Participation of H\textsubscript{1} and H\textsubscript{2} histamine receptors in physiological vasodilator responses

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POWELL, JAMES R., AND MICHAEL J. BRODY. Participation of H\textsubscript{1} and H\textsubscript{2} histamine receptors in physiological vasodilator responses. Am. J. Physiol. 231(4): 1002-1009. 1976.—Histamine causes vasodilation in the dog by activation of H\textsubscript{1} and H\textsubscript{2} receptors blocked by mepyramine and metiamide, respectively. Experiments were conducted in anesthetized dogs to determine the participation of H\textsubscript{1} and H\textsubscript{2} receptors in several forms of physiological dilatation. Mepyramine attenuated both histamine-induced and active-reflex dilatation in the hindlimb. Metiamide caused a further reduction in both sets of dilatation. Neither single nor combined antihistamines reduced dilatation due to exercise or after temporary occlusion of the circulation in the hindlimb. Poststimulation dilatation in the gracilis muscle was partially attenuated by metiamide or mepyramine. Neither dilatation caused by sympathetic nerve stimulation in the hindpaw nor dilatation in the gracilis muscle caused by compound 48/80 was reduced by mepyramine. Following combined H\textsubscript{1}- and H\textsubscript{2}-receptor blockade, portions of both types of dilatation were reduced. These data provide evidence for the participation of both types of histamine receptor in active reflex dilatation, low-frequency neurogenic dilatation, dilatation caused by compound 48/80, and poststimulation dilatation. Neither type of histamine receptor appears to be involved in reactive hyperemia or dilatation caused by exercise.

THE PRESENCE OF LARGE AMOUNTS OF histamine in and near blood vessels and the profound vascular actions of this substance have caused many investigators to propose that histamine is the mediator of several forms of vasodilatation. Lewis (20), in a classic description of the cutaneous circulation, proposed histamine (H-substance) as the mediator of postocclusion-reactive hyperemia. Anrep et al. (2) reported the release of histamine from exercising human forearm muscles and suggested that histamine mediates exercise hyperemia. Histamine has been postulated to mediate the active component of baroreceptor-mediated reflex vasodilation (4-7, 9 11, 16, 19, 25).

Recently, two distinct types of histamine receptor have been described (8). The first type is blocked by classical antihistamines such as mepyramine and is designated as type H\textsubscript{1}. The second is designated as type H\textsubscript{2} and is blocked by metiamide or burimamide. H\textsubscript{1} and H\textsubscript{2} receptors have been shown to mediate the cardiovascular actions of histamine in the dog (18, 23, 24). In the dog, mepyramine, a type H\textsubscript{1} blocker, can only partially attenuate vasodilatation caused by histamine. When an H\textsubscript{2} blocker such as metiamide is given alone, it has no effect on vasodilatation caused by histamine. However, when metiamide is given subsequent to mepyramine, a large attenuation of the vasodilatation due to histamine is obtained. The use of the specific H\textsubscript{2}-receptor agonist, 4-methylhistamine, has allowed for the demonstration that H\textsubscript{2} receptors are activated in the absence of previous H\textsubscript{1}-receptor blockade (24).

The purpose of this investigation was to examine the effects of H\textsubscript{1} and H\textsubscript{2} antihistamines on several forms of vasodilatation which have been proposed to involve the release of endogenous histamine. It is proposed that, by use of the new H\textsubscript{2} antihistamines, several forms of physiological vasodilatation might be shown to involve histamine through activation of H\textsubscript{2} receptors.

METHODS

All experiments were conducted in mongrel dogs of either sex (body wt 18.5 ± 0.4 kg, mean ± SE) anesthetized with sodiumpentobarbital (30 mg/kg iv). The trachea was cannulated and the animals were allowed to breathe room air spontaneously. The brachial artery was cannulated for blood pressure measurement and the brachial vein cannulated for the systemic administration of drugs.

Baroreceptor-mediated active reflex vasodilatation. The right common iliac artery was isolated through a short midline abdominal incision. After heparin administration (1,000 U/kg iv), the vessel was cannulated and perfused with a Sigmamotor pump at constant flow using blood obtained from the left femoral artery. The femoral arterial cannula was advanced into the abdominal aorta, and the aorta was ligated proximal to the iliac bifurcation to improve the vascular isolation of the perfused limb. Pressure was measured between the pump and hindlimb. A flow rate generating a perfusion pressure that approximated arterial pressure was chosen and held constant so that changes in vascular resistance were reflected directly by changes in perfusion pressure. In nine experiments flow averaged 81 ± 10 ml/min. All animals were vagotomized and artificially ventilated with room air.

