Histamine H₂-Receptor Mediated Positive Dromotropic Effect in the Canine Atrioventricular Node

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Abstract—The role of histamine H₂-receptors in AV nodal conduction was estimated in the blood-perfused AV node preparation of the dog. Histamine injected into the AV node artery caused an initial, predominant, dose-related prolongation of the AH interval, which was followed by a slight but significant shortening. Diphenhydramine, an H₁-antagonist, abolished the initial prolongation, but the shortening was slightly enhanced. Cimetidine, an H₂-antagonist, abolished the shortening and potentiated the initial prolongation. Dimaprit, an H₂-agonist, caused only a slight, dose-related shortening of the AH interval, which was abolished by cimetidine. The shortening induced by either histamine or dimaprit was slightly suppressed, but was never abolished by atenolol, a beta-blocker, which completely abolished the noradrenaline-induced shortening. These results indicate that a positive dromotropic effect via H₂-receptors exists in the canine AV node, although the main effect of histamine on AV nodal conduction is a negative one via H₁-receptors.

According to extensive studies by Wolff and Levi (see the review of reference 1) using the guinea pig heart, cardiac effects of histamine are mediated by histamine H₂-receptors, i.e., a positive chronotropic effect on the sinoatrial node automaticity and a positive inotropic effect on the ventricular muscle (2–5), while exceptionally, histamine impairs the atrioventricular (AV) nodal conduction (a negative dromotropic effect) via H₁-receptors (2–6). In the dog heart (7, 8), like in the guinea pig heart, histamine impairs AV nodal conduction completely via H₁-receptors. In addition, 4-methyl-histamine, an H₂-agonist, administered selectively into the AV node artery had no effect on AV nodal conduction (AH interval) and cimetidine itself did not affect the AH interval, while 2-methyl-histamine, an H₁-agonist, prolonged and blocked the AH interval (8). In the same experiment, however, 4-methyl-histamine increased the AV junctional rhythm, while 2-methyl-histamine decreased it (8). Quite recently, however, it has been reported that even in the guinea pig heart, histamine in-

creased the maximum upstroke velocity of the propagated action potential of cells of the central part of the complete AV node, which was blocked by cimetidine (9). Furthermore, in the rabbit AV node preparation, histamine reduced the AH-interval and increased the V_{max} of NH-cells, which were abolished by cimetidine (10).

These diverse results among the previous reports may be explained by several reasons: species difference of experimental animals, route of drug administration, H₁- or H₂-receptor subtype selectivity of the drugs used, dependence of AV nodal conduction upon heart rate and accuracy of measuring AH interval. In addition, these results may suggest that even in the dog heart, H₂-receptors may play a role in AV nodal conduction, mediating an acceleration of AV nodal conduction which may be masked under H₁-receptor mediated negative dromotropic effects. Thus, in the present study, we attempted to prove H₂-receptor mediated positive dromotropic effects on the AV node in the dog heart using the isolated, blood-

perfused AV node preparation, which allows a precise measurement of AH interval by an automated AH interval meter, a constant pacing rate and a selective administration into the AV node artery of selective H_2 -agonists and antagonists.

Materials and Methods

The isolated, blood-perfused AV node preparation (11, 12) was prepared from a mongrel dog of either sex, weighing 8–13 kg, anesthetized with pentobarbital sodium (30 mg/kg, i.v.), given heparin sodium (500 U/

kg, i.v.) and exsanguinated. The AV node preparation (Fig. 1) consists of the right atrium and the interventricular septum, and the posterior septal (the AV node artery), anterior septal and right coronary arteries were cannulated. The preparation was placed in a double-wall glass jacket maintained at 38°C by circulating warm water. The AV node preparation was cross-circulated with the heparinized arterial blood of the support dog through the three cannulated arteries at a constant perfusion pressure of 120 mmHg with a Cole-Parmer Masterflex peristaltic

