Production by R- α -methylhistamine of a histamine H₃ receptor-mediated decrease in basal vascular resistance in guinea-pigs

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1 The effect of the selective histamine H₃ receptor agonist, R- α -methylhistamine given intravenously (10–100 $\mu\text{g kg}^{-1}$) was examined on baseline total peripheral resistance (TPR), and cardiovascular haemodynamics in bilaterally vagotomized, anaesthetized guinea-pigs.

2 R- α -methylhistamine produced a dose-dependent hypotension and fall in TPR at 30 and 100 $\mu\text{g kg}^{-1}$. A decrease in heart rate (HR) was observed at a dose of 100 $\mu\text{g kg}^{-1}$. R- α -methylhistamine (10–100 $\mu\text{g kg}^{-1}$) also produced a dose-dependent fall in rate pressure product (RPP). There was no effect on cardiac output (CO) or stroke volume (SV) at these doses.

3 Histamine H₁ and H₂ blockade in animals pretreated with a combination of chlorpheniramine (0.3 mg kg⁻¹) and cimetidine (3.0 mg kg⁻¹) did not alter the haemodynamic actions of R- α -methylhistamine (100 $\mu\text{g kg}^{-1}$, i.v.). Pretreatment with the selective H₃ antagonist, thioperamide (1 mg kg⁻¹), completely blocked the action of R- α -methylhistamine on haemodynamic parameters.

4 To study the mechanism of action of R- α -methylhistamine, the vasodilator hydralazine (1 mg kg⁻¹, i.v.) was used. Hydralazine lowered BP, TRP and RPP in guinea-pigs pretreated with ipratropium (50 $\mu\text{g kg}^{-1}$, i.v.). Hydralazine had no effect on HR, SV or CO.

5 R- α -methylhistamine (100 $\mu\text{g kg}^{-1}$) did not affect the vasopressor action and increases in TPR produced by adrenaline (1 and 3 $\mu\text{g kg}^{-1}$). On the other hand, the vasodilator hydralazine (1 mg kg⁻¹, i.v.) inhibited the effects of adrenaline (3 $\mu\text{g kg}^{-1}$) on TPR and RPP. The effect of both doses of adrenaline on BP were attenuated by hydralazine. Therefore, the inhibitory effects of R- α -methylhistamine are not mediated through a direct action on vascular smooth muscle.

6 In adrenalectomized guinea-pigs, R- α -methylhistamine (100 $\mu\text{g kg}^{-1}$) produced a drop in BP and HR. There was no difference between the effects of R- α -methylhistamine on blood pressure and heart rate in adrenalectomized and non-adrenalectomized guinea-pigs.

7 These results show that activation of peripheral H₃ receptors lowers basal BP, HR and TPR, most likely by a peripheral prejunctional mechanism. The fall in BP and TPR is probably due to a decrease in noradrenaline release from sympathetic effector nerves innervating the resistance blood vessels.

Keywords: Histamine H₃ receptors; R- α -methylhistamine; haemodynamics; cardiac output; total peripheral resistance; presynaptic inhibition; sympathetic neurotransmission; adrenalectomy; thioperamide

Introduction

Histamine is an ubiquitous biogenic amine that affects a diverse array of physiological and behavioural responses in animals and man. The majority of the peripheral and central effects of histamine on cardiovascular function have been classically associated with histamine (H₁) and/or histamine (H₂) receptor stimulation (Klein & Gertner, 1981; Satoh & Inuli, 1984; Toda, 1986; Tsuru *et al.*, 1987; Poulakos & Gertner, 1989). A third histamine receptor (H₃) has been identified by Arrang *et al.* (1983, 1985) on presynaptic histaminergic nerve terminals within the brain. This receptor has been shown to be pharmacologically distinct from H₁ and H₂ receptors. Activation of H₃ receptors inhibits histamine release and synthesis from histaminergic neurones (Arrang *et al.*, 1988; Timmerman *et al.*, 1990). Furthermore, stimulation of central H₃ receptors has also been shown to inhibit the release of other CNS neurotransmitters such as 5-hydroxytryptamine (Schlicker *et al.*, 1988) and more recently acetylcholine (Clapham & Kilpatrick, 1992). In the peripheral autonomic system, Ishikawa & Sperelakis (1987) showed H₃ receptor activation depresses sympathetic extrajunctional potentials by a prejunctional mechanism.

