Chronotropic and Dromotropic Effects of Histamine on the Canine Heart*

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The actions of 2-methylhistamine (H₁ agonist), 4-methylhistamine (H₂ agonist), and histamine were studied by selective perfusion of the sinus node artery and atrioventricular node artery in 75 dogs anesthetized with pentobarbital sodium. 2-Methylhistamine and histamine had variable and inconsistent effects on the sinus rate. 4-Methylhistamine (100 μg/ml) produced acceleration of the sinus rate from 158 ± 4 to 173 ± 5 beats per minute (P < 0.05) when perfused via the sinus node artery. The effects of the histamine agonists on atrioventricular junctional rhythms were similar to the effects on sinus rhythm. The response of the sinus node to vagal stimulation was attenuated by selective perfusion with histamine; however, the direct negatively chronotropic action of acetylcholine was not affected by histamine. Neither 2-methylhistamine nor 4-methylhistamine affected the response of the sinus node to vagal stimulations. Both 4-methylhistamine and histamine (but not 2-methylhistamine) attenuated (P < 0.05) the response of the sinus node to stimulation of the right stellate ganglion. The positively chronotropic effects of directly perfused norepinephrine were unaffected by histamine or 4-methylhistamine. These results suggest a neural depressing action of histamine on autonomic efferent fibers. In the atrioventricular junction, both histamine and 2-methylhistamine (but not 4-methylhistamine) had negatively dromotropic effects. Cimetidine (an H₂ antagonist) had no significant direct effects on the sinus rate or atrioventricular conduction and failed to prevent the acceleration of the sinus rate produced by local perfusion with 4-methylhistamine.

Histamine produces cardiac stimulatory effects in various species of animals.¹⁻⁴ A positively inotropic response and an increase in heart rate are usually observed after administration of histamine in preparations such as isolated atria, perfused Langendorff hearts, and preparations of the heart and lungs of dogs,¹ rabbits,⁵ guinea pigs,⁶ and cats.⁷ Although histamine does release catecholamines⁸ and is a specific constituent of certain autonomic nerve fibers,⁹,¹⁰ most agree that its cardiac stimulatory actions are not exclusively mediated by adrenergic mechanisms, since they are readily demonstrable after depletion of catecholamines or appropriate blockade of β-adrenergic receptors.⁶,¹¹ Less is known about the dromotropic action of histamine, but some have reported that it impairs atrioventricular conduction.¹¹,¹²,¹³

Utilizing techniques that permit direct and selective perfusion of either the sinus node or the atrioventricular junctional region,¹⁴⁻¹⁶ we have investigated the direct and indirect chronotropic and dromotropic actions of histamine and of the H₁ agonist (2-methylhistamine) and H₂ agonist (4-methylhistamine)¹⁷,¹⁸ in the canine heart in situ, keeping both neural and humoral influences intact. Included in this study are the electrophysiologic effects of the H₂ receptor antagonist, cimetidine.¹⁹,²⁰

**Materials and Methods**

Seventy-five adult mongrel dogs weighing 13 to 27 kg (29 to 60 lb) were anesthetized with pentobarbital sodium (30 mg/kg of body weight intravenously). Ventilation was supported through a cuffed endotracheal tube supplying room air with a constant-infusion pump (Harvard). A femoral venous catheter allowed intravenous administration of test substances. A catheter attached to a transducer was introduced via a carotid or femoral artery to measure central aortic pressure. The chest was opened in the right fourth intercostal space. Following administration of heparin sodium (2 mg/kg intravenously), both the sinus node and atrioven-

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tricular node arteries were cannulated with small poly-
ethylene catheters. Both arteries were ligated at their origin,
leaving the right coronary artery and the distal left circumflex
coronary artery intact. Collateral circulation in these two
regions is abundant and assures continued normal local func-
tion. Details of these methods have previously been
reported.14-16

Throughout each experiment a right atrial electrogram
from near the sinus node was recorded, along with an
electrogram from a ventricular surface. A tachogram was
triggered by successive depolarizations from either the sinus
node or ventricular surface electrogram. A His bundle elec-
trogram was obtained with a catheter positioned in the aortic
root.21

The right cervical vagosympathetic trunk and the right
stellate ganglion were used for stimulation with an electronic
square-wave stimulator at 20 Hz, with a duration of the
stimulus of 1 to 2 msec at either submaximal or supramaximal
voltages. In certain experiments, both cervical vagosym-
pathetic trunks were severed in the neck.