Reflex vasodilatation in the hindlimb was elicited by the intravenous administration of norepinephrine. The perfusion system provided a sufficient delay (62 ± 9 s) so
that intravenously administered norepinephrine did not cause vasoconstriction in the perfused hindlimb until well after the reflex vasodilatation had reached its nadir. Histamine, norepinephrine, and glyceryl trinitrate were injected into the limb through the perfusion tubing near the site of cannulation. Then, 50-150 mg of mepyramine maleate (pyrilamine) dissolved in saline were infused intra-arterially into the hindlimb at a rate of 5-15 mg/min. After at least 15 min had elapsed since antihistamine administration, responses were obtained to norepinephrine, histamine, and glyceryl trinitrate. After these responses had been obtained, 150 mg of metiamide were infused intra-arterially over a 15-min period. At least 15 min after metiamide, responses were again obtained to norepinephrine, histamine, and glyceryl trinitrate.

*Poststimulation dilatation.* A functional correlate of baroreceptor-mediated reflex dilatation in the gracilis muscle has been described by Heitz and Brody (16). This model involves restoration of vasomotor tone in the decentralized gracilis muscle by electrical stimulation of the peripheral end of the severed lumbar sympathetic chain. Upon termination of the electrical stimulation, analogous to baroreceptor sympathoinhibition, there is a poststimulation dilatation. In this series of experiments, the gracilis muscle was perfused as described by Dorr and Brody (13). Flow to the gracilis muscle was 12 ± 2 ml/min. The lumbar sympathetic chain was isolated and sectioned at a level of 1.4 or 1.5. The peripheral end was stimulated with square-wave electrical impulses at supramaximal voltage and with frequencies from 0.25 to 3.0 Hz. The duration of each impulse was 2 ms, and the total duration of stimulation was 5 min. Poststimulation dilatation and responses to histamine and glyceryl trinitrate were obtained before and after metiamide (30 mg) and after the subsequent administration of mepyramine (30 mg), or before and after metiamide or mepyramine alone.

*Reactive hyperemia.* Postocclusion reactive hyperemia was studied in the common iliac artery of the dog. The artery was exposed and an electromagnetic flow probe was placed on it near the aorta. Approximately 2 cm distal from the probe, the artery was fitted with a snare for occlusion. The saphenous artery was cannulated and a small-diameter polyethylene tube (PE-50) was passed retrogradely until its tip was just proximal to the cannula, the artery was fitted with a probe was placed on it near the aorta. Approximately 2 min later, the artery was occluded for 5, 10, 15, and 30 s. Reactive hyperemia was manifested by the transient increase in blood flow over preocclusion values. Similar increases in blood flow were elicited by histamine and glyceryl trinitrate. Blood-flow responses to arterial occlusion, histamine, and glyceryl trinitrate were recorded before antihistamines, after mepyramine, and after the subsequent administration of metiamide.

*Exercise vasodilatation.* This series of experiments also involved the perfusion of the vascularly isolated hindlimb. The sciatic nerve was isolated and fitted with a Harvard bipolar electrode for electrical stimulation. The nerve was sectioned proximal to the electrode. Square-wave impulses were delivered from a Grass model S44 stimulator. The impulses were delivered at 0.5, 1, and 2 Hz with stimulus frequency of 50 Hz. Voltage was supramaximal and ranged from 7 to 15 V. Responses to sciatic nerve stimulation and to the local intra-arterial injections of histamine and glyceryl trinitrate were obtained before and after the infusion of 50 mg of mepyramine. Following this, 100 mg of metiamide was infused, and responses to nerve stimulation, histamine, and glyceryl trinitrate were again obtained. Neuromuscular blockade was then established with decamethonium bromide (0.25 mg/kg iv), and the animals were artificially ventilated. After neuromuscular blockade, the sciatic-nerve stimulation was repeated.

