The Arrhythmogenic Actions ofHistamine
on Human Atrial Fibers

ROBERTO LEVI, JAMES R. MALM, FREDERICK O. BOWMAN, AND MICHAEL R. ROSEN

SUMMARY We used standard microelectrode techniques to study the effects of histamine on right atrial tissues from patients undergoing corrective cardiac surgery. In the 10^{-4} to 10^{-8} M range, histamine increased maximum diastolic potential, action potential amplitude, and automaticity. In some preparations, histamine also induced delayed afterdepolarizations and triggered activity. The potency of histamine in increasing automaticity was about 10 times less than that of epinephrine. Propranolol (2 x 10^{-8} M), which abolished the chronotropic effect of epinephrine, did not alter the effect of histamine. Conversely, the effect of histamine but not that of epinephrine was antagonized by cimetidine (3 x 10^{-4} to 1 x 10^{-3} M). This suggests that H_{3} receptors mediate the chronotropic effects of histamine on the human heart. The slow channel blocker verapamil (2 x 10^{-8} to 2 x 10^{-7} M) counteracted the effects of histamine on automaticity, delayed afterdepolarizations, and triggered activity, suggesting that in human atrium histamine may act by increasing slow inward (presumably Ca^{2+}) current. If one considers these arrhythmogenic effects of histamine and the fact that human cardiac tissue contains large amounts of histamine, our experiments lend further support to the concept that histamine release can induce arrhythmias.


PHARMACOLOGICAL studies using specific agonists and antagonists have demonstrated that the mammalian heart has histamine receptors (see review by Levi et al., 1981). Moreover, there are ample stores of histamine in the mammalian heart that can be released by both immunological and non-immunological mechanisms. Both histamine release and intracardiac administration of exogenous histamine are associated with increases in cardiac rate and contractility and the occurrence of cardiac arrhythmias (Levi et al., 1976; Levi and Allan, 1980). Because studies of the cardiac effects of histamine to date have been performed using the hearts of nonhuman mammalian species and because it has been suggested that histamine may play a role in arrhythmogenesis in the human heart (Levi and Zavecz, 1979; Levi and Allan, 1980), it is important to extend our knowledge of the effects of histamine to the human heart. The purpose of this study, then, was to test the actions of histamine and its pharmacological antagonists on human cardiac tissues.

Methods

Tissues were obtained from the right atria of 43 patients undergoing corrective cardiac surgery. Patient age ranged from 1 to 65 years. The clinical diagnoses included atrial septal defect (8), ventricular septal defect (7), tetralogy of Fallot (7), coronary artery disease (7), mitral insufficiency (4), pulmonary stenosis (3), aortic insufficiency (2), endocardial cushion defect (2), and transposition of the great vessels (2) and AV canal (1). Institutional and Department of Health and Human Services rules for protection of human subjects were observed and informed consent obtained. At the time of surgery, a segment of atrial tissue measuring ~1 cm² was removed from the atriotomy site. This was placed in iced Tyrode’s solution (containing in mM/liter: NaCl, 137; NaHCO₃, 12; NaH₂PO₄, 1.8; KCl, 4.0; CaCl₂, 2.7; MgCl₂, 0.5; dextrose, 5.5) and transported rapidly to the laboratory. The tissue was placed in a Lucite chamber that was perfused with Tyrode’s solution warmed to 37°C and equilibrated with 95% O₂-5% CO₂. Microelectrode impalements were made with 3 M KCl-filled glass pipettes having resistances of 10–30 MΩ. In most experiments the tissues were allowed to beat spontaneously to evaluate the effects of histamine on impulse initiation. We have shown previously that, when permitted to attain stable automatic rhythms, fibers from normal and diseased human atria assume comparable resting and action potential characteristics and spontaneous rates (Mary-Rabine et al., 1980). In addition, in those of the present experiments in which we washed out the drug, control transmembrane potential characteristics and automaticity again were seen.