The drugs utilized for selective perfusion were histamine
phosphate (1 µg/ml to 1,000 µg/ml), histamine dihydro-
chloride (1 µg/ml to 1,000 µg/ml), acetylcholine chloride
(0.1 µg/ml and 1 µg/ml), l-norepinephrine bitartrate (0.1 µg/
ml), 2-methylhistamine dihydrochloride (10 µg/ml to
1,000 µg/ml), 4-methylhistamine dihydrochloride (10 µg/ml
to 1,000 µg/ml), and cimetidine (50 µg/ml to 1,000 µg/ml).
Each tested substance was prepared in Ringer’s solution, was
kept at room temperature, and was injected with a hand-held
syringe in 1-ml aliquots over one to two seconds. The
responses to administration of drugs were routinely compared
with control injections of Ringer’s solution alone. Systemic
blockade of muscarinic receptors was accomplished with
administration of atropine sulfate (0.2 to 1.0 mg/kg intra-
venously). Data were analyzed by standard statistical
methods, and the degree of significance was determined by
Student’s t-test.22 Values are expressed as the mean and
standard error of the mean.

![Figure 1. Positive chronotropic action of 4-methylhistamine dihydrochloride (shaded area of tachogram). Left panel shows characteristic slowing of sinus node during selective perfusion of sinus node artery (SNA). Sinus rate is calibrated in beats per minute. SN, Bipolar electrogram from vicinity of sinus node; and HBE, His bundle electrogram.](image)

![Figure 2. Histogram comparing chronotropic actions of 2-methylhistamine dihydrochloride and 4-methylhistamine dihydrochloride selectively perfused via sinus node artery (SNA) in increasing concentrations. Numbers of dogs are in parentheses.](image)
RESULTS

Histamine via Sinus Node Artery

In four dogs with a control sinus rate of 157 ± 4 beats per minute, selective perfusion of the sinus node artery with the H<sub>1</sub> agonist, 2-methylhistamine, at 10μg/ml caused no significant changes in the sinus rate. The next higher concentration of 2-methylhistamine (100μg/ml) produced a sinus bradycardia in three dogs (decrement in rate ranging between 14 and 56 beats per minute), a sinus tachycardia in four dogs (increment in rate ranging from 10 to 38 beats per minute), and no significant change in the sinus rate in one dog. With 2-methylhistamine at 1,000 μg/ml, there was a sinus bradycardia (slowing of from 14 to 48 beats per minute) in four dogs, a sinus tachycardia (acceleration of from 12 to 22 beats per minute) in three dogs, and no change in the sinus rate in the remaining dog.

In three dogs with a control sinus rate of 160 ± 2 beats per minute, selective perfusion of the sinus node with the H<sub>2</sub> agonist, 4-methylhistamine, at 10μg/ml produced no significant effect. A concentration of 4-methylhistamine of 100μg/ml significantly (P < 0.05) accelerated the sinus rate in 13 dogs from 158 ± 4 to 173 ± 5 beats per minute (Fig 1). 4-Methylhistamine in a concentration of 1,000 μg/ml significantly (P < 0.01) increased the sinus rate in seven dogs even more, from 157 ± 6 to 185 ± 7 beats per minute (Fig 2). Administration of the highest concentration of these analogues of histamine produced, upon recirculation, a variable degree of transient systemic hypotension; however, computation of the changes in sinus rate were determined prior to the changes in blood pressure.