**Sustained neurogenic vasodilatation.** Neurogenically induced vasodilatation was studied in the dog hindpaw using methods described by Zimmerman (31). The cranial tibial artery was cannulated and infused at constant flow. In five experiments flow averaged 24 ± 3 ml/min. The ipsilateral lumbar sympathetic chain was isolated and fitted with a bipolar electrode. Following decentralization, electrical stimulation of the chain with square-wave impulses from a Grass S44 stimulator caused vasoconstriction in the hindpaw. Bretylium tosylate or guanethidine sulfate, agents that prevent the release of norepinephrine from nerve terminals and unmask vasodilator responses (3, 6, 18, 31), were administered at 5 mg/kg iv. Cholinergic blockade was obtained by the local administration of 0.6-1.2 mg of atropine. Following bretylium or guanethidine and atropine, stimulation of the lumbar chain caused vasoconstriction in the hindpaw. Responses in the hindpaw to nerve stimulation, histamine, and glyceryl trinitrate were obtained before and after the infusion of 15 mg of mepyramine and subsequent to the local infusion of 30 mg of metiamide.

**Histamine release by compound 48/80.** This series of experiments was conducted in the perfused gracilis muscle using methods outlined by Dorr and Brody (13). In these experiments, flow was 14 ± 2 ml/min. Vasodilator responses were obtained to the local injections of histamine, compound 48/80, and glyceryl trinitrate. Then, 15-30 mg of mepyramine were infused over a 10-min period and responses were again obtained. Following mepyramine, 30 mg of metiamide were infused and responses were again obtained.

**Statistical analysis.** All drugs except the antihistamines were administered in a random fashion, and data were analyzed by means of paired-t tests as outlined by Steele and Torrie (27).
represents vasodilatation. Vasodilator responses in the hindlimb to the local intra-arterial injection of histamine are also shown. The local intra-arterial administration of mepyramine (middle panel) caused a reduction in the magnitude of the reflex dilatation produced in response to norepinephrine. The responses to histamine obtained after mepyramine were also significantly reduced. The right-hand panel shows that the vasodilator responses following systemic norepinephrine were further reduced following metiamide treatment for the low dose of norepinephrine. Responses to histamine following metiamide were nearly abolished. The arterial pressure increases following intravenous norepinephrine were not significantly altered following either antihistamine. Reflex vasoconstrictor responses in the hindlimb were obtained by 30 s of bilateral carotid occlusion. Baroreceptor-mediated vasoconstriction during carotid occlusion was not significantly altered by the antihistamines nor was the hindlimb perfusion pressure (Table 1). Mepyramine caused a small reduction in vasoconstriction caused by intra-arterial norepinephrine which was significant for the 3-μg dose only. No further attenuation of vasoconstriction was seen with metiamide. Neither antihistamine attenuated vasodilatation due to intra-arterial glyceryl trinitrate (GTN).

The nature of poststimulation dilatation is illustrated in Fig. 2. Stimulation of the lumbar sympathetic chain caused vasoconstriction which persisted for the duration of stimulation. At termination of the stimulation, there was a fall in perfusion pressure which exceeded the prestimulation level. This poststimulation dilatation was reduced by metiamide and abolished by mepyramine. Vasodilator responses after histamine were not altered by metiamide but were attenuated after the administration of mepyramine. Results from several similar experiments are shown in Fig. 3. Metiamide caused a small but significant attenuation of poststimulation dilatation. Metiamide did not attenuate vasodilatation after histamine. The further addition of mepyramine caused an additional attenuation of poststimulation dilatation and nearly abolished vasodilatation due to histamine.

### TABLE 1. Effect of mepyramine and metiamide on vascular responses in the perfused hindlimb

<table>
<thead>
<tr>
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<th>Perfusion Pressure, mmHg</th>
<th>d ± SE</th>
<th>d ± SE</th>
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<tr>
<td></td>
<td>Control</td>
<td>Mepyramine</td>
<td>Metiamide</td>
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<tr>
<td>Norepinephrine 1 μg</td>
<td>129 ± 136</td>
<td>7 ± 5</td>
<td>141 ± 52</td>
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<td></td>
<td>3 μg</td>
<td>49 ± 49</td>
<td>37 ± 53</td>
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<td></td>
<td>10 μg</td>
<td>71 ± 61</td>
<td>60 ± 52</td>
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<tr>
<td>Bilateral carotid occlusion</td>
<td>58 ± 01</td>
<td>8 ± 7</td>
<td>43 ± 8 ± 5</td>
</tr>
<tr>
<td>Glyceryl trinitrate 1 μg</td>
<td>34 ± 36</td>
<td>7 ± 4</td>
<td>52 ± 4 ± 4</td>
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<tr>
<td></td>
<td>3 μg</td>
<td>44 ± 51</td>
<td>21 ± 5 ± 4</td>
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n = 10. d, mean difference. *P < .05.
to histamine. In two additional experiments, the administration of mepyramine alone partially attenuated vasodilatation after histamine and abolished poststimulation vasodilatation. Neither antihistamine reduced significantly the magnitude of vasoconstriction caused by electrical stimulation of the lumbar sympathetic nerves or vasodilatation caused by glyceryl trinitrate.

