynaptic inhibition; neurogenic hypertension; sympathetic neurotransmission; thioperamide; impromidine; burimamide

Introduction

Histamine exerts an inhibitory effect on neurotransmitter release by a prejunctional mechanism in CNS and peripheral autonomic neural systems (Arrang *et al.*, 1983; 1988; Schlicker *et al.*, 1988; 1990). This action is mediated by activation of prejunctional histamine H_3-receptors, a mechanism that is pharmacologically distinct from the classical postjunctional H_1- and H_2-mediated responses to histamine (Timmerman, 1990). Furthermore, recent studies of radioligand binding have revealed two classes of H_3-binding sites designated H_{3A} and H_{3B}, with different sensitivities to the H_3-antagonists, thioperamide and burimamide (West *et al.*, 1990). Therefore, the possibility exists for a tissue selective distribution of H_3-receptor subtypes.

There has been some controversy about the role of H_3-receptors on nerve fibres innervating blood vessels. The early work by Ishikawa & Sperelakis (1987) showed that histamine can depress sympathetic neurotransmission in the mesenteric artery by interacting with prejunctional H_3-receptors that are located on the perivascular nerve terminals. Activation of prejunctional H_3-receptors also inhibited electrically-induced release of [^{3}H]-noradrenaline from human saphenous vein (Molderings *et al.*, 1991). Although Schneider *et al.* (1991) found no evidence for H_3-receptor-mediated inhibition of [^{3}H]-noradrenaline release in the rat vena cava *in vitro*, this same group reported H_3-receptor mediated inhibition of the neurogenic vasopressor response in rats *in vivo* (Malinowska & Schlicker, 1991).

The present studies were undertaken to investigate H_3-receptor modulation of sympathetic vascular responses caused by stimulation of the dorsal medulla oblongata in the anaesthetized guinea-pig. This species has been used previously to identify an inhibitory role for H_3-receptors on neurogenic responses in the ileum (Trzeciakowski, 1987; Menkveld & Timmerman, 1990), duodenum (Coruzzi *et al.*, 1991) and airways (Ichinose *et al.*, 1989; 1990). In addition, the potencies of thioperamide, burimamide and impromidine were examined in order to identify the H_3-receptor subtype responsible for the modulation of sympathetically-evoked vascular responses.

Methods

Animal preparation

Male Hartley guinea-pigs (450–600 g, Charles River, Bloomington, MA, U.S.A.) were anaesthetized with α-chloralose (125 mg kg^{-1}, i.p.) and surgically prepared by catheterization of the trachea, jugular vein and carotid artery. Animals were mechanically ventilated (volume = 4 ml, frequency = 45 breaths min^{-1}) and paralyzed with gallamine (2 mg kg^{-1}, i.v.). The arterial catheter was connected to a pressure transducer for blood pressure (BP) and heart rate (HR) measurements. Pulmonary insufflation pressure (PIP) was measured from a side port in the tracheal cannula and changes in PIP were used to measure bronchoconstriction (Hey *et al.*, 1990a). All physiological parameters were recorded on a MI^2, M-3000 signal processing centre (Modular Instruments, Malvern, PA, U.S.A.).

Electrical stimulation of the medulla

Animals were positioned in a Kopf stereotaxic apparatus (David Kopf Inst., Tujunga, CA, U.S.A.) and an incision was made to expose the dorsal aspect of the skull. A section of the bone overlying the cerebellum was removed. A portion of cerebellar tissue that covers the floor of the fourth ventri-

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cle was removed to expose obex (the most caudal structure on the floor of the fourth ventricle). Concentric bilateral electrodes were inserted into the dorsal medulla. Regions of the dorsal medulla that elicited the largest hypertensive responses with the least changes in airway tone were selected. The stereotaxic coordinates that yielded these effects were: A 1.0–2.0 mm, L 1.5 mm and V 2.0 mm in relation to obex. This area, which was empirically identified through mapping, is more anterior and ventral than the dorsal bronchoconstrictor area previously identified in the guinea-pig (Hey *et al.*, 1990a). To minimize tissue dimpling, the electrodes were placed 1.0 mm ventral to the target site and then gently retracted to the appropriate stereotaxic coordinates.