Submaximal stimulation of the right cervical vagus nerve was performed in a manner to cause slowing of the sinus rate from 154 ± 7 to 55 ± 5 beats per minute in five dogs. Perfusion of 2-methylhistamine (1,000μg/ml) into the sinus node artery did not alter this response. Perfusion into the sinus node artery of 4-methylhistamine (1,000μg/ml) also had no significant effect on the sinus bradycardia induced by vagal stimulation in six dogs.

Control electrical stimulation of the right stellate ganglion in nine dogs induced an acceleration of the sinus rate from 152 ± 5 to 232 ± 9 beats per minute. Perfusion of the sinus node artery with 2-methylhistamine (10μg/ml or 100μg/ml) did not significantly diminish the response of the sinus node to...

Table 1—Response of Heart Rate to Right Stellate Stimulation

<table>
<thead>
<tr>
<th>Drug and Dose*</th>
<th>Heart Rate, beats per minute</th>
<th>No. of Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Methylhistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>232 ± 9</td>
<td>9</td>
</tr>
<tr>
<td>10μg/ml</td>
<td>227 ± 12</td>
<td>4</td>
</tr>
<tr>
<td>100μg/ml</td>
<td>216 ± 8</td>
<td>9</td>
</tr>
<tr>
<td>1,000μg/ml</td>
<td>192 ± 10***</td>
<td>9</td>
</tr>
<tr>
<td>4-Methylhistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>222 ± 5</td>
<td>14</td>
</tr>
<tr>
<td>10μg/ml</td>
<td>218 ± 11</td>
<td>4</td>
</tr>
<tr>
<td>100μg/ml</td>
<td>222 ± 6</td>
<td>13</td>
</tr>
<tr>
<td>1,000μg/ml</td>
<td>216 ± 8</td>
<td>10</td>
</tr>
</tbody>
</table>

*Drugs were perfused via sinus node artery.

**P < 0.01, compared to control.

Figure 3. Left panel shows control positively chronotropic effect of stimulation of right stellate ganglion (RS). Right panel shows attenuated response following perfusion of H<sub>1</sub> agonist (2-methylhistamine dihydrochloride) via sinus node artery (SNA). HBE, His bundle electrogram, with its three components (A, atrial; H, His; and V, ventricle); and RV, right ventricular electrogram.
stimulation of the stellate ganglion; however, in the same nine dogs the same stellate stimulation after perfusion of the sinus node with 2-methylhistamine (1,000 μg/ml) consistently reduced the amount of sinus tachycardia, the response becoming 155 ± 8 to 192 ± 10 beats per minute (Table 1). This response after administration of the H₁ agonist is significantly less (P < 0.01) than the control response (Fig 3). In contrast, no tested concentration of the H₂ agonist (4-methylhistamine) selectively perfused via the same route significantly altered the response of the sinus node to stimulation of the right stellate ganglion (Table 1). Furthermore, delivery of norepinephrine bitartrate (0.1 μg/ml) into the sinus node artery was not significantly affected by any concentration of 2-methylhistamine or 4-methylhistamine perfused via the sinus node artery. The control response of the sinus rate to administration of norepinephrine went from 151 ± 5 to 224 ± 8 beats per minute (ten dogs). Following perfusion with 2-methylhistamine (1,000 μg/ml into the sinus node artery), the response to administration of norepinephrine was 213 ± 8 beats per minute (seven dogs). Following perfusion with 4-methylhistamine (1,000 μg/ml into the sinus node artery), the response to administration of norepinephrine was 219 ± 10 beats per minute (five dogs).

The effects of perfusion of histamine phosphate or dihydrochloride through the sinus node artery were, as expected, a combination of H₁ and H₂ responses. Electrophysiologic responses were similar for both salts of histamine, and their effects will be considered together, except as noted. At a concentration of 10 μg/ml, perfusion with a salt of histamine in 11 dogs produced only slowing of the sinus rate, in three dogs produced only acceleration of the sinus rate, and in five dogs produced a biphasic response (acceleration followed by slowing). The response of the sinus rate to stimulation of the right stellate ganglion was attenuated following perfusion with histamine phosphate through the sinus node artery (five dogs). The control response to stellate stimulation was an acceleration of the sinus rate from 144 ± 12 to 210 ± 14 beats per minute. Following perfusion with histamine phosphate (100 μg/ml) via the sinus node artery, the acceleration of the sinus rate with stellate stimulation was from 140 ± 10 to 174 ± 12 beats per minute. Perfusion of histamine phosphate (100 μg/ml) into the sinus node artery in six dogs attenuated or abolished the slowing of the sinus node induced by vagal stimulation (Fig 4). During the period in which there was a diminished response to vagal stimulation, selective perfusion with acetylcholine chloride (0.1 μg/ml) always exerted its expected normal negative chronotropic effect, indicat-