Fig. 1. Schematic representation of the isolated, blood-perfused atrioventricular (AV) node preparation of the dog (upper left) and typical recordings of atrial (A), His bundle (H) and ventricular (V) electrograms obtained from each bipolar electrodes (bottom). AVN, atrioventricular node; CS, coronary sinus; IVC, inferior vena cava; PA, pulmonary artery; PM, papillary muscle; RA, right atrium; ASA, anterior septal artery; PSA, posterior septal artery; LAD, left anterior descending artery; LCX, left circumflex artery. Upper right: Time course of typical effects of 3 µg of histamine injected into the AV node artery (PSA) on AV, AH and HV intervals. In the control, the AV, AH and HV intervals were 139, 98 and 41 msec, respectively. Histamine produced an initial prolongation of the AV (AH) interval, which was followed by a shortening. The HV interval was unchanged. The electrograms obtained at the times indicated by the open triangles (A, control; B, peak of prolongation of the AH interval; C, maximum decrease in AH interval) are shown in the bottom trace.

pump and a Starling pneumatic resistance placed parallel to the perfusion system. Venous blood from the AV node preparation and excess blood passing through the pneumatic resistance was collected in the blood reservoir and returned to the support dog through the jugular vein. The blood flow through the cannulated arteries was measured with an electromagnetic flowmeter (Nihon Kohden, MFV-1100).

As shown in Fig. 1, the crista terminalis of the right atrium was electrically driven by a stimulator and an isolation unit (Dia Medical, DHM-226-3 and DPS-110) with rectangular pulses of 1–3 V (about 20% above the threshold voltage) at 5 msec duration at a fixed rate of 2 Hz (120 stimuli/min) through bipolar stimulating silver electrodes. Bipolar atrial (A) electrograms obtained from the right atrial free wall, His bundle (H) electrograms obtained from near the interventricular part of the membrane septum behind the septal cuspid of the tricuspid valve, and ventricular (V) electrograms obtained from the base of the anterior papillary muscle of the right ventricle were fed to an automated AH interval meter (Dia Medical, DHM-226-1), which individually measures AV, AH and HV intervals with an analysis pitch of 1 msec. Typical displays of atrial, His bundle and ventricular electrograms and the analogue outputs of AV, AH and HV intervals are shown in the bottom and the right side of Fig. 1, respectively.

Adult mongrel dogs of either sex, weighing 14–23 kg, were used as support dogs, which were anesthetized initially with pentobarbital sodium, 30 mg/kg, i.v., and given an additional 4–5 mg/kg every hour. The animals received an initial dose of 500 U/kg heparin sodium, followed by 200 U/kg every hour. Respiration was controlled using an animal respirator (Harvard Apparatus, model 607). Systemic blood pressure at the femoral artery and heart rate triggered by the R wave of the lead II EKG were monitored continuously with a polygraph (San-ei Instruments, 361-6).

Drugs used were histamine dihydrochloride (E. Merck, Darmstadt, F.R.G.), dimaprit hydrochloride (Smith Kline & French, Welwyn Garden City, U.K.), diphenhydramine hy-

drochloride (Tokyo-Kasei, Tokyo, Japan), cimetidine hydrochloride (Smith Kline & Fujisawa, Tokyo, Japan), noradrenaline bitartrate (Wako Pure Chemical, Osaka, Japan) and atenolol hydrochloride (ICI Pharma, Tokyo, Japan). Drugs were injected intra-arterially into the AV node artery in a bolus fashion. The volume of injection was constant, 30 μ l, and was given over a period of 4 sec with a microsyringe (Terumo, Japan).

Statistical comparisons were evaluated by the *t*-test for paired data. P values less than 0.05 were considered significant.