The introduction of two pharmacological tools (Arrang *et al.*, 1987), R- α -methylhistamine, a selective H₃ chiral agonist,

and thioperamide, a competitive H₃ antagonist, has made it possible to explore the physiological role of H₃ receptors in central and peripheral cardiovascular regulation. Recent studies have shown that H₃ receptor activation in the CNS elicits responses that are different from those resulting from activation of peripheral H₃ receptors. For example, intracerebroventricular injections of R- α -methylhistamine given to conscious guinea-pigs produce an increase in vagal tone resulting in a bradycardia and hypotension (McLeod *et al.*, 1991). However, in the periphery, i.v. R- α -methylhistamine produced a dose-dependent depression of electrically induced sympathetic adrenergically mediated responses in the cat (Koss & Hey, 1992), rat (Malinowska & Schlicker, 1991) and the guinea-pig (Hey *et al.*, 1992a). In all of the above mentioned studies the effects of R- α -methylhistamine were reversed by the H₃ antagonist, thioperamide, but not by the H₂ antagonist, cimetidine or by the H₁ antagonist, chlorpheniramine. Further confirmation of these findings has been provided by *in vitro* studies showing that H₃ activation by R- α -methylhistamine produced a dose-dependent prejunctional inhibition of the sympathetic inotropic responses to electrical stimulation in guinea-pig isolated atria (Lou *et al.*, 1991).

To date, studies examining the role of the H₃ receptors on autonomic cardiovascular function have done so in electrically driven systems. The purpose of the present study was to investigate the role of H₃ receptors in the regulation of basal

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cardiovascular function and characterize the haemodynamic consequences of H_3 activation in the anaesthetized guinea-pig.

Methods

Animal preparation

Male Hartley guinea-pigs (425–600 g, Charles River, Bloomington, MA, U.S.A.) were anaesthetized with α -chloralose (125 mg kg⁻¹, i.p.). The left common carotid artery and the right jugular vein were cannulated with PE-50 tubing for measurement of blood pressure and i.v. administration of drugs. Both the left and right vagus were cut at the cervical level to eliminate vagal contribution to the heart. A catheter (PE-200) was placed in the trachea and animals were mechanically-ventilated ($v = 4$ ml, $f = 45$ breaths min⁻¹) with room air using a rodent respirator. Since the chest was open, animals were paralyzed with gallamine triethiodide (2 mg kg⁻¹, i.v.). Blood pressure and heart rates were derived from the arterial pulse pressure connected to a pressure transducer. Physiological parameters were recorded on a Hewlett Packard polygraph. Adrenalectomized male guinea-pigs (400–500 g) were obtained from Charles River, Bloomington, MA, U.S.A.

Determination of cardiac output

The animal was placed in a left lateral recumbent position. The chest was shaved and cleaned with 70% ethanol. The muscles of the chest were blunt dissected away to reveal the intercostal tissue. A thoracotomy was performed by making an incision through the third right intercostal space. The ribs were retracted and the lung gently pushed aside. The ascending aorta was dissected free and a perivascular 3S transonic flow probe (Transonic Systems Inc., Ithaca, NY, U.S.A.) was placed around the vessel. The signal from the transonic flow probe was directed into a small animal blood flow meter (Model T206, Transonic Systems Inc.). Cardiac output tracing was recorded on a polygraph.

Pharmacological studies

To study the dose-response characteristics of R - α -methylhistamine, blood pressure (BP), heart rate (HR), cardiac output (CO), total peripheral resistance (TPR), stroke volume (SV) and rate pressure product (RPP = systolic blood pressure $\times$ heart rate) were measured. The rate pressure product (RPP) is an index of myocardial oxygen demand (Holmberg *et al.*, 1971; Kitamura *et al.*, 1972; Foltin & Fischman, 1992). The effects of R - α -methylhistamine (10–100 μ g kg⁻¹, i.v.) on these haemodynamic parameters were determined ($n = 8$ –10 animals per group) for a period from 10 min before the drug until 30 min post-drug administration.

To determine the specific histamine receptor type involved in the haemodynamic responses to R - α -methylhistamine, these effects were evaluated in the presence of either thioperamide (1.0 mg kg⁻¹, i.v.), or a combination of cimetidine (3.0 mg kg⁻¹, i.v.) and chlorpheniramine (0.3 mg kg⁻¹, i.v.). In each experiment R - α -methylhistamine (100 μ g kg⁻¹, i.v.) was administered 10 min after the pretreatment drug ($n = 4$ –9 animals per group).