![Figure 4. Temporary vagolytic effects of histamine selectively perfused via sinus node artery (SNA). Right cervical vagus is stimulated in each panel (RV). RVp, Right ventricular electrogram.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21035/...)

**Histamine via Atrioventricular Node Artery**

In three dogs, physostigmine (100 μg/ml) was perfused into the sinus node artery in order to depress the automaticity of the sinus node and allow a stable normal atrioventricular junctional pacemaker to emerge. During each atrioventricular junctional rhythm, selective perfusion through the atrioventricular node artery with 2-methylhistamine (10 μg/ml and 100 μg/ml) depressed this rhythm to varying degrees in two dogs. Quantitation was not possible since atrioventricular junctional bradycardia was profound enough to allow the escape of the previously suppressed sinus node pacemaker. In the third dog, perfusion with 2-methylhistamine (1,000 μg/ml) increased the automaticity of the atrioventricular junctional pacemaker. Perfusion of the atrioventricular node artery with 4-methylhistamine during atrioventricular junctional rhythm increased the rate of this rhythm in all three dogs. With perfusion of 4-methylhistamine (10 μg/ml), the increment in atrioventricular junctional rate ranged from 16 to 29 beats per minute; at 100 μg/ml, the increment in this rate ranged from 20 to 44 beats per minute (Fig 5).
The dromotropic effect of 2-methylhistamine was examined in four dogs by selective perfusion of the atrioventricular node artery during sinus rhythm. Selectivity of the perfusion was first confirmed by the transient heart block elicited with administration of acetylcholine chloride (0.1 \( \mu \)g/ml). The only dromotropic action of 2-methylhistamine was negative. A concentration of 2-methylhistamine of 10 \( \mu \)g/ml caused only a minor prolongation of the atrio-His (A-H) interval; but in three of the four dogs, 100 \( \mu \)g/ml increased the A-H interval by 10 to 135 msec. In the fourth dog, there was second-degree (2:1) heart block which lasted several minutes (Fig 6). There were no changes in the His-ventricle (H-V) intervals in any of the four dogs. In concentrations up to 1,000 \( \mu \)g/ml, 4-methylhistamine dihydrochloride failed to affect the A-H or H-V intervals of the His bundle electrogram of any of the four dogs studied.

**Effects of Cimetidine**

Cimetidine (50 \( \mu \)g/ml to 1,000 \( \mu \)g/ml) was selectively perfused into the sinus node artery in seven dogs. The perfusion had no direct chronotropic effect on its own, since it did not modify the postinjectional bradycardia, the postinjectional sinus tachycardia, or the control final sinus rate. Perfusion with cimetidine did not interfere with the response of the sinus node to stimulation of the right stellate ganglion. The response of the control sinus rate to stellate stimulation went from 168 ± 8 to 226 ± 14
beats per minute (three dogs). Following perfusion with cimetidine via the sinus node artery, the response was virtually identical and averaged 223 ± 19 beats per minute. Cimetidine did not affect the response of the sinus node to norepinephrine directly administered into the sinus node artery (two dogs). In five dogs the sinus tachycardia produced by selective perfusion with 4-methylhistamine (100µg/ml) was not attenuated by prior selective perfusion with cimetidine (50µg/ml to 1,000µg/ml). In those experiments the initial positive chronotropic response to perfusion with 4-methylhistamine was from a rate of 149 ± 11 to 166 ± 12 beats per minute. Following administration of cimetidine, perfusion with 4-methylhistamine accelerated the sinus node from a rate of 155 ± 11 to 181 ± 17 beats per minute (Fig 7).