Reactive hyperemia in the dog hindlimb is shown in Fig. 4. Occlusion of the iliac artery caused cessation of flow for the duration of the occlusion. Following release of the occlusion, there was a transient hyperemia as indicated by the increases in flow over preocclusion values. As shown on the right, the intra-arterial injection of histamine also caused vasodilatation. Several similar experiments are summarized in Fig. 5. Following intra-arterial mepyramine, there was little change in the hyperemic responses and a reduction in responses to histamine. Further treatment with metiamide caused an additional attenuation of histamine-induced vasodilatation, but had no effect on reactive hyperemia or dilator responses to GTN.

Stimulation of the peripheral end of the decentralized sciatic nerve caused intermittent flexion of the limb and a coincident reduction in vascular resistance. The nature of this response is shown in Fig. 6. The dilatation during exercise of the limb is shown by the reductions in perfusion pressure. This dilatation was rapid in onset and persisted for several minutes when the stimulation of the sciatic nerve was terminated. Vasodilatation was also caused by the local intra-arterial injection of histamine. Following mepyramine, the responses to histamine were attenuated and a further attenuation was caused by metiamide. Neither antihistamine attenuated the vasodilatation associated with exercise. A statistical summary of these responses is shown in Fig. 7.

DISCUSSION

The presence of large amounts of histamine in tissues and the profound vascular actions of this substance have long suggested a possible role for histamine in the regulation of the peripheral circulation. Heitz and Brody (16) described a dilator system in the dog gracilis muscle.
FIG. 5. Statistical summary showing effects of mepyramine (50 mg) and metiamide (150 mg) on reactive hyperemia and histamine-induced vasodilatation in hindlimb. Doses of histamine (0.1-3.0 μg) and glyceryl trinitrate (GTN, 0.1-3.0 μg) were chosen for each animal to match magnitude of hyperemic response and are presented as low and high dose. Single asterisks indicate that responses were reduced from control after mepyramine (P < .05), and double asterisks indicate a further reduction after metiamide (P < .05). After mepyramine, mean difference from control responses for low dose of histamine was -74 ± 24 ml/min and -100 ± 19 ml/min in high dose. After metiamide, mean difference from responses to histamine after mepyramine was -16 ± 7 ml/min for low dose and -17 ± 8 ml/min for high dose.

FIG. 6. Tracing showing effect of mepyramine (50 mg) and metiamide (100 mg) on dilatation caused by exercise and histamine in perfused hindlimb. Top tracing shows mean arterial pressure (MAP). Duration of stimulation (30 s) is illustrated by arrows which is under reciprocal control of the sympathetic nervous system. These authors showed that when neurogenic vasoconstrictor tone to the decentralized muscle was restored by electrical stimulation of the sympathetic nerves that, at termination of stimulation, an antihistamine-sensitive dilatation ensued. Sympathetic vasoconstriction was not required for the poststimulation dilatation since β-xylocholine ether (β-TM10), a noradrenergic antirelease agent, prevented vasoconstriction during nerve stimulation but did not prevent the poststimulation dilatation. This system appeared to be under adrenergic control because treatment with the α-adrenergic blocker, phentolamine, prevented the poststimulation dilatation.