The medulla was electrically stimulated with a Grass (S88) dual stimulator connected to the electrodes by means of stimulus isolation units with constant current output (Grass Instruments, Quincy, MA, U.S.A.). The stimulation parameters used to evoke cardiovascular responses were: 32 Hz, 3–5 s trains, 0.5–1.0 ms square pulse and varying intensities from 25–400 μA. The train rate was approximately 180 s. Upon completion of each experiment, a supramaximal stimulus (400 μA) was used to confirm that the intensity range used in the study was submaximal for each animal.

Pharmacological studies

To characterize the hypertensive response to medullary stimulation each animal received, in a step-wise fashion, an increasing stimulation intensity (25–400 μA) and peak changes in BP and HR were recorded for each stimulus train. All animals had been pretreated with ipratropium bromide (10 μg kg^{-1}, i.v.), to block CNS-induced cholinergic bronchospasm and the effects of medullary stimulation on vagal innervation to the heart (Hey *et al.*, 1990a).

The cardiovascular responses to CNS stimulation were evaluated before and after (**R**)-α-methylhistamine (10–300 μg kg^{-1}, i.v.). (**R**)-α-methylhistamine was administered 5 min before medullary stimulation and peak responses were recorded to each stimulus intensity (25–400 μA). The effect of (**R**)-α-methylhistamine (300 μg kg^{-1}) on the hypertensive response due to exogenous adrenaline (1 and 3 μg kg^{-1}, i.v.) was studied to determine whether (**R**)-α-methylhistamine was acting by a postjunctional action on smooth muscle.

To establish the type of histamine receptor involved in the response to (**R**)-α-methylhistamine, animals were treated with chlorpheniramine (30 μg kg^{-1}, i.v.), cimetidine (3 mg kg^{-1}, i.v.), or thioperamide (3 mg kg^{-1}, i.v.) 10 min before (**R**)-α-methylhistamine (300 μg kg^{-1}). In a separate set of experiments, impromidine (0.1–1.0 mg kg^{-1}), burimamide (3–30 mg kg^{-1}) and thioperamide (0.1–3.0 mg kg^{-1}) were evaluated against a single dose of (**R**)-α-methylhistamine (300 μg kg^{-1}) to determine the relative potency of H_3-antagonist activity. From these results, the ID_{50} (the dose causing a 50% blockade of the effect of (**R**)-α-methylhistamine) was calculated for each H_3-antagonist.

Drugs used

Gallamine triethiodide, α-chloralose, chlorpheniramine maleate, cimetidine, ipratropium bromide and (−)-adrenaline bitartrate were purchased from Sigma Chemical Co. (St. Louis, MO. U.S.A.). (**R**)-α-methylhistamine hydrochloride, burimamide and thioperamide were synthesized at Schering-Plough Research (Bloomfield, NJ, U.S.A.). Impromidine was a gift from Smith-Kline-Beecham (King of Prussia, PA, U.S.A.). Thioperamide was dissolved in DMSO. All other drugs were dissolved in 0.9% v/v saline. Doses were calculated as their free base.

Statistics

The statistical evaluation of the results was performed by one-way analysis of variance (ANOVA) and Student's *t* test for paired and unpaired comparisons; $P<0.05$ was considered statistically significant.