Sinus bradycardia caused by stimulation of the cervical vagus was significantly (P < 0.05) attenuated in five of six dogs by selective perfusion of cimetidine (50µg/ml) into the sinus node artery. The control response to vagal stimulation consisted of slowing from 154 ± 8 to 74 ± 10 beats per minute; perfusion with cimetidine attenuated this effect by almost 50 percent, the same vagal stimulation then only causing slowing from 153 ± 8 to 127 ± 10 beats per minute (Fig 8). In one out of six dogs, perfusion with cimetidine did not diminish the amount of sinus bradycardia in response to vagal stimulation. In two dogs, perfusion of the sinus node artery with acetylcholine chloride (0.05µg/ml) produced a slowing of the sinus rate from an average 150 to 62 beats per minute. Following perfusion of the sinus node artery with cimetidine, the response to administration of acetylcholine was from an average 162 to 91 beats per minute.

Perfusion of the atrioventricular node artery with cimetidine in six dogs did not affect A-H or H-V intervals of the His bundle electrogram. In one dog the A-H interval decreased by 10 msec.

**Discussion**

The chronotropic and dromotropic effects of histamine on the canine heart are the net result of a complex interaction between its varied separate actions on autonomic nerves, on adrenergic and cholinergic receptors of the target cells in the specialized tissues, and on the histamine receptors (H₁ and H₂). In understanding this complexity, one must individually consider both the direct and indirect electrophysiologic effects of each of the two different histamine agonists and the selective H₂ antagonist, cimetidine.

The H₁ receptor agonist (2-methylhistamine), when selectively perfused through the sinus node artery, produced inconsistent and statistically insignificant direct effects on the sinus rate; however, there were two important indirect actions. First, the response of the sinus node to stimulation of the right stellate ganglion was significantly depressed (Table 1); however, this depression was not due to a β-adrenergic receptor blocking action, since the response of the sinus node to norepinephrine selectively perfused through the sinus node artery was unaffected by administration of 2-methylhistamine. It seems more likely that this effect occurred on the postganglionic sympathetic neuron. The second action of 2-methylhistamine is cholinomimetic and may, in part, involve the release of acetylcholine.

<table>
<thead>
<tr>
<th>Before Cimetidine</th>
<th>After Cimetidine</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
<td><strong>4-CH₃Hist</strong></td>
</tr>
<tr>
<td>195</td>
<td></td>
</tr>
<tr>
<td>175</td>
<td></td>
</tr>
<tr>
<td>155</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>(5)</td>
</tr>
<tr>
<td>115</td>
<td>(5)</td>
</tr>
<tr>
<td>95</td>
<td>(5)</td>
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</table>

**Figure 7.** Histogram comparing acceleration of sinus rate produced by administration of 4-methylhistamine (4-CH₃Hist) (100µg/ml via sinus node artery) before and after perfusion with cimetidine via sinus node artery. Numbers of dogs are in parentheses.

<table>
<thead>
<tr>
<th>Control</th>
<th>Cimetidine 50 µg/ml, SNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td><strong>RV Response</strong></td>
</tr>
<tr>
<td>175</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>(6)</td>
</tr>
<tr>
<td>125</td>
<td>(6)</td>
</tr>
<tr>
<td>100</td>
<td>(6)</td>
</tr>
<tr>
<td>75</td>
<td>(6)</td>
</tr>
<tr>
<td>50</td>
<td>(6)</td>
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</tbody>
</table>

**Figure 8.** Attenuation of vagal response by cimetidine. This histogram compares cardiac response to right cervical stimulation (RV) before and after selective perfusion of sinus node artery (SNA) with cimetidine. Numbers of dogs are in parentheses.
from parasympathetic neurons. The H1 agonist depressed atrioventricular transmission; however, although this negatively dromotropic effect was attenuated in animals given atropine, it was not abolished.