The haemodynamic effects of R - α -methylhistamine (100 μ g kg⁻¹, i.v.) were compared to the effects of the direct vasodilator, hydralazine (1 mg kg⁻¹, i.v.) in intact guinea-pigs. Animals were pretreated with ipratropium (50 μ g kg⁻¹, i.v.) to block parasympathetic effects on the heart. Animals were then given vehicle, R - α -methylhistamine or hydralazine. The dose of hydralazine chosen (1 mg kg⁻¹) produced a fall in BP similar to that produced by R - α -methylhistamine (100 μ g kg⁻¹).

To determine whether a direct vascular smooth muscle

action contributes to the effects of R - α -methylhistamine (100 μ g kg⁻¹, i.v.), the vasopressor and haemodynamic effects of adrenaline (1 and 3 μ g kg⁻¹, i.v.) were evaluated before and 5 min after treatment with the direct vasodilator, hydralazine (1 mg kg⁻¹, i.v.) or R - α -methylhistamine (100 μ g kg⁻¹, i.v.).

The possible relationship between adrenal catecholamines and the cardiovascular actions of i.v. R - α -methylhistamine was also studied. R - α -methylhistamine was given to adrenalectomized bilaterally vagotomized, anaesthetized guinea-pigs. The effects of R - α -methylhistamine on TPR and cardiovascular haemodynamics were compared with its effects in non-adrenalectomized guinea-pigs.

Drugs

α -Chloralose, hydralazine, chlorpheniramine maleate, cimetidine and ipratropium bromide were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). R - α -methylhistamine and thioperamide maleate was purchased from Research Biochemical Incorporated (Natick, MA, U.S.A.). Cimetidine was dissolved in a 5% dextrose, 5% glycol and water (w/v solution). All other drugs were dissolved in physiological saline (0.9%). Drug doses refer to their respective free base.

Statistics

Mean arterial blood pressure was mathematically derived from the arterial pulse pressure using the relationship pulse pressure divided by three plus diastolic blood pressure. TPR and SV were calculated from the equations [BP/CO] and [CO/HR] respectively. Values represent the mean $\pm$ s.e.mean. Statistical significance was evaluated by a one way analysis of variance (ANOVA) in conjunction with Dunnett's two tailed t test. Statistical significance was set at $P < 0.05$.

Results

Figure 1 illustrates the hypotensive actions of R - α -methylhistamine (10–100 μ g kg⁻¹, i.v.) in anaesthetized guinea-pigs. The maximum hypotensive effect of R - α -methylhistamine was observed at 5 min. Only the highest dose of R - α -methylhistamine (100 μ g kg⁻¹) produced a significant bradycardia. Baseline haemodynamic values for the R - α -methylhistamine-treated (10–100 μ g kg⁻¹) groups were not different from the vehicle group. Baseline (BP) values were 40 ± 2 mmHg for the saline group and 43 ± 4 , 42 ± 2 and 39 ± 5 for animals given R - α -methylhistamine (10, 30 and 100 μ g kg⁻¹, i.v.) respectively. Baseline (HR) values were 245 ± 8 , 242 ± 6 , 245 ± 8 and 231 ± 10 beats min⁻¹ for vehicle and R - α -methylhistamine groups (10, 30 and 100 μ g kg⁻¹) respectively. Total peripheral resistance (TPR) was decreased at 30 and 100 μ g kg⁻¹ of R - α -methylhistamine (Figure 1). TPR baseline values for the control group were 0.88 ± 0.06 mmHg min⁻¹ ml⁻¹. R - α -methylhistamine (10–100 μ g kg⁻¹) baseline TPR values were 0.78 ± 0.08 , 0.88 ± 0.09 and 1.2 ± 0.02 . Rate pressure product (RPP) was decreased with all doses of R - α -methylhistamine. R - α -methylhistamine however, did not alter cardiac output (CO) or stroke volume (SV) in these animals (Table 1).

The histamine H_3 antagonist, thioperamide (1 mg kg⁻¹, i.v.), antagonized the actions of R - α -methylhistamine (100 μ g kg⁻¹) on BP, HR, TPR and RPP (Figure 2). These values were not different from animals given saline vehicle. The combination of histamine H_1 and H_2 receptor blockade with cimetidine (3.0 mg kg⁻¹) and chlorpheniramine (0.3 mg kg⁻¹) did not alter the haemodynamic actions of R - α -methylhistamine (100 μ g kg⁻¹). The BP, HR, TPR and RPP effects of R - α -methylhistamine in the presence of H_1 and H_2 blockade and in animals given R - α -methylhistamine were not different from each other. Both of these groups however, were different from the saline group.