After the tissues had equilibrated in the Tyrode’s solution, 10–20 microelectrode impalements were made in each preparation to determine its cellular electrophysiological properties. Standard techniques were used to record the resting and action potentials and the effects of histamine on the transmembrane potential. Histamine was then superfused at concentrations between 1 x 10^{-8} and 1 x 10^{-6} M in the presence of 3 M KCl. The effects of histamine on the transmembrane potential were recorded and the resulting changes were plotted on a graph. The data were then analyzed statistically using the Student’s t-test for paired samples. The results were considered significant if the probability value was less than 0.05.
potentials, display them on oscilloscopes, and photograph them (Rosen et al., 1973; Hordof et al., 1976). The variables recorded were maximum diastolic potential, activation voltage (measured from 0 potential to the voltage at which phase 0 was initiated), action potential amplitude (measured from maximum diastolic potential to the peak of phase 0), mean slope of phase 4 depolarization, and spontaneous rate. In those preparations in which there was a relatively smooth transition between phase 4 and phase 0, we laid a straight edge along phase 0 and phase 4, and the potential opposite their point of intersection was considered the activation voltage. We then impaled a single cell and commenced the pharmacological studies (see below). Results reported here are from single implants maintained throughout the duration of a study.

In those experiments in which triggered rhythms were studied, we used previously described techniques (Rosen et al., 1973; Hordof et al., 1976) to deliver rectangular pulses to the tissues via Teflon-coated bipolar silver electrodes.

In the pharmacological experiments, EDTA, 5 $\times\ 10^{-5}$ M, was included in the Tyrode's. Some preparations were superfused with histamine (histamine 2HCl; Sigma) for 20 minutes at concentrations from $1 \times 10^{-8}$ to $1 \times 10^{-4}$ M. Measurements were made at the end of each 20-minute period. In other experiments, the preparations were superfused with epinephrine, $1 \times 10^{-11}$ to $1 \times 10^{-4}$ M (lepinephrine bitartate; Sigma), for 20 minutes at each concentration. In studies of $\beta$-adrenergic receptor blockade, propranolol, $2 \times 10^{-7}$ M (dl-propranolol HCl; Ayerst), was used, and in experiments on the effects of H$_2$ receptor blockade, cimetidine, $3 \times 10^{-8}$ M (Smith, Kline & French), was used. In preliminary studies, this concentration had no effect on the action potential or automaticity. In other experiments, verapamil $2 \times 10^{-8}$ to $2 \times 10^{-6}$ M (Knoll), was used.

Statistical analysis of the data was performed using analysis of variance and, where appropriate, $t$-tests for paired or grouped data. In Figure 4 linear regression analysis was used to test the relationship between slope of phase 4 and spontaneous rate. With increasing histamine concentrations, the positive chronotropic effect was accompanied by a concomitant increase in the slope of phase 4. When linear regression analysis was used to test the relationship between the slope of phase 4 and spontaneous rate, a good correlation was found ($r = 0.854; P < 0.05$).

Because the actions of histamine (as shown in Figs. 1-4) appear to be similar to those of epinephrine...

**Results**

The control action potential characteristics recorded from 43 preparations on the attainment of a stable spontaneous rhythm were: maximum diastolic potential, $-49.2 \pm 1.3$ mV; action potential amplitude, $55.5 \pm 1.6$ mV; slope of phase 4 depolarization, $12.3 \pm 0.9$ mV/sec; and spontaneous rate, $40.1 \pm 1.8$ beats/min. These results are similar to those recently reported by us for spontaneously beating human atria (Mary-Rabine et al., 1980).

The concentration-response curve for the effects of histamine on spontaneous rate and a comparison of its effects with those of epinephrine are shown in Figure 1. Whereas a negative chronotropic effect was observed with epinephrine, $10^{-11}$ to $1 \times 10^{-7}$ M, no negative chronotropic effect occurred with histamine. Histamine, $10^{-6}$ to $10^{-5}$ M, increased the spontaneous rate in a concentration-dependent fashion. This effect was qualitatively similar to that of epinephrine, although histamine was about 10 times less potent.