The H2 receptor agonist (4-methylhistamine), when selectively perfused through the sinus node artery, produced both consistent and significant increases in the sinus rate (Fig 1). This positive chronotropic action is in accordance with observations published by others.6,11,27,28 There was no significant dromotropic effect from 4-methylhistamine selectively perfused through the atrioventricular node artery.

Following selective perfusion with either salt of histamine, the response of the sinus node to cervical vagal stimulation was attenuated (Fig 4), while the response to directly administered acetylcholine was not affected. This presynaptic effect of depressed release of neurotransmitters on postganglionic sympathetic nerves is characteristic for histamine (Table 1).4,25 and it now appears to be applicable to parasympathetic nerves. Whether the effect is on preganglionic or postganglionic parasympathetic nerves or both is unknown. Furthermore, it has recently been shown that a comparable sympatholytic effect mediated via the H2 receptor can be demonstrated by systemic administration of histamine followed by the H2 antagonist, metiamide.29

The effects of histamine on atrioventricular junctional automaticity were similar to those on the sinus node. The H2 agonist accelerated the atrioventricular junctional rhythm,23 whereas the H1 agonist and histamine had mixed effects similar to those seen in the sinus node. It was not possible to manipulate the atrioventricular junction with blocking agents as easily as the sinus node is treated, since the automaticity of the atrioventricular junctional pacemaker is much more dependent on its local adrenergic nerves than is the sinus node.16

Actions by histamine on cardiac conduction were confined to those in the atrioventricular junction, since there was prolongation of the A-H interval of the His bundle electrogram but no change in the H-V interval. The negatively dromotropic action of histamine appears to be mediated exclusively via the H1 receptor, since 4-methylhistamine was ineffective while 2-methylhistamine was effective in depressing atrioventricular conduction. These actions of histamine may contribute to some dysrhythmias.12,13

The effects of the H1 agonist or the H2 agonist or histamine on the resistance of the sinus node artery or atrioventricular node artery were not determined in this study. Other investigators have determined that histamine generally dilates coronary vessels through the H1 receptor or through both the H1 and H2 receptors.31 This relaxation of the coronary arteries results in an increased diameter of the vessels and could have a negatively chronotropic effect on the pacemaker cells of the sinus node.24

At the highest concentrations tested (1,000μg/ml), perfusion with cimetidine caused no significant change in the sinus rate and no change in the response of the sinus node to sympathetic stimulation. Cimetidine was not tested against the H2 receptor of the nerves which mediated the sympatholytic effects of the 4-methylhistamine; however, perfusion with cimetidine did diminish the response to cervical vagal stimulation and to selectively perfused acetylcholine (Fig 8). In this respect, cimetidine has atropinic properties which are characteristic of anti histamines; however, cimetidine did not affect the sinus node's positively chronotropic response to selectively perfused 4-methylhistamine (Fig 7). Thus, the cardiac H2 receptors in this respect differ from the H2 receptors of the gastrointestinal system, where cimetidine is an effective blocking agent.19,20

REFERENCES

3 Verma SC, McNeill JH: Cardiac histamine receptors and cyclic AMP. Life Sci 19:1797-1802, 1976
4 Verna SC, McNeill JH: Cardiac histamine receptors: Differences between left and right atria and right ventricle. J Pharmacol Exp Ther 200:352-362, 1977
7 Trendelenburg H: The action of histamine and 5-hydroxytryptamine on isolated mammalian atria. J Pharmacol Exp Ther 130:450-460, 1960
11 Owen DAA: Histamine receptors in the cardiovascular system. Gen Pharmacol 8:141-156, 1977
12 Hashimoto H: Transient change in the auriculoventricular condition following the injection of histamine. Arch Intern Med 35:609-625, 1925
18 Hageman GR, Urthaler F, James TN. Chronotropic and dromotropic effects of histamine (H-1 and H-2) agonists upon the canine heart. Physiologist 20:39, 1977
30 Broadley KJ: The role of H1 and H2-receptors in the coronary vascular response to histamine of isolated perfused hearts of guinea-pigs and rabbits. Br J Pharmacol 54:511-521, 1975