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R-(−)-α-methyl-histamine has nitric oxide-mediated vasodilator activity in the mesenteric vascular bed of the cat

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Abstract

Responses to the histamine H_3 receptor agonist *R*-(−)-α-methyl-histamine were investigated in the mesenteric vascular bed of the cat under constant-flow conditions. Injections of *R*-(−)-α-methyl-histamine and histamine caused dose-related decreases in mesenteric perfusion pressure with *R*-(−)-α-methyl-histamine being 1000-fold less potent than histamine when doses were compared on a nmol basis to take molecular weight into account. Responses to *R*-(−)-α-methyl-histamine were not altered by histamine H_1 or H_2 receptor antagonists at a time when responses to histamine were significantly reduced. The histamine H_3 receptor antagonist thioperamide reduced responses to *R*-(−)-α-methyl-histamine but was without effect on responses to histamine {6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl)heptanecardoxamide dimaleate] (HTMT), or dimaprit. These data suggest the presence of histamine H_1, H_2 and H_3 receptors mediating vasodilation in the mesenteric vascular bed. Responses to *R*-(−)-α-methyl-histamine and histamine were reduced by the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME) but were not altered by the cyclooxygenase inhibitor meclofenamate, the α-adrenoceptor blocker phentolamine, or adrenergic nerve terminal depleting agent reserpine. The present data suggest that histamine H_3 receptors mediating vasodilation are present in the mesenteric vascular bed and that responses are mediated by the release of nitric oxide but not vasodilator prostaglandins or an effect on the adrenergic nervous system. These results indicate that vasodilator responses to histamine involve the activation of histamine H_1 and H_2 receptors and the release of nitric oxide in the mesenteric vascular bed of the cat. © 1998 Elsevier Science B.V.

Keywords: Histamine H_3 receptor; Vasodilator response; Nitric oxide (NO); Vascular bed, regional; Thioperamide

1. Introduction

Histamine is released from a variety of cell types in inflammatory and allergic states and has potent vascular smooth muscle stimulating activity (Levi et al., 1991; Göthert et al., 1995). The vascular actions of histamine have been attributed to an interaction with histamine H_1 and histamine H_2 receptors (Flynn and Owen, 1975; Harvey et al., 1980; Levi et al., 1991; Göthert et al., 1995; Neely et al., 1995). The histamine H_3 receptor, first identified in rat brain cortical slices, has been shown to inhibit histamine release, and inhibitory presynaptic H_3 receptors have also been found on nonhistaminergic nerves (Arrang et al., 1983; Ishikawa and Sperelakis, 1987; Schlicker et al., 1988, 1993, 1994; McLeod et al., 1991, 1993, 1994; Hey et al., 1992; Hutchinson and Hey, 1994; Koss, 1994; Beyak and Vanner, 1995; Celuch, 1995; Coruzzi et al., 1995; Göthert et al., 1995; Rizzo et al., 1995).

The characterization of histamine H_3 receptor-mediated responses has been made possible by the development of selective histamine H_3 receptor agonists and antagonists (Arrang et al., 1987; Timmerman, 1990). *R*-(α)-methylhistamine is a selective histamine H_3 receptor agonist (Arrang et al., 1987; Timmerman, 1990; Hegde et al., 1994). Responses to *R*-(−)-α-methyl-histamine are not altered by histamine H_1 and H_2 receptor antagonists but are reduced by the histamine H_3 receptor antagonist thioperamide (Ishikawa and Sperelakis, 1987; McLeod et al., 1991, 1993, 1994; Hey et al., 1992; Hutchinson and Hey, 1994; Koss, 1994; Göthert et al., 1995). It has been reported that intravenous administration of *R*-(−)-α-methyl-histamine produces biphasic changes in systemic

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arterial pressure (short-lasting hypotension followed by a pressor effect) in the rat and that responses are blocked by the histamine H_1 receptor antagonist, but not by histamine H_2 or H_3 receptor antagonists (Hegde et al., 1994).

Vasodepressor responses to *R*-(−)-α-methyl-histamine have been observed in the guinea pig and the rabbit (Kim et al., 1992; McLeod et al., 1993). It has been reported that activation of histamine H_3 receptors on adrenergic nerve terminals inhibits norepinephrine release and pressor responses to medullary and spinal cord stimulation in the pithed guinea pig (Hey et al., 1992; Hutchinson and Hey, 1994). An inhibitory effect of *R*-(−)-α-methyl-histamine on sympathetic neurotransmission has also been documented in the guinea pig mesenteric artery (Ishikawa and Sperelakis, 1987). It has also been reported that *R*-(−)-α-methyl-histamine has direct vasodilator activity in the isolated dog cerebral artery mediated by the release of nitric oxide and prostacyclin (Kim et al., 1992).

