Histamine Induced or Enhanced Delayed Afterdepolarization and Triggered Activity in Guinea-pig Papillary Muscles

A Preliminary Study

Tsunemi TAJIMA, M.D. *and* Yutaka DOHI, M.D.

SUMMARY

We used standard microelectrode techniques to study the histamine induced or enhanced delayed afterdepolarization (DAD) and triggered activity (TA) of guinea-pig papillary muscle superfused with low-potassium Tyrode's solution. Before histamine, a series of driven action potentials did not induce DAD and TA. Immediately after histamine (10^{-5}M), DAD was induced and, finally, TA was induced after high rate pacing (150/min to 300/min). The effect of histamine was antagonized by cimetidine (5×10^{-6} to $5 \times 10^{-5}\text{M}$) but not by diphenhydramine. Also, the amplitude of DAD decreased after verapamil (10^{-7} to $3 \times 10^{-6}\text{M}$) and lidocaine (4×10^{-5} to $8 \times 10^{-5}\text{M}$). To investigate indirect evidence of increased cyclic AMP mediation in this histamine induced DAD, we studied the effects of a phosphodiesterase inhibitor (papaverine 10^{-5}M) or activator (N-methylimidazole 20 mM) on the histamine induced or enhanced DAD. The former enhanced and the latter depressed the histamine-induced (or enhanced) DAD. Thus, histamine may induce or enhance the DAD and TA by increasing the slow inward current. This mechanism may be mediated by histamine H_2 -receptors and the adenylate cyclase system in the cardiac ventricular muscle.

Additional Indexing Words:

Microelectrode techniques	Histamine	Low-potassium
H_2 -receptor	Cyclic AMP	Guinea-pig papillary muscle
Delayed afterdepolarization	Triggered activity	

IT has been reported from animal models¹⁾⁻³⁾ that released cardiac histamine is a major mediator of arrhythmias that occur during anaphylaxis and

From the Second Department of Internal Medicine, Saitama Medical School, Saitama, Japan.
Address for reprint: Tsunemi Tajima, M.D., Second Department of Internal Medicine, Saitama Medical School, Moroyama-machi, Iruma-gun, Saitama 350-04, Japan.

Received for publication June 1, 1984.

Manuscript revised October 8, 1984.

following the administration of histamine-releasing drugs. These arrhythmogenic effects of histamine included enhancement of normal automaticity, induction of triggered tachyarrhythmias, depression of atrioventricular conduction and increased vulnerability of the ventricles to fibrillation. In fact, frequent arrhythmias (non-sinus) including ventricular arrhythmias and asystole are present in the state of anaphylactic and anaphylactoid shock in humans.^{4),5)} The present study was undertaken to investigate whether histamine could induce ventricular tachyarrhythmias in the guinea-pig ventricular muscle by induction of delayed afterdepolarization (DAD) and triggered activity (TA). This possibility is raised by reports that histamine and catecholamine produce remarkably similar effects on the heart through the stimulation of adenylate cyclase^{6),7)} and catecholamines have been known to induce or enhance DAD and TA in many experimental studies.^{8),9)}

MATERIALS AND METHODS

Experiments were performed with right ventricular papillary muscles isolated from guinea-pigs. These animals were sacrificed by a blow to the head. The papillary muscles were isolated in Tyrode's solution of the following composition (millimolar concentration): NaCl 137; KCl 5.4; CaCl₂ 1.2; MgCl₂ 1.1; NaH₂PO₄ 0.42; NaHCO₃ 24; Glucose 5.0. The papillary muscles were mounted in a tissue bath perfused with Tyrode's solution at 37°C and equilibrated with 95% O₂-5% CO₂. The preparation was stimulated with rectangular pulses of 1 Hz in frequency, 2 msec in duration and 2 times threshold with an electronic stimulator (Nihon Kohden, SEN-7103). Microelectrode recordings were made with 3 M KCl-filled glass microelectrodes having resistances of 10-30 MΩ. After the tissues had equilibrated in the Tyrode's solution, standard techniques were used to record the resting and action potentials. Results reported here are from single penetrations maintained throughout the duration of a session. After a period of equilibration of at least 60 min for recording control action potentials, the preparations were exposed to a low-potassium Tyrode's solution (0.54 mM). After a 15 min superfusion with low-potassium Tyrode's solution, the preparations were paced in a stepwise fashion by a train of 8 to 10 impulses. Delayed afterdepolarization (DAD) is defined as an afterpotential after repolarization is complete. If the DAD amplitude reached the action potential threshold after train impulses of increasing frequency, the resulting extrasystole or repetitive activity, was termed triggered activity (TA). If DAD or TA was not induced, histamine (10⁻⁵ M) was administered to the bathing solution. DAD was induced immediately after addition of histamine. The sensitivity of the DAD to