This concept of reciprocal control of a histaminergic system is consistent with the concept of histamine mediation of reflex dilatation outlined by Beck (5). Beck proposed that the dilatation associated with reflex withdrawal of sympathetic efferent activity was composed of both active and passive components. The passive component is caused by the reflex withdrawal of sympathetic vasoconstrictor tone. He also proposed that the active

FIG. 7. Effects of H₁ and H₂ antihistamines on histamine-induced dilatation and dilatation accompanying exercise of hindlimb. Single asterisks indicate that responses after mepyramine were less than control (P < .05), and double asterisks indicate a further attenuation of responses after metiamide (P < .05). Mean differences in responses after mepyramine as compared to control were -27 ± 8, -30 ± 10 and -20 ± 8 mmHg for 1-, 3-, and 10-μg doses of histamine. After metiamide, mean differences from mepyramine were -11 ± 5, -16 ± 4, and -26 ± 5 mmHg for 1-, 3-, and 10-μg doses of histamine.

FIG. 8. Effect of antihistamines on dilatation in perfused hindpaw after bretylium and atropine pretreatment. Dilatation was caused by stimulation of lumbar sympathetic chain, intraarterial histamine, and glyceryl trinitrate (GTN). Use of asterisks same as Fig. 3. Mean differences between control responses to histamine and responses after mepyramine were -35 ± 7 and -21 ± 7 mmHg for 1- and 3-μg doses, respectively. After metiamide, mean differences from responses after mepyramine were -14 ± 2 and -26 ± 3 mmHg for 1- and 3-μg doses of histamine. Mean difference in vasodilator responses after 3 Hz stimulation between mepyramine and metiamide treatment was -13 ± 3 mmHg.
component involves the release of histamine. This has been demonstrated experimentally by Beck et al. (7) and Brody (11). Release of histamine during nerve stimulation in the dog that is associated with dilatation has also been described by Lioy and White (21) and in the cat by Tuttle (28, 29). Weaver and Gebber (30), in an electrophysiological analysis of nerve activity in the lumbar sympathetic chain, found no evidence of nerve fibers whose activity increased during baroreceptor-mediated dilatation, thus confirming the fact that reflex vasodilatation involves only sympathoinhibition. Ryan and Brody (25) measured histamine in dog skeletal muscle, the major site of baroreceptor-mediated active reflex vasodilatation, and found high levels of histamine which did not decrease after denervation. These authors proposed that the storage site of vascular histamine may be non-neuronal and under reciprocal control of the adrenergic nerves, i.e., when adrenergic discharge is increased during baroreceptor-mediated dilatation, it inhibits the stabilizing effect of norepinephrine on the histamine pool so that it is lost and histamine is liberated. The pharmacologic evidence for histamine mediation of active reflex dilatation was obtained originally with the use of classical antihistamines of the H₁-receptor type. There are numerous reports of partial attenuation of the active component of reflex vasodilatation by H₁ antihistamines in the dog (4–7, 9–11), cat (28), and monkey (19). In the dog, H₁ and H₂ antihistamines block histamine responses in a specific manner (23, 24). H₂ antihistamines given alone have little or no effect on histamine-induced dilatation. H₁ antihistamines such as mepyramine cause a partial attenuation of responses to histamine. However, when H₂ antihistamines are added, there is specific additional inhibition of responses to histamine. In another study (24), it was determined that histamine was the only one of several vasodilators to be affected in this specific manner. The parallel reduction of responses to histamine and the reflex vasodilatation caused by increasing arterial pressure by the sequential administration of H₁ and H₂ antihistamines provides additional pharmacological evidence for histamine mediation of the active component of reflex vasodilatation and provides new evidence for the participation of H₂ receptors.

Examination of Fig. 1 reveals that the magnitude of the reduction in dilatation was greater for the exogenous administration of histamine than for the reflex vasodilatation. In light of the two components that constitute reflex vasodilatation, namely the active and passive components, this is to be expected. A large portion of the reflex dilatation is due to the passive withdrawal of adrenergic vasoconstrictor tone from the hindlimb (4, 5). This portion would not be expected to be altered by the antihistamines. The findings that neither vascular tone, as reflected by perfusion pressure, nor reflex vasoconstrictor responses were reduced by either or both antihistamines further indicate that the attenuation of reflex vasodilatation did not involve the passive component, i.e., that portion of the response produced by withdrawal of adrenergic vasoconstrictor tone. Vascular responsiveness did not appear to be altered because there were no significant modifications of responses of glyceryl trinitrate or intra-arterial norepinephrine. It follows, therefore, that the portion of the dilatation that was reduced with combined antihistamines represents the contribution of histamine to the dilatation because responses to exogenous histamine were nearly abolished.