Results

Baseline BP and HR in ipratropium-treated guinea-pigs were 54 ± 5 mmHg and 302 ± 7 beats min^{-1}, respectively. Bilateral electrical stimulation of regions within the medulla oblongata evoked intensity-dependent increases in both BP and HR (Figure 1). The responses to CNS stimulation were near maximal at 100 μA, as higher intensities did not yield larger increases in BP or HR. Repeated stimulation intensity response curves could be generated in the same animal without dimunition or augmentation of the hypertensive or tachycardia responses (data not shown). Treatment with (**R**)-α-methylhistamine (300 μg kg^{-1}, i.v.) caused decreases in baseline BP (12 ± 2 mmHg) and HR (34 ± 2 beats min^{-1}) ($n = 4$). (**R**)-α-methylhistamine (300 μg kg^{-1}, i.v.) attenuated the CNS-induced hypertensive and tachycardia responses between 25–100 μA as indicated by a shift in the stimulus intensity-response curves (Figure 1). At higher stimulus intensities such as 400 μA, (**R**)-α-methylhistamine did not inhibit these cardiovascular responses (Figure 1). In these studies, the changes in BP were consistent and reproducible, while the changes in HR were more variable, so we focused on changes in BP as a measure of H_3-modulation of the neurogenic responses.

The dose-dependent inhibition of CNS-induced hypertension by (**R**)-α-methylhistamine (10–300 μg kg^{-1}, i.v.) was studied at 75 μA (Figure 2), which was submaximal but produced consistent changes in BP. To avoid the develop-

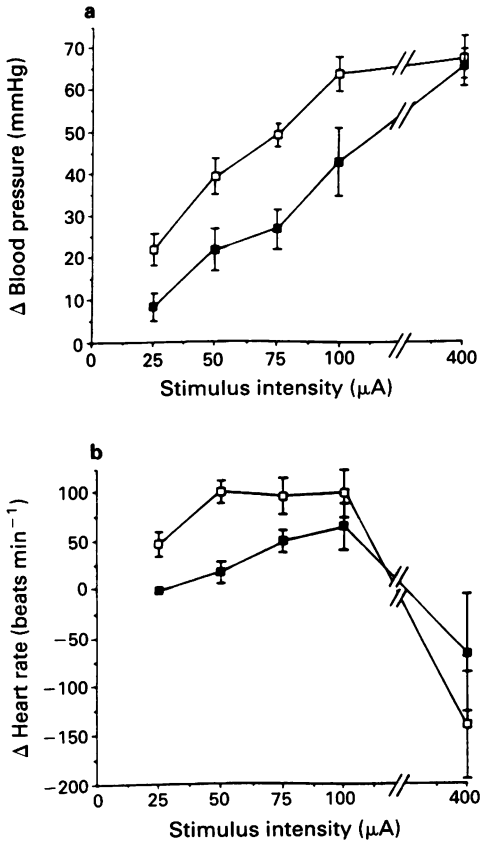

Figure 1 (a) Hypertensive and (b) tachycardia responses to CNS stimulation in the absence and presence of (**R**)-α-methylhistamine. Responses in (**R**)-α-methylhistamine (300 μg kg^{-1}, i.v.)-treated animals (●) were significantly ($P<0.05$) less than in control animals (○) that received only the CNS stimulation. Values represent the mean (± s.e.mean shown by vertical bars) ($n = 4$) increase in blood pressure and heart rate due to CNS stimulation.

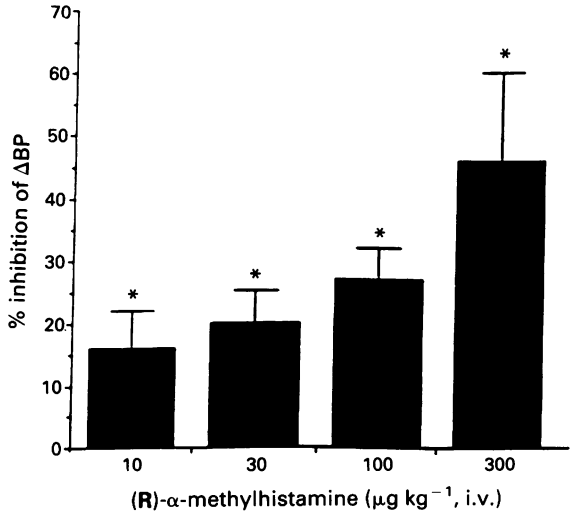

Figure 2 Dose-dependent inhibitory effects of (R)-α-methylhistamine on CNS-induced hypertension. The graph shows responses (ΔBP) at a stimulus intensity of 75 μA. Values are the mean (± s.e.mean shown by vertical bars) ($n = 4-7$).