R-(−)-α-methyl-histamine has been shown to inhibit sympathetically evoked pupillary dilation in the cat (Koss, 1994), and it has recently been shown that histamine has vasodilator activity in the hindlimb vascular bed of the cat (Champion and Kadowitz, 1997). However, little if anything is known about responses to *R*-(−)-α-methyl-histamine and the role of histamine H_3 receptors in mediating responses to histamine in the mesenteric vascular bed of the cat. The purpose of the present study, therefore, was to investigate responses to and the mechanism of action to *R*-(−)-α-methyl-histamine in the mesenteric vascular bed of the cat under constant blood flow conditions.

2. Materials and methods

Fifty-five adult cats of either sex weighing 2.2–4.3 kg were sedated with ketamine hydrochloride (10–15 mg/kg i.m.) and were anesthetized with pentobarbital sodium (30 mg/kg i.v.). Supplemental doses of pentobarbital were given as needed to maintain a uniform level of anesthesia. Assurance is given that animals were cared for in accordance with the principles and guidelines of the Tulane University Animal Care and Use Committee. The trachea was cannulated and the animals either breathed spontaneously or were ventilated with a Harvard model 607 ventilator at a volume of 40–60 ml at 15–22 breaths/min. An external jugular vein was catheterized for the i.v. administration of drugs and a carotid artery was catheterized for the measurement of systemic arterial (aortic) pressure. For constant-flow perfusion of the mesenteric vascular bed, the superior mesenteric artery was approached through a midline abdominal incision and carefully cleared of surrounding connective tissue. The mesenteric vascular bed was denervated by ligating and cutting the perivascular nerves to the small intestine as they course along the superior mesenteric artery. Following administration of heparin sodium (1000 U/kg), the femoral artery was cannulated and connected to the inlet side of a perfusion circuit. The outlet side of the perfusion circuit was connected to a catheter inserted into the superior mesenteric artery. Blood flow to the small intestine was maintained constant with a Sigmamotor model T-8 perfusion pump. Superior mesenteric arterial perfusion pressure was measured by way of a lateral tap in the perfusion circuit located between the pump and the outlet side of the perfusion circuit. Superior mesenteric arterial perfusion pressure and systemic arterial pressure were measured with Statham P23 transducers and were recorded on a Grass model 7 polygraph. Mean pressures were derived by electronic averaging, and the perfusion rate was set so that superior mesenteric arterial perfusion pressure approximated systemic arterial pressure and was not changed during the experiment. The flow rate was determined by timed collection and ranged from 26–36 ml/min. The vasoactive agonists used in these experiments were injected directly into the superior mesenteric artery perfusion circuit distal to the pump in small volumes (30 and 100 μl), these procedures have been described previously (Champion et al., 1996).

In the first series of experiments, mesenteric vasodilator responses to *R*-(−)-α-methyl-histamine were determined and compared with responses to histamine when doses were expressed on a nmol basis to take molecular weight into account. In the second series of experiments, the influence of the histamine H_1 receptor antagonist pyrilamine on responses to the histamine H_3 receptor agonist

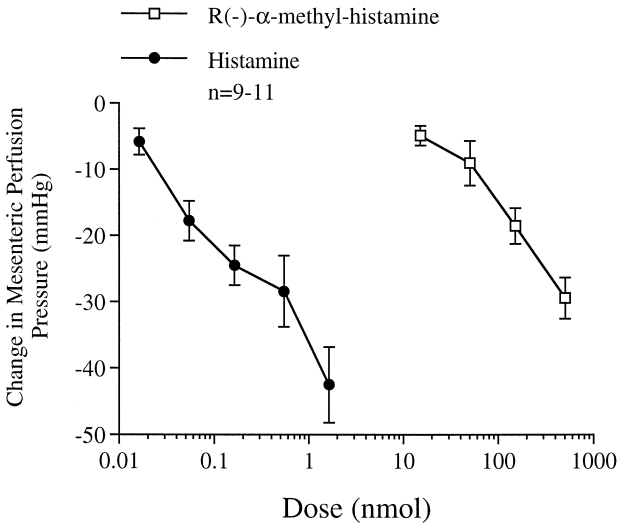

Fig. 1. Dose–response curves comparing the decreases in mesenteric perfusion pressure in response to the histamine H_3 receptor agonist *R*-(−)-α-methyl-histamine and histamine when doses are compared on a nmol basis to take molecular weight into account. The vasoactive agents were injected directly into the mesenteric perfusion circuit. *n* indicates number of experiments.