Results

After approximately 1 hr equilibration, AV, AH and HV intervals were 134 ± 9 , 96 ± 7 and 38 ± 4 msec ($n=10$), respectively. When histamine was injected into the AV node artery, predominant and dose-related prolongations of AV and AH intervals followed by slight but significant shortenings were induced, but HV interval was unchanged. A typical experiment of an i.a. injection of 3 μ g of histamine is shown in Fig. 1, in which atrial (A), His bundle (H) and ventricular (V) electrograms were recorded at control (A), at the peak of prolongation (B) and at the maximum shortening (C) of the AV intervals. In each of the electrograms, the configurations were unaffected, but the interval between the A and H, i.e., the A and V electrograms was initially increased (B) and then decreased (C). The interval between the H and V electrograms was little affected by the injection of histamine into the AV node artery. In Fig. 2 are shown typical dose-related negative and positive dromotropic effects of histamine in a dose range of 1 to 30 μ g. As compared with the prolongation, the shortening of AH interval was very small (approximately 7 msec even at 10 μ g), but it was statistically significant ($P < 0.05$). At 30 μ g, the shortening was masked by a predominant and lasting prolongation of AH interval. Furthermore, although the second degree AV nodal conduction block was not produced by 30 μ g of histamine in the case of Fig. 2, the AV block was readily produced by 30 μ g of histamine in 7 of 10 AV node preparations. Coronary blood flow through the AV node artery was dose-relatedly increased by histamine (Fig.

Fig. 2. A typical experiment to observe the effects of histamine injected into the AV node artery on AV, AH and HV intervals and blood flow (BF) through the artery. The AV interval was dose-relatedly prolonged in parallel with the AH interval, but the HV interval was unchanged in doses of 1 to 30 μg of histamine. The shortenings of the AH (AV) interval followed the initial prolongation in doses of 1 to 10 μg . In this case, AV conduction was not blocked by 30 μg of histamine. Blood flow was dose-relatedly increased.

2). On the other hand, as shown in Fig. 3, when dimaprit, an H_2 -agonist, was injected into the AV node artery, only shortenings of the AH interval, which were small but significant and dose-related, were produced in a dose range of 10–300 μg . In 2 of 6 AV node preparations, 300 μg of dimaprit caused an initial 1–2 msec increase in the AH interval, followed by a long-lasting decrease, but no increase was observed in the remaining 4 preparations. Coronary blood flow was dose-relatedly increased by dimaprit (Fig. 3). The dose-related negative and positive dromotropic effects of histamine averaged from 10 AV node preparations and that for the positive one of dimaprit from 6 preparations are shown in Fig. 4 A and B, respectively. In Fig. 5 are shown dose-related increases in coronary blood flow through the AV node artery by histamine and dimaprit averaged from 10 and 6 preparations, respectively.

When diphenhydramine (30 μg), an H_1 -antagonist, which itself prolonged the AH

interval, was previously given into the same artery, histamine (10 μg)-induced prolongation of the AH interval was completely abolished and the shortening was slightly enhanced (Fig. 6A). Cimetidine (300 μg), an H_2 -antagonist, which itself only slightly increased the AH interval, completely abolished the histamine (3 μg)-induced shortening of the AH interval and slightly enhanced the prolongation (Fig. 6B). Similarly, the shortening of the AH interval induced by 100 μg of dimaprit was abolished by 300 μg of cimetidine (Fig. 7A). Both histamine (3 μg)- and dimaprit (100 μg)-induced shortenings were only slightly suppressed but never abolished by 100 μg of atenolol, a beta-blocker, 1 min after injection of the blocker, which abolished noradrenaline (0.1 μg)-induced shortening of the AH interval (approximately 25 msec) even 5 min after the injection (Fig. 6C and 7B). Figure 8 shows the summarized data obtained from 6 AV node preparations of the influences of diphenhydramine and cimetidine.

Fig. 3. A typical experiment to observe the effects of dimaprit injected into the AV node artery on AV, AH and HV intervals and blood flow (BF) through the artery. AV and AH intervals dose-relatedly shortened, but the HV interval remained unchanged. The shortening was blunted, but no initial and slight increase in AH (AV) interval was produced by 300 μ g of dimaprit in this experiment. Blood flow was dose-relatedly increased.