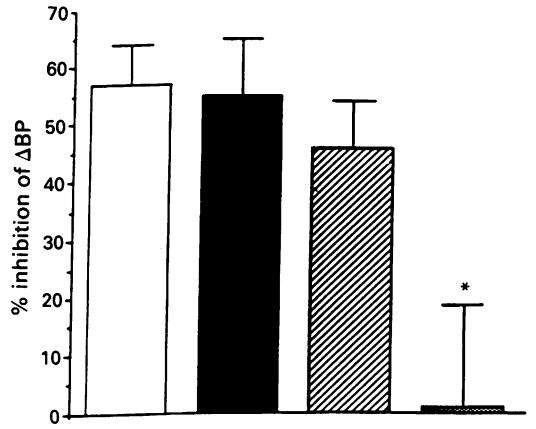

Figure 3 Effects of histamine H_1-, H_2- and H_3-antagonists on the inhibition of CNS-induced hypertension by (R)-α-methylhistamine. The graph illustrates the effect on blood pressure (ΔBP) of (R)-α-methylhistamine (300 μg kg^{-1}, i.v.) given alone (open column), or in the presence of chlorpheniramine (30 μg kg^{-1}; solid column), cimetidine (3 mg kg^{-1}; hatched column), or thioperamide (3 mg kg^{-1}; stippled column). The stimulus-intensity was 75 μA. *$P < 0.05$ compared to (R)-α-methylhistamine alone. Values represent the mean (± s.e.mean shown by vertical bars) ($n = 4$).

ment of tachyphylaxis, each animal received a single dose of (R)-α-methylhistamine. Under these conditions, 300 μg kg^{-1} of (R)-α-methylhistamine produced a maximal inhibition of 48 ± 10%. Higher doses of (R)-α-methylhistamine could not be tested, because they cause histamine H_1-receptor-mediated responses (Hey *et al.*, 1992). The ED_{50} (dose producing 50% of maximal inhibition) for (R)-α-methylhistamine was 100 μg kg^{-1}, i.v. To determine whether the action of (R)-α-methylhistamine was prejunctional or postjunctional, we studied its effect on the hypertensive response to intravenous adrenaline. There was no difference in the magnitude of the hypertensive responses to (−)-adrenaline (1 and 3 μg kg^{-1}) between saline-treated (ΔBP = 21 ± 2 and 71 ± 4 mmHg) and (R)-α-methylhistamine-treated (300 μg kg^{-1}; ΔBP = 22 ± 5 and 73 ± 4, respectively) animals ($n = 3-6$), indicating a prejunctional site of action for (R)-α-methylhistamine.

The selective H_3-antagonist, thioperamide (3 mg kg^{-1}, i.v.), blocked the inhibitory effect of (R)-α-methylhistamine on CNS-induced hypertension (Figure 3). In contrast, chlorpheniramine (30 μg kg^{-1}) and cimetidine (3 mg kg^{-1}), at doses that block H_1- and H_2-receptor mediated responses, did not block the action of (R)-α-methylhistamine.

To determine a rank order potency of the H_3-antagonists, thioperamide, impromidine and burimamide, were given before a single dose of (R)-α-methylhistamine (300 μg kg^{-1}, i.v.) (Figure 4). Impromidine (ID_{50} = 0.22 mg kg^{-1}, i.v.) and thioperamide (ID_{50} = 0.39 mg kg^{-1}, i.v.) were essentially equipotent in blocking the inhibitory effects of (R)-α-methylhistamine. Burimamide (ID_{50} = 6 mg kg^{-1}, i.v.) was 15 fold weaker than impromidine or thioperamide.