Figure 3 illustrates the effects of R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$) and hydralazine (1 mg kg^{-1} , i.v.) on BP, HR, TPR and RPP in intact guinea-pigs pretreated with the muscarinic antagonist, ipratropium ($50 \mu\text{g kg}^{-1}$, i.v.). Ipratropium was used in these studies to allow cardiovascular reflexes to remain intact. The response to i.v. R- α -methylhistamine in the ipratropium-treated group was identical to the response obtained in vagotomized animals. This dose of ipratropium has been shown to block vagal input to the heart (McLeod *et al.*, 1991). Baseline haemodynamic values between the groups were not different (data not shown). Both R- α -methylhistamine and hydralazine produced similar falls in BP, TPR and RPP. Only R- α -methylhistamine lowered HR. Neither drug altered CO or SV. Table 2 shows that R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$) had no effect on the haemodynamic actions of exogenous adrenaline (1 and $3 \mu\text{g kg}^{-1}$, i.v.). Hydralazine (1 mg kg^{-1} , i.v.)-attenuated the effects of adrenaline on BP, TPR and RPP.

In the adrenalectomized guinea-pig, R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.) lowered BP, TPR, HR and RPP (Figure

Figure 1 Figure illustrating dose-dependent inhibitory effect of R- α -methylhistamine on cardiovascular haemodynamic parameters. The effects (Δ BP, Δ TPR, Δ HR and Δ RPP) of R- α -methylhistamine (10 – $100 \mu\text{g kg}^{-1}$, i.v.) are shown at 5 min. Each column represents the mean $\pm$ s.e. mean ($n = 8$ – 10 per group). The data were analyzed by one-way ANOVA in conjunction with Dunnett's *t* test. * $P < 0.05$ compared to saline vehicle.

Figure 2 Haemodynamic effects of R- α -methylhistamine in the presence of H₁, H₂ and H₃ blockade. Figure displays the Δ BP, Δ TPR, Δ HR and Δ RPP responses of i.v. saline vehicle ($\circ$, $n = 20$), R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v., $n = 9$) given alone ($\bullet$), R- α -methylhistamine in animals pretreated with thioperamide (1 mg kg^{-1} , i.v.; $\blacksquare$, $n = 4$) or in animals pretreated with a combination of chlorpheniramine (0.3 mg kg^{-1} , i.v.) and cimetidine (3.0 mg kg^{-1} ; $\square$, $n = 6$). R- α -methylhistamine alone and in animals pretreated with a combination of cimetidine and chlorpheniramine lowered BP, TPR, HR and RPP compared to saline vehicle and the thioperamide pretreated group. Haemodynamic values of animals pretreated with thioperamide were not different from the saline control group. Each point represents the mean $\pm$ s.e. mean. The data were analyzed by one-way ANOVA in conjunction with Dunnett's *t* test; statistical significance was set at $P < 0.05$.

4). There was no difference in the haemodynamic effects of R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.) in adrenalectomized and non-adrenalectomized guinea-pigs. Baseline haemodynamic values for adrenalectomized and non-adrenalectomized guinea-pigs were not different. Baseline BP values were $37 \pm 2 \text{ mmHg}$ for adrenalectomized guinea-pigs and $43 \pm 2 \text{ mmHg}$ for non-adrenalectomized animals given R- α -methylhistamine. Basal HR and TPR were $245 \pm 10 \text{ beats min}^{-1}$ and $1.03 \pm 0.06 \text{ ml min}^{-1} \text{ mmHg}^{-1}$ for adrenalectomized guinea-pigs, and $246 \pm 13 \text{ beats min}^{-1}$ and $0.95 \pm 0.10 \text{ ml min}^{-1} \text{ mmHg}^{-1}$ for non-adrenalectomized guinea-pigs.