R-(−)-α-methyl-histamine, histamine, the histamine H_1 receptor agonist {6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoro-methylphenyl)heptanecardoxamide dimaleate] (HTMT) and the histamine H_2 receptor agonist dimaprit was compared. In a separate series of experiments, the influence of the histamine H_2 receptor antagonist cimetidine on responses to *R*-(−)-α-methyl-histamine, histamine, HTMT, and dimaprit was determined. Pyrilamine and cimetidine were administered in a dose of 1 mg/kg i.v. and had no significant effect on mesenteric perfusion or systemic arterial pressures. In another series of experiments, the effect of the histamine H_3 receptor antagonist thioperamide on responses to *R*-(−)-α-methyl-histamine, histamine, HTMT and dimaprit was determined. Thioperamide was administered in a dose of 3 mg/kg i.v. and had no significant effect on mesenteric perfusion or systemic arterial pressure.

In the third series of experiments, the mechanism of vasodilator responses to histamine and related agonists was investigated. N^{ω}-Nitro-L-arginine methyl ester (L-NAME; 100 mg/kg i.v.) was used to evaluate the role of nitric oxide release in mediating responses to *R*-(−)-α-methyl-histamine and was injected over a 10-min period and responses to the vasoactive agents were evaluated beginning 20 min after completion of the injection. In a separate series of experiments, sodium meclofenamate, a cyclooxygenase inhibitor, was used to evaluate the role of the release of vasodilator prostaglandins in mediating responses to *R*-(−)-α-methyl-histamine. In the fourth series of experiments, the role of the adrenergic nervous system in mediating responses to *R*-(−)-α-methyl-histamine was investigated and responses were compared before and after administration of the α-adrenoceptor antagonist phentolamine. The extent of α-adrenoceptor blockade was assessed by comparing responses to norepinephrine before and after administration of phentolamine. In other experiments, the effect of adrenergic nerve terminal depletion on responses to *R*-(−)-α-methyl-histamine was investigated