Fig. 4. Dose-response curves for the positive (open symbols) and negative (solid symbols) dromotropic effects of histamine (A, circles; $n=10$) and dimaprit (B, squares; $n=6$) injected into the AV node artery. Histamine caused biphasic responses of initial prolongations of the AH interval (solid circles), followed by shortenings (open circles) in doses of 1–10 μ g. At 30 μ g of histamine, an AV conduction block (AVB) was induced in 7 of 10 AV node preparations. Dimaprit caused only the shortenings of the AH interval (open squares) in doses of 10 to 100 μ g. At 300 μ g of dimaprit, a slight increase in the AH interval (a solid square) preceded the shortening in a half of the preparations.

Fig. 5. Dose-response curves for coronary vasodilator effects of histamine (solid circles) and dimaprit (solid squares).

dine on the negative and positive dromotropic effects of histamine, in which the prolongation of AH interval was statistically significantly ($P < 0.01$) abolished by the H_2 -antagonist (Fig. 8A) and enhanced by the H_2 -antagonist ($P < 0.05$) (Fig. 8B). On the other hand, the shortening induced by histamine was statistically significantly abolished by the H_2 -antagonist ($P < 0.01$) (Fig. 8B) and enhanced by the H_1 -antagonist ($P < 0.05$) (Fig. 8A). The shortening induced by dimaprit was completely abolished ($P < 0.01$), and the slight but significant increase in AH interval was uncovered in the presence of the H_2 -antagonist cimetidine (Fig. 8C). Figure 9 shows the summarized data on the influences of atenolol on the positive dromotropic effects of histamine and dimaprit obtained from 6 AV node preparations, in which the shortenings (6–7 msec) were only slightly but significantly ($P < 0.05$) suppressed by the beta-blocker, despite the almost complete ($P < 0.01$) abolishment of the noradrenaline-induced shortening (more than 20 msec).

Fig. 6. Influences of diphenhydramine (A), cimetidine (B) and atenolol (C) on the dromotropic effects of histamine. NA, noradrenaline.

Fig. 7. Influences of cimetidine (A) and atenolol (B) on the dromotropic effects of dimaprit. NA, noradrenaline.

Fig. 8. Summarized data on the influences of diphenhydramine (A) and cimetidine (B, C) on the dromotropic effects of histamine (A, B) and dimaprit (C). The negative dromotropic effect of 10 or 3 µg of histamine (H10 or H3, open columns in A and B) was suppressed by 30 µg of diphenhydramine (DP30, dotted column in A) and was potentiated by 300 µg of cimetidine (CM300, dotted column in B). The positive dromotropic effects of histamine (H10 or H3, hatched columns in A and B) was enhanced by diphenhydramine (DP30, cross-hatched column in A) and was suppressed by cimetidine (CM300, cross-hatched column in B). The positive dromotropic effect of 100 µg of dimaprit (DM100, lateral striped column in C) was abolished by cimetidine (CM300), and a slight increase in AH interval was unmasked by cimetidine. Dotted and cross-hatched columns show the negative and positive dromotropic effects, respectively, after the treatments. Vertical bars mean S.E. *P < 0.05, **P < 0.01.

Fig. 9. Summarized data on the influences of atenolol on the dromotropic effects of histamine (A), dimaprit (B) and noradrenaline (C). The positive dromotropic effects of 3 μ g of histamine (H3, hatched column in A), 100 μ g of dimaprit (DM100, lateral striped column in B) and 0.1 μ g of noradrenaline (NAO.1, vertical striped column in C) were significantly suppressed by 100 μ g of atenolol (AT100, cross-hatched columns in A, B and C). The negative dromotropic effect of histamine (H3, open column in A) was unaffected by atenolol (AT100, dotted column in A). Vertical bars mean S.E. * $P < 0.05$, ** $P < 0.01$.

Increases in coronary blood flow by histamine were suppressed, but not abolished, by either diphenhydramine (Fig. 10A) or cimetidine (Fig. 10B), while the increase was unaffected by atenolol (Fig. 10D). The increase by dimaprit was suppressed by cimetidine (Fig. 10C), but unaffected by atenolol (Fig. 10E).