several agents was examined. First, diphenhydramine HCl 10^{-5} M (Kowa) and cimetidine 5×10^{-6} to 5×10^{-5} M (Smith Kline & Fujisawa) were used as H_1 and H_2 receptor antagonists, respectively. The effect of the Ca^{2+} antagonist-verapamil (10^{-7} to 3×10^{-6} M, Eisai) on the DAD was tested. To know indirect mediation of cyclic AMP to induce DAD, we used papaverine HCl 10^{-5} M (Dainihon Seiyaku), a potent inhibitor of phosphodiesterase (PDE) and N-methylimidazole 20 mM (Tokyo Kasei), an activator of PDE. Also, we studied the effects of lidocaine (4×10^{-5} to 8×10^{-5} M, Fujisawa) on the DAD.

RESULTS

In our study, DAD was not induced after histamine (10^{-5} M) in the preparation superfused with normal Tyrode's solution. We used preparations superfused with low potassium medium. However, we used histamine before DAD will appear either spontaneously or after stimulation because transient depolarization was reported after prolonged exposure to potassium depleted solution.¹⁰⁾ After we ascertained after about 15 min superfusion with low potassium solution that DAD and TA were not induced by a high rate stimulus train, we administered histamine (10^{-5} M) to the bathing solution. After about 20 sec, DAD was induced by a high stimulation rate and finally, TA was induced in some preparations. We investigated pharmacological effects of various drugs on the histamine induced DAD. Generally, action potential duration shortened and the plateau phase increased after histamine.

Fig. 1 shows one example of DAD and TA induced immediately after histamine. The left and right panels show the results before and after histamine, respectively, and indicate the effects of 3 drive cycle lengths (CLs) on the after-potential characteristics. Although in the control left panel

Fig. 1. Histamine induced delayed afterdepolarization and triggered activity. The left and the right panels show the results of before histamine and after histamine, respectively. Although DAD was not induced in the control panel (left) for 3 drive cycle lengths, DADs (in the upper 2 rows of right panel) and triggered activity (lowest row of right panel) were induced after histamine.

Fig. 2. Cimetidine suppression of histamine induced DADs. The upper, middle and lower records show the results before histamine, after histamine and after cimetidine, respectively. Drive cycle lengths were 800, 600 and 400 ms. After histamine (the second row), DADs were induced by each cycle length. These DADs were depressed after cimetidine (the third row).

Fig. 3. The effects of verapamil on histamine-induced DADs. The upper, middle and lower rows show the results before histamine, after histamine and after verapamil, respectively. Drive cycle lengths were 500, 400, 300 and 250 ms. As shown in the lower record, verapamil suppressed the histamine induced DADs for all the drive cycle lengths.

DAD was not induced, DAD was already seen during nine 1000 ms drive CLs (upper row of right panel). The amplitude of DAD after nine shortened drive CLs increased progressively until TA was induced after nine train pacing at a CL of 400 ms (arrow in lowest row of right panel). The TA rate was 165/min, and the maximum diastolic potential just before TA was -125 mV. Generally, TAs were induced by a drive CLs of 400 to 200 ms in these experiments.

These histamine induced DADs were depressed by cimetidine (5×10^{-6} to 5×10^{-5} M). The upper, middle and lower traces of Fig. 2 show the results before histamine, after histamine and after cimetidine, respectively. Drive CLs were 800, 600 and 400 ms. After histamine (the second row), DADs were seen in each CL. These DADs were depressed after cimetidine (5×10^{-5} M) administration. These histamine induced DADs were not affected by diphenhydramine. Also, the amplitude of the histamine induced DAD was suppressed after verapamil (10^{-7} to 3×10^{-6} M). Fig. 3 shows the effect of verapamil on the histamine induced DAD. The upper, middle and

Fig. 4. The effects of lidocaine on the amplitude of histamine-induced DADs. The first, the second, the third and the fourth rows show the results before histamine, after histamine (DADs are seen), after 4×10^{-5} M lidocaine and 8×10^{-5} M lidocaine, respectively. Lidocaine 8×10^{-5} M suppressed the histamine induced DADs.

Fig. 5. The effects of papaverine on histamine induced DADs. Papaverine enhanced histamine induced DADs.