An example of the effects of histamine, $10^{-6}$ and $10^{-5}$ M, on automaticity of a single atrial fiber is shown in Figure 2. Superfusion with histamine caused an increase in spontaneous rate from 35 beats/min (panel A) to 52 and 85 beats/min with histamine, $10^{-6}$ and $10^{-5}$ M (panels B and C), respectively; also, there was a concentration-dependent increase in the slope of phase 4 depolarization and a moderate increase in maximum diastolic potential.

The effects of histamine on action potential characteristics are summarized in Figure 3. Action potential amplitude increased and activation voltage and maximum diastolic potential became significantly more negative ($P < 0.05$) at histamine, $1 \times 10^{-6}$ M, and failed to show further changes at higher histamine concentrations.

In Figure 4 are summary data concerning the effects of histamine on the slope of phase 4 depolarization and on spontaneous rate. With increasing histamine concentrations, the positive chronotropic effect was accompanied by a concomitant increase in the slope of phase 4. When linear regression analysis was used to test the relationship between the slope of phase 4 and spontaneous rate, a good correlation was found ($r = 0.854; P < 0.05$).

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Figure 2 Effects of histamine on the transmembrane potentials of a spontaneously firing human right atrial fiber. Zero potential is given by the horizontal line in each panel in this and subsequent figures. Histamine was superfused for 20 minutes at each concentration. A was recorded before histamine superfusion and B and C at the time of plateau effect of each histamine concentration.

Figure 3 Effects of histamine on action potential characteristics of human atrial fibers. Each point ± SE represents the maximum percent change in action potential amplitude, activation voltage, and maximum diastolic potential. Average control values (n = 22) were: action potential amplitude, 52 ± 3 mV; activation voltage, −36 ± 2 mV; maximum diastolic potential, −47 ± 2 mV.

Figure 4 Effects of histamine on automaticity of human atrial fibers. Each point ± SE represents the maximum increase in spontaneous rate and slope of phase 4. Average control values (n = 22) were: spontaneous rate, 41 ± 3 beats/min; slope of phase 4, 12 ± 2 mV/sec.

In the presence of propranolol, spontaneous rate was not increased by epinephrine (46/min; panel E), but was increased by histamine (70/min; panel F). Moreover, in the presence of propranolol, histamine increased the slope of phase 4 depolarization and the maximum diastolic potential, whereas epinephrine did not (panels D, E, and F).

A quantitative evaluation of the effects of histamine and epinephrine on spontaneous rate, in the presence and absence of propranolol, is shown in Figure 6. Propranolol completely abolished the positive chronotropic effect of epinephrine (left upper panel), but failed to modify the positive chronotropic effect of histamine (right upper panel), suggesting that histamine's action is not mediated by catecholamine effects on the β receptor.

Since the effects of histamine on human atrial fibers were clearly independent of adrenergic mechanisms and since histamine-induced stimulation of atrial automaticity in the guinea pig heart is antagonized by histamine H2 receptor antagonists (Levi and Pappano, 1978), we next studied whether the effects of histamine on the human atrium were...
Spontaneous Rate

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**Figure 6** Effects of epinephrine (left panels) and histamine (right panels) on the spontaneous rate of human right atrial fibers and their modification by propranolol (upper) or cimetidine (lower). The results are means ± SE of changes from control (control = 0). Initial control spontaneous rates were: left upper, 39 ± 6 (n = 8) and 30 ± 5 beats/min in propranolol; right upper, 40 ± 7 (n = 7) and 29 ± 5 in propranolol; left lower, 41 ± 5 (n = 5) and 21 ± 8 in cimetidine; right lower, 35 ± 6 (n = 5) and 21 ± 9 in cimetidine.