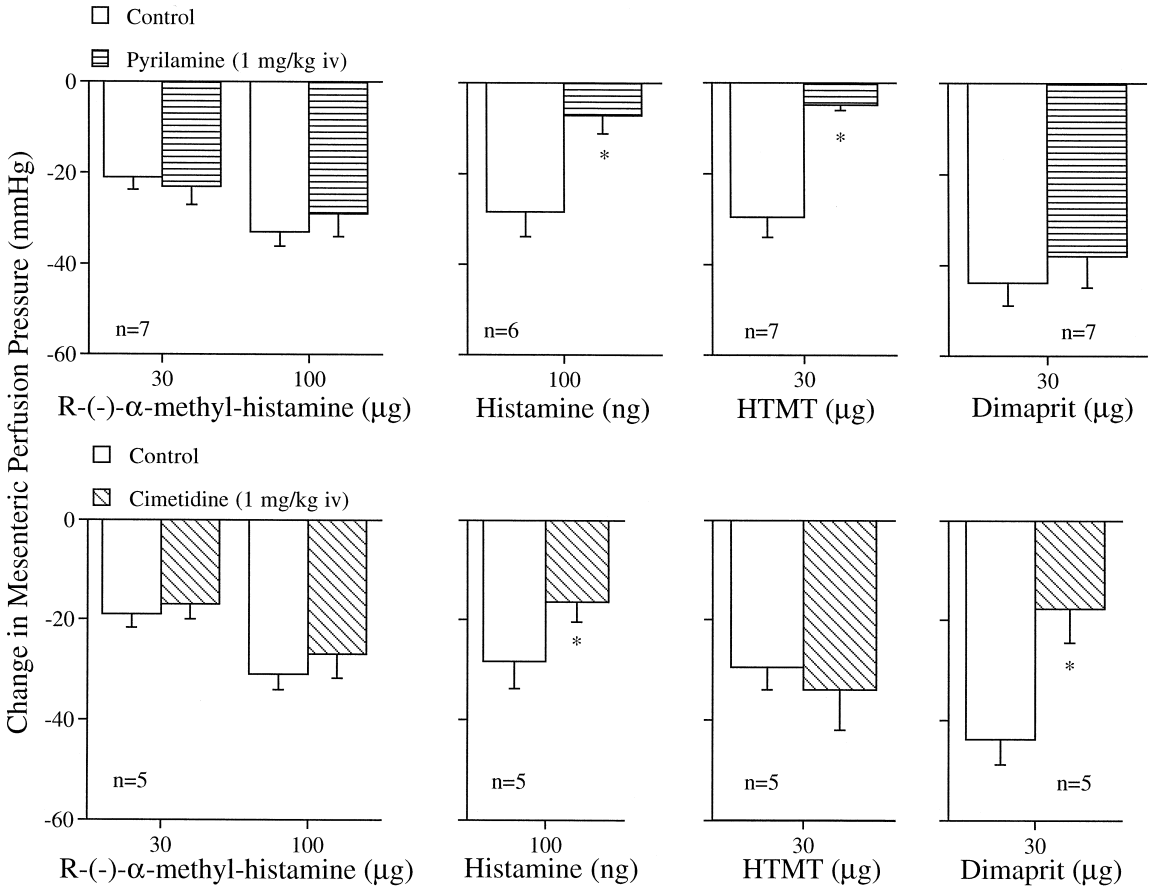

Fig. 2. Top: Influence of the histamine H_1 receptor antagonist pyrilamine (1 mg/kg i.v.) on decreases in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine (151.4–504.8 nmol), histamine (0.54 nmol), the histamine H_1 receptor agonist HTMT (48.8 nmol) and the histamine H_2 receptor agonist dimaprit (128.1 nmol). Bottom: Influence of the histamine H_2 receptor antagonist cimetidine (1 mg/kg i.v.) on decreases in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine, histamine, HTMT and dimaprit. Responses to the agonists were compared before and beginning 15–20 min after administration of the blocking agents. *n* indicates number of experiments. * Indicates that the response is significantly different from control.

and responses were compared before and beginning 3 h after administration of reserpine in a dose of 3 mg/kg i.v. The extent of adrenergic nerve terminal depletion was assessed by comparing responses to the indirect-acting agonist tyramine before and after administration of reserpine.

Histamine dihydrochloride, acetylcholine chloride, sodium arachidonate, N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME), sodium meclofenamate, tyramine hydrochloride (Sigma Chemical Co., St. Louis, MO), *R*-(−)-α-methyl-histamine, thioperamide maleate, dimaprit dihydrochloride (Research Biochemical International, Natick, MA), reserpine phosphate and phentolamine mesylate (Ciba-Geigy Corp., Summit, NJ) were dissolved in 0.9% NaCl. HTMT {6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoro-methylphenyl)heptanecardoxamide dimaleate] (Tocris-Cookson, St. Louis, MO) was dissolved in 5% ethanol–saline solution at a concentration of 1 mg/kg and diluted with 0.9% saline. The vehicles for these agents had no effect on baseline vascular pressures or on responses to the vasoactive agonists. All drug solutions were stored in a freezer in amber bottles and working solutions were prepared on a frequent basis and kept on crushed ice.

The hemodynamic data are expressed as mean ± S.E. and were analyzed using a one-way analysis of variance and Scheffe's *F*-test or a paired *t*-test. A *P*-value of less than 0.05 was used as the criterion for statistical significance.

3. Results

3.1. Comparison of responses

Injections of the histamine H_3 receptor agonist *R*-(−)-α-methyl-histamine and histamine into the mesenteric perfusion circuit caused dose-related decreases in mesenteric perfusion pressure (Fig. 1). In terms of relative vasodilator activity, the ED_{20} mmHg for histamine was approximately 0.1 nmol, whereas the ED_{20} mmHg for *R*-(−)-α-methyl-histamine was approximately 100 nmol, suggesting that histamine was approximately 1000-fold more potent than *R*-(−)-α-methyl-histamine when doses are compared on a nmol basis (Fig. 1).

3.2. Influence of the histamine receptor antagonists

The effects of the histamine H_1 receptor antagonist pyrilamine on vasodilator responses to *R*-(−)-α-methyl-histamine, histamine, HTMT, and dimaprit were investigated, and these data are summarized in Fig. 2. Following administration of pyrilamine in a dose of 1 mg/kg i.v., vasodilator responses to histamine and HTMT were decreased significantly, while vasodilator responses to dimaprit and *R*-(−)-α-methyl-histamine were not altered (Fig. 2).

The effect of the histamine H_2 receptor antagonist cimetidine on vasodilator responses was investigated and these data are summarized in Fig. 2. Following administration of cimetidine in a dose of 1 mg/kg i.v., vasodilator responses to histamine and dimaprit were decreased significantly while vasodilator responses to HTMT and *R*-(−)-α-methyl-histamine were not altered (Fig. 2).

In contrast to the effects of histamine H_1 and histamine H_2 receptor blocking agents, the histamine H_3 receptor antagonist thioperamide (3 mg/kg i.v.) had no significant effect on vasodilator responses to histamine, HTMT and dimaprit at a time vasodilator responses to *R*-(−)-α-methyl-histamine were significantly attenuated (Fig. 3).