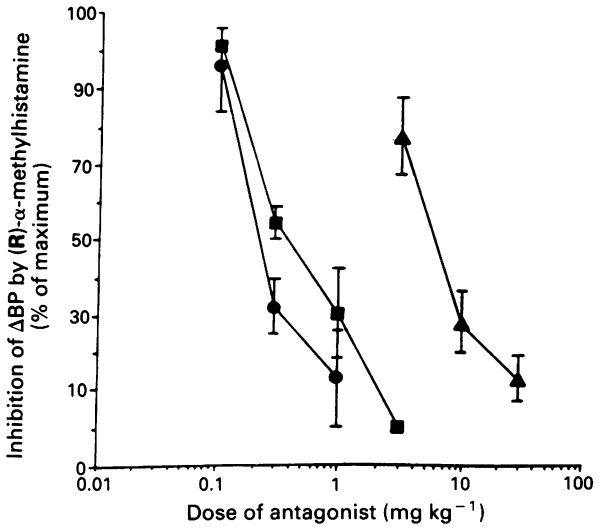

Figure 4 Potencies of H_3-antagonists on (R)-α-methylhistamine inhibition of CNS-induced hypertension. The graph shows the response to (R)-α-methylhistamine (300 μg kg^{-1}, i.v.) in the presence of increasing doses of impromidine (●), thioperamide (■) and burimamide (▲). The values represent the mean (± s.e.mean shown by vertical bars) ($n = 4-5$) percentage maximum inhibition of CNS-induced hypertension. Maximum inhibition produced by 300 μg kg^{-1} of (R)-α-methylhistamine was 47 ± 12%.

Discussion

The present study demonstrates that activation of prejunctional H_3-receptors, with the selective H_3-agonist, (R)-α-methylhistamine, produces an inhibition of centrally-evoked hypertension and tachycardia in guinea-pigs. The inhibition by (R)-α-methylhistamine of CNS-induced hypertension is dose-related and dependent upon the stimulus intensity. Furthermore, the effect of (R)-α-methylhistamine is blocked by pretreatment with H_3-antagonists. These results are consistent with the findings of Ishikawa & Sperelakis (1987) who showed that activation of prejunctional perivascular H_3-receptors inhibits sympathetic neurotransmission. Other investigators have recently shown that (R)-α-methylhistamine inhibits the release of noradrenaline from postganglionic sympathetic nerves in pigs and in guinea-pigs (Schlicker *et al.*, 1990; Luo *et al.*, 1991; Malinowska & Schlicker, 1991). Our studies build upon the growing body of work that establishes that the H_3-receptor is an important prejunctional inhibitory modulator both in the CNS (Schwartz *et al.*, 1986; 1991; Arrang *et al.*, 1983; 1988) and in the periphery (Ichinose *et al.*, 1990).

The sympathetically driven hypertensive responses that are elicited by activation of structures within the dorsal medulla have been well characterized in cats (Alexander, 1949; Chai & Wang, 1968), rabbits (Goodchild & Dampney, 1985) and, more recently, in guinea-pigs (Hey *et al.*, 1990b). These hypertensive events are mediated by activation of bulbospinal

sympathetic pathways as they are blocked with α-adrenoceptor antagonists, ganglionic blockers such as hexamethonium and spinal cord transection with lignocaine (Hey *et al.*, 1990b). Our results in guinea-pigs indicate that (**R**)-α-methylhistamine inhibits the hypertension produced by electrical stimulation of the dorsal medulla (Hey *et al.*, 1992) and that the effects of (**R**)-α-methylhistamine are not blocked by H_1- or H_2-receptor antagonists. On the other hand, thioperamide, which is a selective H_3-antagonist (Arrang *et al.*, 1987) blocks the effect of (**R**)-α-methylhistamine, implicating the H_3-receptor. Additional dose-response studies with the H_3-antagonists, thioperamide, impromidine and burimamide reveal an antagonist potency profile that is consistent with an H_{3B}-receptor subtype (West *et al.*, 1990) mediating responses on vascular sympathetic neurotransmission. It should be noted, however, that these *in vivo* findings may also reflect a possible uneven tissue distribution and/or metabolism of these antagonists. Nevertheless, these conclusions are consistent with those of West *et al.* (1990) that the guinea-pig mesenteric artery contains the H_{3B} receptor.