Discussion

The present experiments clearly demonstrate that H_2 -receptors, exist on the AV node of the dog, mediating a positive dromotropic effect, although the negative dromotropic effect through H_1 -receptors is predominant. In other words, it is demonstrated that even in the AV node as well as other cardiac tissues such as the sinoatrial node and the ventricular muscle, histamine can cause an excitatory response via H_2 -receptors.

In the dog heart, it has been reported that histamine given either intravenously (7) or

selectively into the AV node artery (8) impairs AV nodal conduction completely via H_1 -receptors. Furthermore, neither 4-methylhistamine, an H_2 -agonist, nor cimetidine, an H_2 -antagonist, affected the AH interval, even when they were given selectively into the AV node artery of the *in situ* heart (8). These results are inconsistent with the present results obtained by selective injection of the agents into the AV node artery in the isolated AV node preparation. In the present experiments, the AH interval was accurately measured using the automated AH interval meter with an analysis pitch of 1 msec, in order to define the small shortening (several msec) of AH interval mediated via H_2 -receptors. Since an increase in heart rate via stimulation of H_2 -receptors can prolong the AH interval (5, 6), which may mask the small shortening via H_2 -receptors, the AV node preparation was electrically driven at a fixed rate of 2 Hz in the

Fig. 10. Summarized data of influences of diphenhydramine (A), cimetidine (B, C) and atenolol (D, E) on the coronary vasodilator effects of histamine (A, B, D) and dimaprit (C, E). The coronary vasodilator effects of 10 or 3 μ g of histamine (H10 or H3, open columns in A, B and D) were suppressed by 30 μ g of diphenhydramine (DP30) to approximately two-thirds of the control (vertical striped column in A) and by 300 μ g of cimetidine (CM300) to approximately two-thirds of the control (cross-hatched column in B), respectively, but unaffected by 100 μ g of atenolol (AT100, hatched column in D). The coronary vasodilator effect of 100 μ g of dimaprit (DM100, dotted columns in C and E) was suppressed by 300 μ g of cimetidine (CM300) to about a half of the control (cross-hatched column in C), but unaffected by 100 μ g of atenolol (AT100, hatched column in E). Vertical bars mean S.E. ** $P < 0.01$.

present experiments. Furthermore, 4-methyl-histamine is less selective as an H₂-agonist than dimaprit (13), the latter of which slightly but significantly and dose-relatedly shortened the AH interval of the dog heart in the present experiments.

In the guinea pig heart, it has been strongly recognized that both endogenous and exogenous histamine slowed and blocked AV nodal conduction (2–6), and it was completely suppressed by H₁-antagonists such as diphenhydramine (4, 5). In contrast to the present results, any shortening of the PR interval was not unmasked by histamine in the presence of H₁-antagonists. However, although burimamide, an H₂-antagonist, did not affect the histamine-induced prolongation of the PR interval in the isolated guinea pig heart (3, 5), in the guinea pig *in vivo* the slowing of

AV conduction induced by intravenous injection of histamine was slightly, but not significantly, potentiated by burimamide (5). Furthermore, 4-methyl-histamine, an H₂-agonist, induced only a moderate negative dromotropic effect, and the dose-response curve of 4-methyl-histamine for prolongation of the PR interval was not parallel to that of histamine (5, 6). These evidences may suggest that even in the guinea pig heart, H₂-receptors may modulate the AV nodal conduction to the opposite direction. In fact, quite recently, it was demonstrated that in the guinea pig heart, histamine enhanced the V_{max} of propagated action potentials of cells in the AV node (9). Similarly, in the rabbit AV node preparation, histamine decreased the AH interval, increased the V_{max} of NH-cells and induced AV arrhythmias, all of which

were suppressed by cimetidine (10). Thus, it is probable that H_2 -receptors can mediate an acceleration of AV conduction resulting from increases in amplitude and V_{max} of the action potential of cells in the dog AV node, which should be estimated in the dog heart for confirming the present results.