Fig. 6. The effects of N-methylimidazole on histamine induced DADs. N-methylimidazole suppressed histamine induced DADs.

lower traces show the results of before histamine, after histamine and after verapamil, respectively. As shown in this figure, verapamil suppressed the histamine induced DADs in all the drive CLs. Fig. 4 shows the effects of lidocaine on the amplitude of histamine induced DADs. The first, second, third and fourth rows show the results before histamine, after histamine, after 4×10^{-5} M lidocaine and 8×10^{-5} M lidocaine. As shown in this figure, lidocaine 8×10^{-5} M suppressed the histamine induced DADs.

To investigate a possible role of increased cyclic AMP through the adenylate cyclase system in these histamine induced DADs, we studied the effects of PDE inhibitor (papaverine HCl 10^{-5} M) and PDE activator (N-methylimidazole 20 mM). As shown in Figs. 5 and 6, histamine induced DADs were enhanced by papaverine and suppressed by N-methylimidazole.

DISCUSSION

According to Levi et al,^{3),11)} histamine is released into the systemic circulation during anaphylaxis by drugs and by surgical procedures. Studies in animal models have conclusively demonstrated that released cardiac histamine is a major mediator of arrhythmias that occur during anaphylaxis and following the administration of histamine releasing drugs.¹⁾⁻³⁾ During in vitro and in vivo anaphylaxis utilizing guinea pigs, ventricular dysrhythmias ranging from isolated multifocal ectopic beats to ventricular tachycardias and fibrillation were frequently seen.^{1),2)} Several lines of evidence^{3),12)} suggest a similar arrhythmogenic role for cardiac histamine in the human heart: (1) The human heart is rich in histamine; (2) Cardiac histamine can readily be released from human heart cells in vitro by therapeutic concentrations of drugs; (3) Histamine has potent arrhythmogenic effects on the heart in vitro. Levi et al³⁾ classified the mechanisms of the arrhythmogenic effects of histamine into five categories: (1) enhancement of normal automaticity, (2) induction of abnormal automaticity, (3) induction of triggered arrhythmias, (4) slowing of atrioventricular conduction and (5) increased vulnerability of the ventricles to fibrillation. In this report, we will refer only to the induction of triggered arrhythmias. Histamine induces DADs and triggered tachyarrhythmias in both spontaneously active and quiescent atrial fibers.¹²⁾ Our study may be the first one concerning histamine induced DADs and TA in the ventricular muscle. We could not induce DADs and TA in the guinea-pig papillary muscle superfused with normal Tyrode's solution. Therefore, we used Tyrode's solution with low-potassium to induce or enhance DAD and TA more easily because transient depolarizations develop spontaneously in guinea-pig papillary muscle superfused with potassium depleted solutions.¹⁰⁾ However, we used histamine before DAD developed spontaneously or in response to a train of pacing. It might be considered that our histamine-induced DADs might be the results of enhancement of DADs due to low potassium medium. Thus, we have observed a possible role of histamine in the induction of DADs under specific conditions, but the relationship of these conditions to clinical phenomena is not clear. Also, these histamine induced DADs and TAs might be induced through the histamine H₂ receptors as indicated in Fig. 2. These effects of histamine through the histamine H₂ receptors in the ventricular muscles were consistent with previous studies utilizing laboratory animals.¹³⁾⁻¹⁶⁾

It has already been suggested^{6),7)} that histamine might produce its positive inotropic and phosphorylase activating effects by increasing cardiac cyclic AMP in a manner analogous to that proposed for norepinephrine. We

investigated the effects of a PDE inhibitor, papaverine, and an activator, N-methylimidazole, on the histamine induced DAD to study the participation of increased cyclic AMP in the induction of DAD; the former and the latter enhanced and suppressed the DAD amplitude, which is circumstantial evidence for a role of increased cyclic AMP. Increased cyclic AMP induced by histamine has been suggested to activate cyclic AMP-dependent protein kinase and eventually facilitate the inward current of Ca^{2+} .^{16)–18)} Additionally, it is suggested that Ca^{2+} -triggered release of Ca^{2+} from the sarcoplasmic reticulum may amplify the Ca^{2+} flux across the sarcolemma.¹⁹⁾ Kass et al²⁰⁾ studied the ionic basis of the strophanthidin-induced transient inward current (TI) in cardiac Purkinje fibers utilizing voltage clamp techniques and suggested that cells eventually reach a state of Ca^{2+} overload (as in digitalis intoxication), which is accompanied by transient or oscillatory movements of Ca^{2+} between intracellular stores and cytoplasm. They stated that this oscillatory Ca^{2+} release from an intracellular store is the primary event underlying both the aftercontraction and the conductance change which generates TI. Furthermore, they suggested that TI is carried by a pathway that is permeable to both Na^+ and K^+ ions and that TI may be distinguished from the slow inward current by its kinetic, pharmacological and ionic properties. According to their hypothesis, TI may be evoked when intracellular Ca^{2+} is elevated by procedures other than digitalis intoxication. Thus, histamine may also evoke DAD and TA as a result of a Ca^{2+} overload which was caused by these mechanisms, mediated by histamine H_2 receptors, the adenylate cyclase system and the DAD induced effects of superfusion with low K^+ medium. It is also possible that verapamil, a slow channel blocker, can suppress the histamine induced DAD and TA by inhibiting the slow inward current.