Table 1 Effect of R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.) on cardiac output and stroke volume

	Baseline	Δ Cardiac output (ml min^{-1})		
		3 min	5 min	15 min
Vehicle	44.0 ± 1.8	-0.5 ± 0.4	-1.9 ± 0.7	-2.7 ± 0.8
R- α -methylhistamine	40.8 ± 4.6	-3.8 ± 1.3	-2.7 ± 1.1	-4.4 ± 1.8
	Baseline	Δ Stroke volume (ml beat^{-1})		
		3 min	5 min	15 min
Vehicle	0.19 ± 0.01	-0.01 ± 0.004	-0.01 ± 0.004	-0.02 ± 0.01
R- α -methylhistamine	0.18 ± 0.02	-0.01 ± 0.01	-0.00 ± 0.01	-0.01 ± 0.01

Figure 3 Comparative profile of haemodynamic effects of R- α -methylhistamine and hydralazine. Figure displays the Δ BP, Δ TPR, Δ HR and Δ RPP responses of saline vehicle ($\circ$), R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v., $\bullet$) and hydralazine (1.0 mg kg^{-1} , i.v.; $\square$) in intact guinea-pigs pretreated with the muscarinic antagonist, ipratropium ($50 \mu\text{g kg}^{-1}$, i.v.). Both R- α -methylhistamine and hydralazine lowered BP, TPR and RPP compared to the saline group. Note that only R- α -methylhistamine lowered HR. Each point represents the mean $\pm$ s.e.mean ($n = 6-8$ per group). The data were analysed by one-way ANOVA in conjunction with Dunnett's t test; statistical significance was set at $P < 0.05$.

Figure 4 Haemodynamic effects of R- α -methylhistamine in the adrenalectomized guinea-pig. Figure displays the Δ BP, Δ TPR, Δ HR and Δ RPP responses of i.v. saline vehicle ($\circ$), R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.; $\bullet$) in adrenalectomized guinea-pigs and R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.; $\square$) in non-adrenalectomized guinea pigs. R- α -methylhistamine lowered BP, TPR, HR and RPP in both non-adrenalectomized and adrenalectomized guinea pigs. There was no difference in the haemodynamic responses to R- α -methylhistamine between these two groups. Each point represents the mean $\pm$ s.e.mean ($n = 6-8$ per group). The data were analyzed by one-way ANOVA in conjunction with Dunnett's t test; statistical significance was set at $P < 0.05$.

Table 2 Effect of adrenaline before and after treatment with R- α -methylhistamine ($100 \mu\text{g kg}^{-1}$, i.v.) and hydralazine (1 mg kg^{-1} , i.v.)

	Adrenaline $1 \mu\text{g kg}$		Adrenaline $3 \mu\text{g kg}$	
	Δ mean blood pressure (mmHg)		Δ mean blood pressure (mmHg)	
Saline	Before	After	Before	After
R- α -methylhistamine	28 ± 5	30 ± 3	46 ± 6	44 ± 5
Hydralazine	33 ± 6	28 ± 2	47 ± 5	54 ± 4
	25 ± 4	$13 \pm 3^*$	44 ± 2	$24 \pm 4^*$
	Δ TPR ($\text{mmHg ml}^{-1} \text{ min}^{-1}$)		Δ TPR ($\text{mmHg ml}^{-1} \text{ min}^{-1}$)	
Saline	Before	After	Before	After
R- α -methylhistamine	0.58 ± 0.20	0.67 ± 0.11	0.91 ± 0.18	1.12 ± 0.28
Hydralazine	0.59 ± 0.19	0.54 ± 0.09	0.65 ± 0.17	1.00 ± 0.05
	0.63 ± 0.18	0.33 ± 0.09	1.02 ± 0.22	$0.47 \pm 0.06^*$
	Δ heart rate (beats min^{-1})		Δ heart rate (beats min^{-1})	
Saline	Before	After	Before	After
R- α -methylhistamine	29 ± 11	16 ± 9	34 ± 16	33 ± 14
Hydralazine	22 ± 6	20 ± 4	28 ± 7	16 ± 7
	15 ± 7	12 ± 5	23 ± 7	18 ± 5
	Δ RPP ($\text{beats min}^{-1} \text{ mmHg}^{-1}$)		Δ RPP ($\text{beats min}^{-1} \text{ mmHg}^{-1}$)	
Saline	Before	After	Before	After
R- α -methylhistamine	10134 ± 1687	8813 ± 1614	18890 ± 3563	13521 ± 2021
Hydralazine	10605 ± 1520	9040 ± 1082	16660 ± 2649	16435 ± 1684
	6233 ± 1228	3433 ± 1029	12425 ± 1286	$6054 \pm 1311^*$

TPR: total peripheral resistance. RPP: rate pressure product.

* $P < 0.05$.