3.3. Influence of L-NAME

The effect of the nitric oxide synthesis inhibitor L-NAME on vasodilator responses to *R*-(−)-α-methyl-histamine and histamine was investigated and these data are shown in Fig. 4. L-NAME increased mesenteric perfusion pressure from 125 ± 11 to 223 ± 15 and systemic

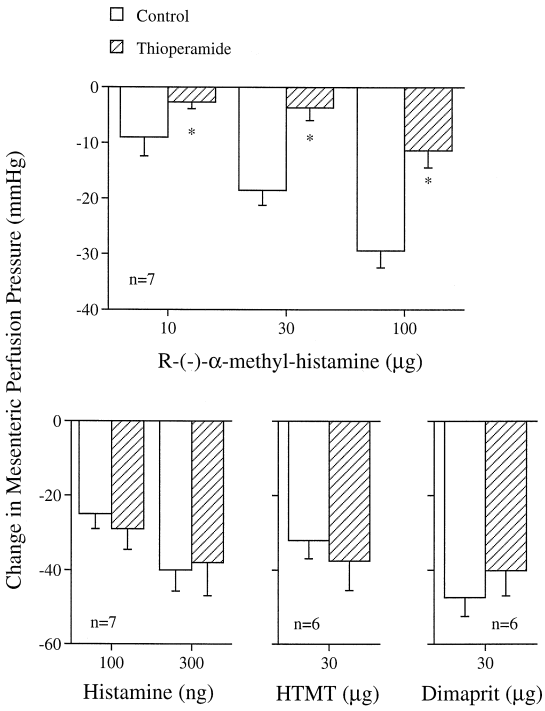

Fig. 3. Influence of the histamine H_3 receptor antagonist thioperamide (3 mg/kg i.v.) on decreases in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine (50.5–504.8 nmol), histamine (0.54–1.63 nmol), the histamine H_1 receptor agonist HTMT (48.8 nmol) and the histamine H_2 receptor agonist dimaprit (128.1 nmol). Responses to the agonists were compared before and beginning 15–20 min after administration of the histamine H_3 receptor antagonist. The response to the midrange dose of *R*-(−)-α-methyl-histamine was still suppressed after all doses of histamine, HTMT, and dimaprit were injected. *n* indicates number of experiments. * Indicates that the response is significantly different from control.

arterial pressure from 116 ± 7 to 208 ± 9. After treatment with L-NAME (100 mg/kg i.v.), vasodilator responses to *R*-(−)-α-methyl-histamine, histamine and acetylcholine were reduced significantly (Fig. 4). Vasodilator responses to albuterol and levcromakalim were not significantly changed after administration of L-NAME (data not shown).

3.4. Influence of meclofenamate

The role of the release of vasodilator prostaglandins in mediating responses to *R*-(−)-α-methyl-histamine and histamine was investigated and these data are shown in Fig. 4. Sodium meclofenamate, when administered in a dose of 2.5 mg/kg i.v., had no significant effect on systemic arterial or mesenteric perfusion pressure. After administration of the cyclooxygenase inhibitor sodium meclofenamate in a dose of 2.5 mg/kg i.v., vasodilator responses to *R*-(−)-α-methyl-histamine and histamine were not altered at a time when vasodilator responses to the prostaglandin precursor arachidonic acid were significantly attenuated (Fig. 4).

3.5. Role of the adrenergic nervous system

The role of the adrenergic nervous system in mediating vasodilator responses to *R*-(−)-α-methyl-histamine in the mesenteric vascular bed of the cat was investigated and these data are summarized in Fig. 5. Phentolamine (1 mg/kg i.v.) decreased mesenteric perfusion pressure from 136 ± 11 to 116 ± 9 mmHg and systemic arterial pressure from 128 ± 7 to 106 ± 9 mmHg. Following administration of the α-adrenoceptor blocking agent in a dose of 1 mg/kg i.v., vasodilator responses to *R*-(−)-α-methyl-histamine were not altered whereas the vasoconstrictor response to norepinephrine was significantly reduced (Fig. 5). Vasodilator responses to histamine were not altered after administration of phentolamine (data not shown). In animals treated with reserpine in a dose of 3 mg/kg i.v.,