Hcitz and Brody (16) reported that poststimulation vasodilatation in the dog gracilis muscle was nearly abolished by triphenylamine as were responses to small doses of histamine. This would suggest that only H₁ receptors participate in this response. In this current study, H₂ blockade by metiamide had little effect on responses to histamine but did cause a significant attenuation of the poststimulation dilatation. This could suggest that 1) metiamide has a weak H₁ receptor-blocking effect; 2) metiamide has a nonantihistamine effect on a nonhistamine mechanism; or 3) during poststimulation dilatation, a portion of the response involves H₂-receptor activation. The first proposal seems unlikely because metiamide in the doses used has no effect on responses to a specific H₁-receptor agonist 2-(2-pyridyl)ethylamine (24). The second proposal also seems unlikely because metiamide has been shown to have no effects on vascular responses to nitroglycerin, acetylcholine, isoproterenol (24), bradykinin (18), or norepinephrine (Table 1). It would appear therefore that a portion of the response involves H₂-receptor activation. As in most vasodilator responses in the dog involving histamine, the majority of this response appears to involve H₂ receptors. This is evidenced by the complete, or nearly complete, abolition of poststimulation dilatation by mepyramine alone or by mepyramine following metiamide. The involvement of H₂ receptors is shown by the partial attenuation of the dilatation by metiamide given alone. The H₂ receptors activated during poststimulation dilatation appear to be different from those activated by the exogenous administration of histamine. This is suggested by the findings that metiamide...
alone attenuated poststimulation dilatation but not dilatation due to exogenous histamine. It would appear that the H₂ receptors activated during poststimulation dilatation do not play a major physiological role because the response could be abolished by mepyramine.

Lewis (20) proposed that the hyperemia accompanying the removal of an occlusion to the forearm was caused by the liberation of histamine. Indeed, Anrep et al. (2) reported an increased amount of histamine in venous blood from muscle during reactive hyperemia. Duff et al. (14) examined the effects of the antihistamines triprolidine, antazoline, and mepyramine on postocclusion hyperemia in the human forearm. After 3 min of occlusion, none of the antihistamines had an effect on the magnitude of the hyperemia. However, when the period of occlusion was extended to 10–25 min, there was a partial attenuation of the hyperemia. The data of the present study are in agreement with those of Duff et al. (14) in that the hyperemia after short periods of occlusion is not attenuated by H₁ antihistamines. However, as described previously, histamine interacts with H₂ as well as H₁ vascular receptors in the dog (18, 23, 24). It was therefore possible that reactive hyperemia could involve histamine as the mediator through activation of H₂ receptors. The present study provides evidence that the additional blockade of H₂ receptors by metiamide does not alter the magnitude of the reactive hyperemia. The combined blockade of H₁ and H₂ receptors causes a large reduction in histamine-induced vasodilatation without causing a coincident reduction in the hyperemia. These data do not support the postulate of Schayer (26) that histamine is the vasodilator mediator of reactive hyperemia produced by short periods of occlusion, at least not through direct interaction with vascular receptors.

Muscular exercise is known to be accompanied by vasodilatation. In the present study, exercise was produced in the dog hindlimb by stimulation of the sciatic nerve. Anrep et al. (2) demonstrated the release of histamine from exercising muscle and suggested that histamine was responsible for the dilatation seen with exercise. It follows that, if histamine mediates exercise hyperemia, then responses to histamine and the hyperemic responses should be reduced in parallel by H₁ and H₂ antihistamines. Such was not the case, however. Histamine-induced responses were attenuated by mepyramine and further attenuated by the subsequent administration of metiamide. Attenuation of the responses to histamine was obtained without a similar attenuation of the dilatation occurring with exercise. This dilatation seen with sciatic nerve stimulation was not neurogenic in origin because no changes in perfusion pressure occurred after neuromuscular blockade with decamethonium. Thus, these data do not support a role for histamine in the mediation of the hyperemia associated with exercise in this study.

Sympathetic vasodilatation in the dog’s paw or limb after adrenergic and cholinergic blockade has been described by Zimmerman (31), Brody and Shaffer (12), and Beck et al. (6). Zimmerman found that the combination of atropine and the H₁ blocker, triprolidene, reduced the magnitude of the sympathetic dilatation in the paw.