Since atenolol slightly suppressed both histamine- and dimaprit-induced shortenings of the AH interval, noradrenaline released from the sympathetic nerve endings (7) might be related to the shortenings. However, histamine itself attenuated the tachycardia produced by stimulation of cardiac sympathetic nerves via presynaptic mechanisms (8, 14, 15). Furthermore, positive chronotropic and positive inotropic effects of histamine in the isolated dog atrium were not blocked by tetrodotoxin (a blocker of nerve excitation), desmethylimipramine (an uptake blocker) and alprenolol (a beta-blocker), although desmethyl-imipramine slightly but insignificantly suppressed the histamine-induced positive chronotropic effect (16). Even in the present experiments, both the shortenings were never abolished by atenolol which almost completely abolished the noradrenaline-induced shortening (Fig. 9), but were entirely suppressed by cimetidine (Fig. 8). Thus, the present results strongly suggest the existence of H_2 -receptors in the AV node of the dog, which mediate the positive dromotropic effect, although the role of noradrenaline released from the sympathetic nerve endings through the tyramine-like actions in the H_2 -receptor mediated positive dromotropic effects of histamine and dimaprit can not be excluded.

The possibility that increased coronary blood flow may shorten the AH interval, which was occasionally observed in the underperfused heart, remains to be elucidated. Certainly, the increases in blood flow by 3 μ g of histamine and 100 μ g of dimaprit were suppressed by 300 μ g of cimetidine to two thirds and a half of the controls (Fig. 10B and C), and the shortenings of the AH interval was concomitantly abolished (Fig. 8B and C). However, the shortening of the AH interval by 10 μ g of histamine was rather potentiated by 30 μ g of diphenhydramine (Fig. 8A), although the increase in blood flow by his-

tamine was suppressed by the H_1 -antagonist to almost the same extent as that in the presence of cimetidine (Fig. 10A and B). In other words, the shortening of the AH interval by histamine was abolished by cimetidine, even though the increase in blood flow was the same as that in the presence of diphenhydramine. Furthermore, the shortenings of the AH interval by histamine and dimaprit were observed in the AV node preparations perfused at constant-flow (S. Motomura et al., unpublished observation). Thus, the influence of increased blood flow upon the shortening of AH interval could be excluded.

Although Hageman et al. (8) could not demonstrate the positive dromotropic effect as mentioned above, they reported the H_2 -receptor mediated increase in the AV junctional rhythm (positive chronotropic effect) in the dog heart. In the rabbit heart, histamine increased the automaticity of a rabbit AV node pacemaker cell as well as the V_{max} of cells in the complete AV node, which were blocked by cimetidine, but not by chlorphenamine, an H_1 -antagonist (9). Similar to the rabbit heart, however, in the dog heart, AV nodal conduction is regulated at the proximal portion (AN and N regions), but AV junctional rhythm originates from the distal portion (NH and H regions) in the AV junctional area (12). Thus, H_2 -receptor induced enhancement of the amplitude and V_{max} of the NH-cells, which was observed in the rabbit AV node (10), does not always mean an acceleration of AV nodal conduction via H_2 -receptors in the AV node, because electrophysiological properties of the NH-cells closely resemble those of the cells in the intraventricular conductive tissues such as the His bundle and bundle branches (17), where H_2 -receptors predominantly distribute (1, 18). Nonetheless, experiments to estimate the effects of histamine and H_2 -agonists and antagonists on action potentials of the N-cells in the dog AV node, on which AV nodal conduction almost entirely depends, remains to be elucidated.

In conclusion, it is certain that H_2 -receptor mediated positive dromotropic effects could occur in the AV node of the dog heart, although the physiological significance of H_2 -receptor mediated positive dromotropism is still unclear. H_2 -Receptors

mediated acceleration of AV nodal conduction might play a role in particular conditions, such as myocardial infarction, in which adverse electrophysiological effects of histamine are enhanced (19). Undoubtedly, however, the H₁-receptor mediated negative dromotropic effect on the AV node is the major arrhythmogenic action of histamine released endogenously and given exogenously (1).

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