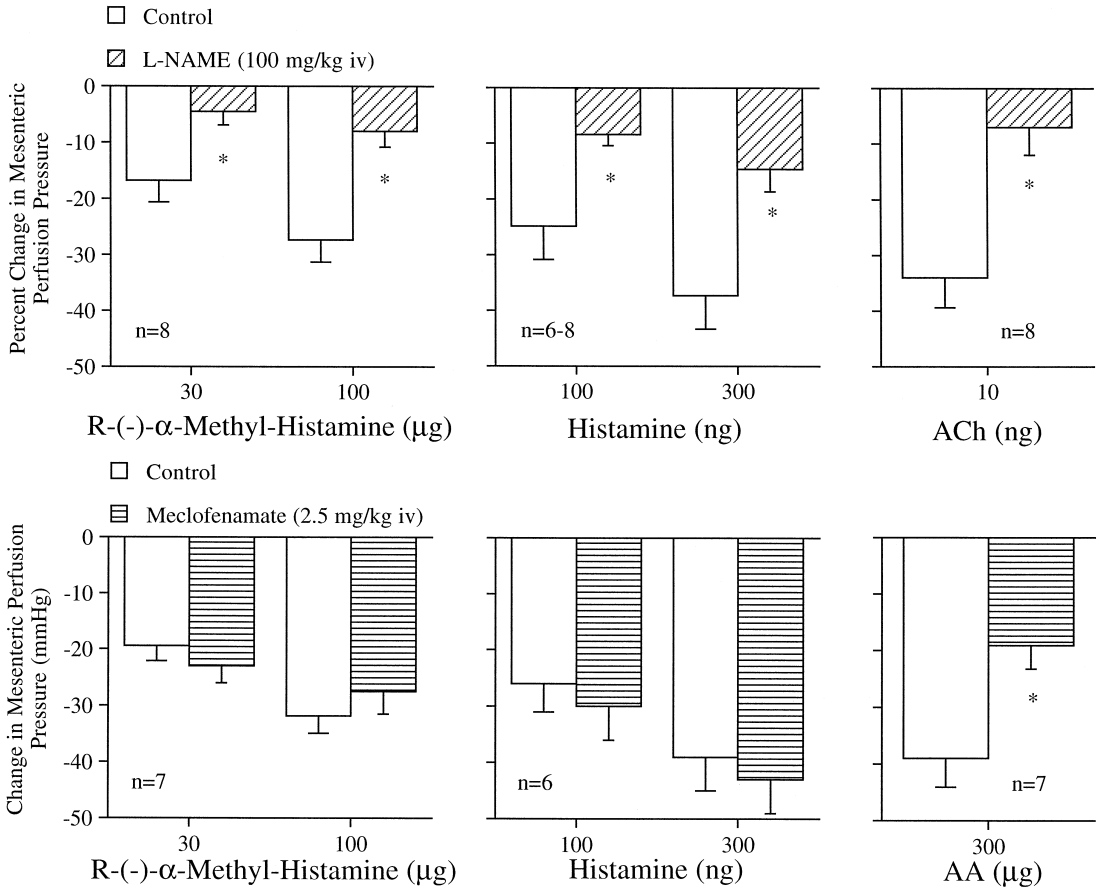

Fig. 4. Top: Influence of the nitric oxide synthase inhibitor L-NAME (100 mg/kg i.v.) on decreases in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine, histamine, and acetylcholine (ACh). Bottom: Influence of the cyclooxygenase inhibitor meclofenamate (2.5 mg/kg i.v.) on decreases in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine, histamine, and sodium arachidonate (AA). Responses to the agonists were compared before and beginning 20–30 min after administration of the blocking agents. *n* indicates number of experiments. * Indicates that the response is significantly different from control. Vasodilator responses in experiments with L-NAME are expressed as percent change from baseline in order to take L-NAME-induced changes in baseline perfusion pressure into account.