Discussion

The present study indicates that prejunctional H₃ activation with i.v. R- α -methylhistamine produces a decrease in mean basal blood pressure and heart rate. This fall in mean blood pressure is probably the result of a decrease in sympathetic tone to resistance vessels. This is based on the finding that R- α -methylhistamine produced a fall in total peripheral resistance without a fall in cardiac output. These vascular effects are not likely to be the result of direct smooth muscle dilatation because R- α -methylhistamine does not reverse the cardiopressor effects of a direct agonist, adrenaline (Hey *et al.*, 1992a). We have presented findings that R- α -methylhistamine does not alter the effects of adrenaline on vascular resistance and cardiovascular haemodynamics. In contrast, the vasodilator, hydralazine, inhibited the vasopressor actions of adrenaline indicating that these two drugs lowered blood pressure by different mechanisms.

It has been proposed that activation of preganglionic H₃ receptors inhibits ganglionic neurotransmission (Tamura *et al.*, 1988; Christian & Weinreich, 1992). Thus the inhibitory effect on the cardiovascular system may be due in part to inhibition of adrenal catecholamines. In adrenalectomized guinea-pigs however, the haemodynamic profile of R- α -methylhistamine is not different from that in non-adrenalectomized guinea-pigs. The results from the present study, therefore do not rule out the possibility that part of the action of R- α -methylhistamine may involve an inhibitory effect on sympathetic ganglionic neurotransmission. The present findings are consistent with studies by Koss & Hey (1992) who showed that R- α -methylhistamine acts at post-ganglionic prejunctional H₃ receptors.

R- α -methylhistamine has been shown to cross the blood brain barrier (Garbarg *et al.*, 1989; Oishi *et al.*, 1989). Furthermore, we have demonstrated that i.c.v. R- α -methylhistamine elicits bradycardia and hypotension by activation of CNS vagal pathways (McLeod *et al.*, 1991). However, in the current study, it is unlikely that vagal enhancement due to central H₃ activation is involved in the bradycardic and hypotensive effects of i.v. R- α -methylhistamine because both vagi were cut at the cervical level to inhibit parasympathetic effects on the heart. The present findings show that R- α -methylhistamine lowered basal heart rate and vascular resistance by activation of peripheral prejunctional H₃ receptors.

R- α -methylhistamine also has H₁ agonist properties at doses greater than 0.3 mg kg⁻¹, i.v. (Hey *et al.*, 1992b). The dose of R- α -methylhistamine used in this study is below the

threshold dose that has been demonstrated to produce H₁ effects in the anaesthetized guinea-pig. Additional proof that the inhibitory actions of R- α -methylhistamine are solely mediated through H₃ receptors is provided by the observation that only thioperamide, a selective H₃ antagonist with negligible effect on H₁ and H₂ receptors, blocked the haemodynamic actions of R- α -methylhistamine. Blockade of H₁ and H₂ receptors did not alter the haemodynamic actions of R- α -methylhistamine indicating a lack of H₁ or H₂ involvement. Furthermore, it is not likely that histamine H₁ receptors play a role in the inhibitory actions of R- α -methylhistamine because it has been shown that H₁ receptor activation elicits a stimulatory action on ganglionic sympathetic neural traffic that is not observed in our studies (Christian *et al.*, 1989; Christian & Weinreich, 1992).

Evidence is emerging to suggest important species variations in the pharmacological responses to H₃ activation. In the present study R- α -methylhistamine had prominent effects on basal cardiovascular function of the guinea-pig. In contrast, in the rat i.v. R- α -methylhistamine does not lower basal BP and HR with doses as high as 10 mg kg⁻¹ i.v. (unpublished observations). However in an electrically driven system, R- α -methylhistamine inhibits neurogenically induced hypertensive responses in the pithed rat (Malinowska & Schlicher, 1991). The differences in the pharmacological responses to H₃ activation may not be unexpected because it is well known that the responses to histamine on the cardiovascular system vary greatly among species (Levi *et al.*, 1982). The physiological implications for autonomic function remain to be elucidated further.

In summary, the results presented here demonstrate that the H₃ agonist R- α -methylhistamine given by systemic i.v. route lowers blood pressure, total peripheral resistance, heart rate and rate pressure product in the anaesthetized guinea-pig. It is concluded that the hypotension is produced by prejunctional activation of H₃ receptors located on sympathetic neurones. Activation of these receptors probably acts to inhibit noradrenaline release from sympathetic effector nerves to resistance vessels, resulting in a decrease of total peripheral resistance.

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