Modified by the H2 blocker, cimetidine. Preparations were superfused with histamine (10^{-8}, 5 × 10^{-8}, and 10^{-7} M) and, after a wash, with epinephrine (10^{-8}, 5 × 10^{-8}, and 10^{-7} M). Superfusion with histamine and epinephrine subsequently was repeated in the presence of cimetidine (3 × 10^{-8} or 10^{-5} M). Figure 7 demonstrates the results of one experiment. The spontaneous rate increased from a control value of 53 beats/min (panel A) to 102/min with histamine, 10^{-5} M (panel B), and to 95/min with epinephrine, 5 × 10^{-6} M (panel C). Both amines also increased the slope of phase 4 depolarization and the maximum diastolic potential (panels B and C, compared to A). In the presence of cimetidine, 10^{-5} M (panel D), there was a negative chronotropic effect (39/min) accompanied by a small decrease in maximum diastolic potential. When histamine was superfused together with cimetidine (panel E), no changes in spontaneous rate or slope of phase 4 occurred. However, when epinephrine was superfused together with cimetidine, the spontaneous rate increased to 96/min (panel F), the slope of phase 4 increased, and there was moderate hyperpolarization. A quantitative evaluation of the effects of histamine and epinephrine on spontaneous rate in the presence and absence of cimetidine is shown in Figure 6 (lower panels). Cimetidine blocked the positive chronotropic effect of histamine, but not that of epinephrine.

We then tested whether the slow channel blocker, verapamil, might modify automatic rhythms induced by histamine. An example of the effect of verapamil is shown in Figure 8. Here histamine, 10^{-4} M, increased the resting membrane potential of a quiescent preparation and then induced a spontaneous rhythm at 26 beats/min (panel B). This rhythm was slowed to 20/min by verapamil, 2 × 10^{-8} M (panel C), and abolished when the concentration of verapamil was increased to 2 × 10^{-7} M (panel D). The slowing and/or abolition of histamine-induced automaticity by verapamil as a function of its concentration was observed in all experiments in which verapamil was superfused (n = 5).

In considering the arrhythmogenicity of histamine, it is important to note that an increase in automaticity was not the only means whereby spontaneous rate was increased. In eight of the 22 preparations in which histamine was superfused, delayed afterdepolarizations developed during phase 4 (Fig. 9).

**Figure 7** Effects of histamine and epinephrine on transmembrane action potentials recorded from a spontaneously firing human atrial fiber in the presence and absence of cimetidine. The records are taken from a single impalement. Panel A, control. Records in B–F were taken at plateau effect. The preparation was washed free of histamine between B and C and again between E and F. The preparation was superfused continuously with cimetidine from D to F. For spontaneous rates, see text.
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Figure 8  Histamine-induced automaticity in a quiescent human atrial fiber and its antagonism by verapamil. The records are taken from a single impalement. See text for discussion.

Polarizations increased with the histamine concentration (see panels B, C, and D) until the fiber was triggered into sustained rhythmic activity (panel D).

Figure 10 demonstrates the effects of cimetidine on a histamine-induced triggered arrhythmia. Here, histamine-induced triggered activity occurred in response to an electrical stimulus. Moreover, an increase in the concentration of histamine superfusing this preparation from 10^{-5} to 5 \times 10^{-5} M caused an increase in the frequency of the repetitive firing initiated by a single stimulus (compare panels A and B). Both the firing frequency and the duration of the triggered rhythm were reduced greatly by cimetidine, 3 \times 10^{-5} M (panel C).

Discussion

We have found that histamine induces the following concentration-dependent changes in the electrophysiological properties of human right atrial fibers: hyperpolarization, increased activation voltage, increased action potential amplitude, induction of automaticity in quiescent preparations, and increased automaticity of spontaneously beating fibers. In addition, histamine displays important arrhythmogenic characteristics in that it induces delayed afterdepolarizations and triggered arrhythmias. Interestingly, the effects of histamine on human atrial automaticity occur within the same concentration range as in the hearts of the guinea pig and rabbit (Levi and Giotti, 1967; Levi and Pappano, 1978). Thus, the human heart is as sensitive to histamine as the guinea pig heart, the traditional animal model for studies of histamine and allergy.