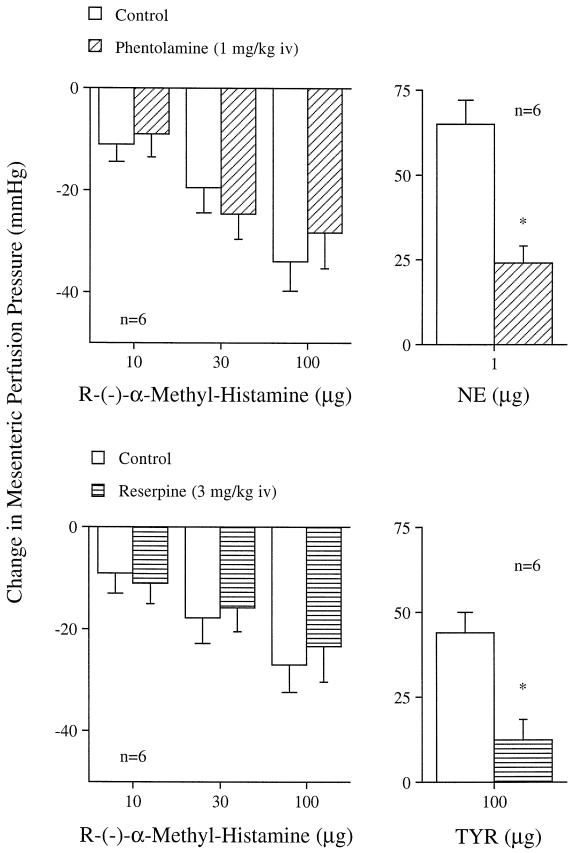

Fig. 5. Influence of the α-adrenoceptor blocker phentolamine (1 mg/kg i.v.) on changes in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine and norepinephrine (NE). Bottom: Influence of the adrenergic nerve terminal depleting agent reserpine (3 mg/kg i.v.) on changes in mesenteric perfusion pressure in response to *R*-(−)-α-methyl-histamine and tyramine (TYR). *n* indicates number of experiments. * Indicates that the response is significantly different from control.

vasodilator responses to *R*-(−)-α-methyl-histamine were not different from control (Fig. 5). Vasodilator responses to histamine were not altered after administration of reserpine (data not shown). However, the vasoconstrictor response to the indirect-acting sympathomimetic amine tyramine was decreased significantly by reserpine treatment (Fig. 5). The vasoconstrictor response to norepinephrine was increased significantly after treatment with reserpine (data not shown).

4. Discussion

The results of the present study show that *R*-(−)-α-methyl-histamine has significant vasodilator activity in the mesenteric vascular bed of the cat, and that *R*-(−)-α-methyl-histamine is approximately 1000-fold less potent than histamine when doses were compared on a nmol basis to take molecular weight into account. Although 1000-fold less potent than histamine, *R*-(−)-α-methyl-histamine is capable of producing a substantial vasodilator response. Responses to *R*-(−)-α-methyl-histamine were not altered by the histamine H_1 receptor antagonist pyrilamine or the histamine H_2 receptor antagonist cimetidine, while responses to histamine were significantly reduced by both histamine H_1 and histamine H_2 receptor blocking agents. Responses to *R*-(−)-α-methyl-histamine were significantly reduced by the histamine H_3 receptor antagonist thioperamide at a time when responses to histamine, HTMT, and dimaprit were not altered. The present data suggest that histamine H_1, histamine H_2 and histamine H_3 receptors mediating vasodilation are present in the mesenteric vascular bed of the cat. These data suggest that histamine H_1 receptors mediate the majority of the vasodilator response to histamine, that histamine H_2 receptor activation plays a smaller role and that histamine H_3 receptor activation is not involved in the mesenteric vasodilator response to histamine. Responses to *R*-(−)-α-methyl-histamine and histamine were reduced after administration of the nitric oxide synthase inhibitor L-NAME but were not altered after administration of the cyclooxygenase inhibitor meclofenamate. Treatment with the α-adrenoceptor blocking agent phentolamine and the adrenergic nerve terminal depleting agent reserpine did not alter vasodilator responses to *R*-(−)-α-methyl-histamine or to histamine.

The observation that responses to *R*-(−)-α-methyl-histamine were not altered by the histamine H_1 and histamine H_2 receptor antagonists provides support for the hypothesis that *R*-(−)-α-methyl-histamine is a selective histamine H_3 receptor agonist (Arrang et al., 1987; Timmerman, 1990). Data with the histamine H_3 selective receptor antagonist thioperamide provides additional support for this hypothesis in that responses to *R*-(−)-α-methyl-histamine were significantly reduced at a time when responses to histamine, HTMT, and dimaprit were not changed. These data suggest that thioperamide is a selective histamine H_3 receptor antagonist, and that histamine in the doses studied does not have agonist activity at the histamine H_3 receptor in the mesenteric vascular bed of the cat. The present data are in agreement with previous studies in the cat demonstrating the involvement of both histamine H_1 and histamine H_2 receptors in mediating vasodilator responses to histamine and extend these findings by showing that histamine H_3 receptor activation is not involved in mediating the vasodilator response to histamine (Flynn and Owen, 1975; Harvey et al., 1980; Neely et al., 1995). The observation that the histamine H_3 receptor does not play a role in mediating vasodilator responses to histamine under the conditions of the present experiments may be interpreted to suggest that the histamine H_3 receptor may not play a role in mediating vasodilator responses in the denervated mesenteric vascular bed of the cat.