REFERENCES

1. Capurro N, Levi R: The heart as a target organ in systemic allergic reactions. *Circ Res* **36**: 520, 1975
2. Senges J, Randolph U, Katus H: Ventricular arrhythmias in cardiac anaphylaxis. *Naunyn-Schmiedeberg's Arch Pharmacol* **300**: 115, 1977
3. Levi R, Chenouda AA, Trzeciakowski JP, Guo ZG, Aaronson LM, Luskind RD, Lee CH: Dysrhythmias caused by histamine release in guinea pig and human hearts. *Klin Wochenschr* **60**: 965, 1982
4. Pavsek K, Wegmann A: Pathophysiologie des anaphylaktischen und anaphylaktoiden schocks. *Fortschr Med* **99**: 47, 1981
5. Pavsek K, Wegmann A, Nordstrom L, Schwander D: Cardiovascular and respiratory mechanisms in anaphylactic and anaphylactoid shock reactions. *Klin Wochenschr* **60**: 941, 1982
6. Kukovetz WR, Pösch G, Wurm A: Effect of catecholamines, histamine and oxyfedrine on isotonic contraction and cyclic AMP in the guinea pig heart. *Naunyn-Schmiedeberg's Arch Pharmacol* **278**: 403, 1973

7. Mcneill JH, Verma SC: Blockade by burimamide of the effects of histamine and histamine analogs on cardiac contractility, phosphorylase activation and cyclic adenosine monophosphate. *J Pharmacol Exp Ther* **188**: 180, 1974
8. Wit AL, Cranefield PF: Triggered activity in cardiac muscle fibers of the simian mitral valve. *Circ Res* **38**: 85, 1976
9. Wit AL, Fenoglio JJ, Hordof AJ, Reemtsma K: Ultrastructure and transmembrane potentials of cardiac muscle in the human anterior mitral valve leaflet. *Circulation* **59**: 1284, 1979
10. Eisner DA, Lederer WJ: Inotropic and arrhythmogenic effects of potassium-depleted solutions on mammalian cardiac muscle. *J Physiol* **294**: 255, 1979
11. Levi R, Zavecz JH: Acceleration of idioventricular rhythms by histamine in guinea pig heart. *Circ Res* **44**: 847, 1979
12. Levi R, Malm JR, Bowman FO, Rosen MR: The arrhythmogenic actions of histamine on human atrial fibers. *Circ Res* **49**: 545, 1981
13. Ledda F, Fantozzi R, Mugelli A, Moroni F, Mannaioni PF: The antagonism of the positive inotropic effects of histamine and noradrenaline by H_1 and H_2 receptor blocking agents. *Agents and Actions* **4**: 193, 1974
14. Ledda F, Mantelli L, Mugelli A: Blockade by burimamide of the restorative effect of histamine in tetrodotoxin-treated heart preparations. *Br J Pharmacol* **57**: 247, 1976
15. Ledda F, Mugelli A, Mantelli L: A histamine-induced decrease of action potential duration in cardiac muscle mediated by H_2 receptors. *Agents and Actions* **7**: 199, 1977
16. Inui J, Imamura H: Restoration by histamine of the calcium-dependent electrical and mechanical response in the guinea-pig papillary muscle partially depolarized by potassium. *Naunyn-Schmiedeberg's Arch Pharmacol* **294**: 261, 1976
17. Kukovetz W, Pösch G: The positive inotropic effects of cyclic AMP. *Advanc Cyclic Nucl Res* **1**: 261, 1972
18. Reuter H: Localization of beta adrenergic receptors, and effects of noradrenaline and cyclic nucleotides on action potentials, ionic currents and tension in mammalian cardiac muscle. *J Physiol* **242**: 429, 1974
19. Fabiato A, Fabiato F: Contractions by a calcium-triggered release of calcium from the sarcoplasmic reticulum of single skinned cardiac cells. *J Physiol* **249**: 469, 1975
20. Kass RS, Lederer WJ, Tsien RW, Weingart R: Role of calcium ions in transient inward current and aftercontractions induced by strophantidin in cardiac Purkinje fibers. *J Physiol* **281**: 187, 1978