Although histamine and epinephrine induced similar increases in the spontaneous rates of human atrial fibers, histamine was about 10 times less potent than epinephrine. This result is similar to that found in guinea pig atria (Levi and Pappano, 1978). Moreover, whereas low concentrations of epinephrine slowed the spontaneous rate of human atrial fibers, histamine did not. The biphasic effect of epinephrine, decreasing automaticity at low concentrations and increasing it at high concentrations, already has been described in human atrial fibers (Mary-Rabine et al., 1978) and in the canine ventricular specialized conducting system (Posner et al., 1976; Rosen et al., 1977). The decrease in automaticity has been attributed to the action of epinephrine on \(\alpha\) receptors and the increase to a \(\beta\) adrenergic action. In comparison, histamine does not decrease automaticity; rather, the concentration-response curve appears to be monophasic. This suggests that there are no \(\alpha\)-adrenergic effects induced by histamine either directly or indirectly via catecholamine release. Moreover, the effects of histamine appear to involve receptors of one class only, i.e., histamine H\(_2\) receptors. That the histamine H\(_2\) receptor antagonist cimetidine abolished the positive chronotropic effect of histamine,
whereas the β-adrenergic antagonist propranolol did not, is evidence for this argument. Thus, in the human heart, as in those of most laboratory animals, histamine-induced tachycardia appears to be an H2 response (Levi et al., 1981).

The positive chronotropic effect of histamine has been explained on the basis of an increase in slow inward Ca2+ current (Houki, 1973; Inui and Imamura, 1976; Ledda et al., 1976; Levi and Pappano, 1978). The induction by histamine of delayed afterdepolarizations and triggered activity, and their abolition by the slow channel blocker verapamil (see Figs. 8–10), are consistent with the hypothesis that histamine acts by enhancing slow inward (presumably Ca2+ ) current. A similar mechanism has been proposed for the cardiac effects of catecholamines (Pappano, 1970; Thyrum, 1974; Levi and Pappano, 1978). Thus histamine and catecholamine actions, although involving different receptors, both appear to be calcium-mediated.

In conclusion, the human atrium appears to be highly sensitive to histamine, and the actions of histamine here are mediated by specific H2 receptors. Like catecholamines, histamine appears to enhance slow inward current. In human cardiac tissue, histamine displays many of those actions that generally are recognized as arrhythmogenic (Cranefield and Wit, 1979), i.e., increased automaticity and initiation of delayed afterdepolarizations and triggered activity. This evidence suggests that histamine has the capability to be highly arrhythmogenic in the diseased human heart. It might be argued that in the normal heart histamine would not have these same effects. However, normal human atrial fibers that are permitted to beat spontaneously usually depolarize to the low membrane potentials seen in diseased fibers (Mary-Rabine et al., 1980). Therefore, considering the protocol used in these experiments, it is likely that some of the atria we studied were relatively normal. However, no definitive statement concerning the arrhythmogenicity of histamine in normal atria can be made without electrophysiological and/or ultrastructural evidence of the absence of disease.

In another study, we found that human cardiac tissue contains large amounts of histamine (2.81 ± 1.04 μg/g; n = 9) that can be released by appropriate chemicals and drugs (Levi and Allan, 1980). Since the arrhythmogenic effects of histamine can be potentiated selectively by therapeutic concentrations of commonly used drugs [e.g., digitalis (Levi and Capurro, 1975)] and since histamine release, by immunological and nonimmunological mechanisms, occurs fairly commonly (Levi and Allan, 1980), our experiments lend further support to the concept that histamine release can induce cardiac arrhythmias in patients.

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References

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