The mechanism mediating vasodilator responses to *R*-(−)-α-methyl-histamine and histamine is uncertain. While vasodilator responses to histamine have been reported to involve the release of nitric oxide and/or prostacyclin,

responses to *R*-(−)-α-methyl-histamine are generally believed to be mediated by the inhibition of neurotransmitter release from adrenergic terminals (Arrang et al., 1983; Ishikawa and Sperelakis, 1987; Bhardwaj and Moore, 1988; Schlicker et al., 1988, 1993, 1994; Matsuki and Ohhashi, 1990; Timmerman, 1990; McLeod et al., 1991, 1993, 1994; Ortiz et al., 1991; Hey et al., 1992; Kim et al., 1992; Hegde et al., 1994; Hutchinson and Hey, 1994; Koss, 1994; Van de Voorde et al., 1994; Beyak and Vanner, 1995; Celuch, 1995; Coruzzi et al., 1995; Göthert et al., 1995; Rizzo et al., 1995). However, vasodilator responses to *R*-(−)-α-methyl-histamine have been reported to be mediated by nitric oxide and prostaglandin I_2 release in the isolated cerebral artery of the dog (Kim et al., 1992). The data from the present study in which responses to *R*-(−)-α-methyl-histamine and histamine were attenuated by the nitric oxide synthase inhibitor L-NAME suggest that the release of nitric oxide plays a significant role in mediating vasodilator responses to the histamine H_3 selective agonist and to histamine in the denervated mesenteric vascular bed of the cat. However, responses to *R*-(−)-α-methyl-histamine were not altered by the cyclooxygenase inhibitor sodium meclofenamate, suggesting that the synthesis of products in the cyclooxygenase pathway does not play a role in mediating mesenteric vasodilator responses to *R*-(−)-α-methyl-histamine or histamine.

The first description of the histamine H_3 receptor was based on the ability of histamine H_3 receptor agonists to inhibit histamine release from histaminergic nerve terminals in the rat cerebral cortex (Arrang et al., 1983). Studies on the central effects of *R*-(−)-α-methyl-histamine have shown that injection of the histamine H_3 receptor agonist into the cerebral ventricles of the guinea pig caused dose-dependent bradycardia and hypotension at low doses with higher doses producing a biphasic response characterized by an initial pressor, followed by a secondary depressor response (Göthert et al., 1995). Therefore, this central action of *R*-(−)-α-methyl-histamine may increase vagal tone and produce a hypotensive response. Although *R*-(−)-α-methyl-histamine has been shown to have centrally-mediated effects on blood pressure, reflex changes in vasomotor tone are not involved in the present experiments, since the vasomotor nerves to the mesenteric vascular bed were surgically removed.

Vasodepressor responses to *R*-(−)-α-methyl-histamine have been observed in the guinea pig and rabbit (Kim et al., 1992; McLeod et al., 1993). It has been reported that activation of histamine H_3 receptors on adrenergic nerve terminals inhibits pressor responses to medullary and spinal cord stimulation in the pithed guinea pig (Hey et al., 1992; Hutchinson and Hey, 1994). This inhibitory effect on sympathetic neurotransmission has also been observed in the guinea pig mesenteric artery (Ishikawa and Sperelakis, 1987). Intravenous injection of *R*-(−)-α-methyl-histamine in the conscious guinea pig causes hypotension and bradycardia and it has been hypothesized that this response is due to increased vagal tone or the inhibition of adrenergic neurotransmission in the heart (McLeod et al., 1994). It is, however, unlikely that the adrenergic system plays a role in mediating the vasodilator response to *R*-(−)-α-methyl-histamine in the mesenteric vascular bed of the cat, since the vascular bed is surgically denervated. Data from the present study in which responses to *R*-(−)-α-methyl-histamine were not altered after administration of phentolamine or reserpine are not unexpected and suggest that an inhibitory effect on the adrenergic nervous system does not play an important role in mediating vasodilator responses in the denervated mesenteric vascular bed of the cat.

In summary, the results of the present study show that *R*-(−)-α-methyl-histamine produces dose-related decreases in mesenteric perfusion pressure and that *R*-(−)-α-methyl-histamine is 1000-fold less potent than histamine. Responses to *R*-(−)-α-methyl-histamine were not altered by histamine H_1 or histamine H_2 receptor antagonists and responses to *R*-(−)-α-methyl-histamine, but not to histamine, were attenuated by the histamine H_3 antagonist thioperamide, suggesting that histamine H_3 receptors mediating vasodilation are present in the mesenteric vascular bed of the cat. These data suggest that the vasodilator responses to *R*-(−)-α-methyl-histamine and histamine are mediated by the release of nitric oxide, and that the release of vasodilator prostaglandins or an inhibitory effect on the adrenergic nervous system is not involved under the conditions of the present experiments.

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