Attenuation of this dilatation by H₁ antihistamines was found neither by Ballard et al. (3) nor in the present study. Mepyramine significantly reduced responses to histamine but did not alter neurogenic dilatation or dilatation due to glyceryl trinitrate. After the further administration of metiamide, there was an additional attenuation of responses to histamine and a reduction in the dilatation obtained by 3 Hz stimulation. These data provide evidence that histamine may mediate a portion of the low-frequency neurogenic dilatation in the paw. In these studies the dilatation in the hindpaw appears to involve a histaminergic component acting through H₂ receptors and a component obtained by higher frequencies of nerve stimulation with a yet unidentified mediator (3, 12, 31).

In a recent study, Kraft and Zimmerman (18) reported a reduction in the sustained dilator response to nerve stimulation in the dog hindpaw and a reduction in responses to histamine by H₁- and H₂-receptor blockade. However, these authors concluded that this reduction was not due to a specific antihistamine action and instead suggested that the reduction in sustained dilatation was due to a potentiation of residual adrenergic function. Such would not appear to be the case in these studies, however. Enhanced vasoconstrictor effects due to the antihistamines should cause 1) enhanced vasoconstriction due to norepinephrine, 2) enhanced reflex vasoconstriction, or 3) increased vascular tone (measured as perfusion pressure). Because none of these possibilities was observed, it seems unlikely that mepyramine or metiamide causes a potentiation of adrenergic vasoconstrictor effects. As described by Isaac and Goth (17), some H₁ antihistamines display a cocainelike effect, i.e., the potentiation of responses to norepinephrine. In that study, mepyramine, unlike some other H₁ antihistamines, failed to display a cocainelike potentiation of responses to norepinephrine.

Compound 48/80 has been reported by Paton (22) to cause the release of histamine in the dog. After the systemic administration of compound 48/80, there was a fall in blood pressure and an increase in plasma histamine which presumably caused vasodilatation. The effects of H₁ and H₂ antihistamines on dilatation associated with the chemically induced release of endogenous histamine were studied in the perfused gracilis muscle. Both histamine and compound 48/80 caused dilatation in the muscle. Mepyramine attenuated the histamine-induced dilatation but not the dilatation associated with compound 48/80. The subsequent administration of metiamide reduced further the responses to histamine and caused a reduction in the dilatation associated with compound 48/80. These results were somewhat unsuspected in light of the pharmacology of compound 48/80, i.e., histamine release, and the effects of H₁ and H₂ blockade on histamine-induced responses. However, compound 48/80 not only causes the liberation of histamine, but also releases slow reacting substances (SRS-A), serotonin, and unsaturated fatty acids (1, 22). It is possible to conclude then that the failure of mepyramine to reduce dilatation after compound 48/80 could be due to the release of nonhistamine vasodilator materials in addition to histamine. Only after the combined blockade
of both H₁ and H₂ receptors was it possible to reduce the histamine component of the dilatation due to compound 48/80. An alternative hypothesis is that compound 48/80 releases histamine that reacts only with H₂ receptors. However, in one additional experiment, metiamide given alone failed to attenuate vasodilatation caused by compound 48/80. It is not likely that the reduction in responses to compound 48/80 was due to tachyphylaxis because responses produced by repetitive injection of 30 μg of compound 48/80 were unaltered.

A fourth possibility is that there is different distribution of H₁ and H₂ histamine receptors across the vessel wall. It is conceivable that there exists a high concentration of H₁ receptors on the inner portions of blood vessels. This would allow intra-arterially administered histamine to act primarily on H₁ receptors. As described by El-Ackad and Brody (15), there are apparently no histamine-containing mast cells in dog blood vessels. Mast cells are found outside blood vessels, however. Histamine released by compound 48/80 from tissue stores might preferentially interact with the outer portions of vessels. If there is a high concentration of H₁ receptors on inner portions of vessels and a high concentration of H₂ receptors on outer portions, this possibility could explain the fact that mepyramine only attenuated the vasodilator responses following intra-arterial histamine and did not attenuate the vasodilatation caused by compound 48/80.

These data regarding the actions of compound 48/80 illustrate the usefulness of combined H₁- and H₂-receptor blockade in the investigation of vasodilatation though to involve histamine. If only a classical antihistamine had been used such as mepyramine, that did not attenuate the vasodilatation following compound 48/80, it might have been concluded that histamine was not involved in this vasodilatation. However, after combined blockade of receptors for histamine, an attenuation was observed, suggesting a role for histamine in this form of vasodilatation.

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