In a recent study in rats, Malinowska & Schlicker (1991) found that (**R**)-α-methylhistamine inhibited the pressor response to sympathetic nerve stimulation. The results from our study confirm and extend these findings. We demonstrate an inhibitory effect of (**R**)-α-methylhistamine on sympathetically-driven hypertension in guinea-pigs. This species is highly responsive to (**R**)-α-methylhistamine (Trzeciakowski, 1987; Ichinose *et al.*, 1989; 1990; Menkveld & Timmerman, 1990; Coruzzi *et al.*, 1991) including inhibitory effects on sympathetic neurotransmission in perivascular nerves (Ishikawa & Sperelakis, 1987). However, the H_3-mediated effects on blood pressure responses *in vivo* have not been previously shown in the guinea-pig. Furthermore, although an inhibitory effect of (**R**)-α-methylhistamine on electrically-stimulated contractile responses in the guinea-pig isolated myocardium has been reported (Luo *et al.*, 1991), this is the first report describing an inhibitory effect of (**R**)-α-methylhistamine on neurally stimulated tachycardia *in vivo*. Finally, Malinowska & Schlicker (1991) used only thioperamide to characterize the H_3-effects of (**R**)-α-methylhistamine. In our study, we have used thioperamide, impromidine and burimamide to characterize this more fully as an H_{3B}-receptor-mediated response.

(**R**)-α-methylhistamine appears to inhibit the CNS-induced hypertension by a prejunctional mechanism on sympathetic nerves. The fact that the inhibitory effect of (**R**)-α-methylhistamine is dependent on the stimulus intensity and is less at supramaximal intensities is consistent with a prejunctional site of action (Starke, 1987; van der Vliet *et al.*, 1990). This had been demonstrated by other peripherally acting prejunctional inhibitory modulators such as α_2-adrenoceptor agonists and $GABA_B$ receptor agonist (Armstrong & Boura, 1973; Doxey *et al.*, 1977; Kohlenbach & Schlicker, 1990). Further evidence that (**R**)-α-methylhistamine acts prejunctionally comes from the studies of Ishikawa & Sperelakis (1987), who demonstrated an inhibition by H_3-receptor activation of postganglionic sympathetic perivascular nerve terminals in guinea-pigs. Histamine H_3-receptor activation also depresses ganglionic neurotransmission (Tamura *et al.*, 1988), so we cannot rule out a possible ganglionic component. On the other hand, there is no evidence to support the notion that (**R**)-α-methylhistamine inhibits sympathetic outflow to vascular nerves at the level of the CNS (McLeod *et al.*, 1991) and it is unlikely that (**R**)-α-methylhistamine acts postjunctionally on smooth muscle because it did not inhibit pressor responses to i.v. adrenaline. The finding that (**R**)-α-methylhistamine lowered basal blood pressure and heart rate without causing the reflex tachycardia also suggests an effect on vascular sympathetic nerves rather than dilatation of vascular smooth muscle. Furthermore, the fact that our studies were performed in the presence of ipratropium bromide to block peripheral muscarinic receptors also rules out the possibility that bradycardia and hypotensive effects of (**R**)-α-methylhistamine were the result of activation of vagal output from the CNS (McLeod *et al.*, 1991).

In summary, our findings indicate that (**R**)-α-methylhistamine inhibits sympathetic hypertensive responses in guinea-pigs by activation of prejunctional H_3-receptors, possibly located on postganglionic nerve terminals. Furthermore, our results suggest that the H_{3B}-receptor subtype is involved with H_3-receptor responses on vascular sympathetic nerves. It is speculated that activation of the prejunctional H_3-receptor in allergic reactions may contribute to local vascular engorgement by inhibiting sympathetic vasoconstrictor tone to the affected vascular bed.

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