Acceleration of Idioventricular Rhythms by Histamine in Guinea Pig Heart

Mediation by H₂ Receptors

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SUMMARY. To evaluate the ability of histamine to induce ventricular arrhythmias, we studied the effects of histamine on ventricular rhythmicity in the isolated guinea pig heart with complete atrioventricular conduction block. As a function of dose (0.1—30 μg), histamine enhanced the idioventricular rate by increasing the rate of firing of the original pacemaker and also by causing the sudden appearance of faster idioventricular rhythms that coincided with changes in pacemaker site. Anaphylaxis in the isolated guinea pig heart with complete atrioventricular conduction block caused histamine release and acceleration of idioventricular rate. The effects of histamine on idioventricular rhythmicity were not attenuated by the histamine H₁ receptor antagonist chlorpheniramine, but were antagonized by the H₂ receptor antagonist cimetidine. Moreover, the selective H₂ agonist 4-methylhistamine (4MeH) accelerated the idioventricular rate, whereas 2-(2-thiazolyl) ethylamine (ThEA), at doses selective for H₁ receptor activation, did not. The effects of histamine on idioventricular rhythmicity were not modified by the β-adrenergic blocker pindolol. The mechanism by which histamine increases idioventricular rate probably involves two components: (1) an enhancement in automaticity of the original pacemaker, and (2) the induction of faster rhythms via reentry and/or afterdepolarizations. Whatever the mechanism, both components of the ventricular chronotropic action of histamine appear to involve exclusively histamine receptors of the H₂ type. Thus, our results suggest that H₂ receptor antagonists may have a role as specific antiarrhythmic agents in the treatment of cardiac dysfunctions caused by histamine release. Circ Res 44: 847-855, 1979

IN THE course of our studies on the cardiac effects of histamine we had become intrigued by the fact that histamine, whether exogenously administered or endogenously released, could induce ventricular dysrhythmias ranging from isolated multifocal ectopic beats to ventricular tachycardia and fibrillation. The severity of the arrhythmia was related to the amounts of histamine injected or released (Levi, 1972; Capurro and Levi, 1975; Levi and Capurro, 1975; Zavecz and Levi, 1977). The purpose of the present study was to investigate the mechanism of histamine-induced ventricular tachyarrhythmias by studying the influence of histamine on ventricular rhythmicity. We chose as an experimental model the isolated mammalian heart with complete atrioventricular conduction block. In this preparation idioventricular rate is not influenced by atrial pacemakers.

Methods

Male Hartley guinea pigs weighing 300–400 g were stunned by a blow to the base of the skull. The heart was quickly excised and mounted in a Langendorff apparatus (Levi, 1972) and was perfused at constant pressure (40 cm H₂O) with oxygenated Ringer's solution at 37°C. The ionic composition of the Ringer's solution was (in mM): Na⁺, 160; Cl⁻, 164; K⁺, 5.6; Ca²⁺, 2.2; HCO₃⁻, 5.9; glucose, 5.5 The apex of the heart was connected by a nylon thread to a force-displacement transducer (model FT03B, Grass Instruments). Isometric ventricular contractions were displayed on a pen recorder (model RS11, Beckman Instruments, Inc.). A bipolar surface electrogram, recorded from the right atrium and the left ventricle, was displayed on another channel of the pen recorder.

Following an equilibration period of 30–45 minutes, the right atrium was cut open and a ligature (5-0 surgical silk attached to a curved C-1 needle) was placed around the area of the bundle of His (Cavoto et al., 1973). It was judged that the ligature had produced complete atrioventricular conduction block when: (1) a completely random relationship between P and R waves was obtained, (2) the ventricular rate was stable and consistently slower than the atrial rate, and (3) there was total lack of conduction to the ventricles of responses to electrical stimuli applied to the right atrium. To verify
point 3, the hearts were paced electrically through the right atrium by means of a pulse generator (model 161, Tektronix Inc.) via an isolation unit (model IS2B, Bioelectric Instruments, Inc.). Each heart was driven at frequencies ranging between the lowest and highest rates attained by the atria in the presence of histamine or norepinephrine. Not more than three subsequent ligatures per heart were used to produce complete atrioventricular conduction block. If this did not succeed, the preparation was discarded. A period of 30 minutes was allowed to ensure that atrial and idioventricular rates were stable. In 65 preparations, average rates (beats/min, ± SE) were: atrial, 233 ± 8; idioventricular, 146 ± 6. Atrial or ventricular rates were determined from the electrogram by measuring the time intervals between two consecutive atrial deflections (P waves) or ventricular deflections (R waves), respectively. Changes in idioventricular pacemaker site were defined as the emergence of a new rhythm that coincided with a change in the configuration of the R wave.

Histamine, norepinephrine, 4-methylhistamine (4MeH), or 2-(2-thiazolyl) ethylamine (ThEA) was dissolved in warm Ringer’s solution and injected intra-aortically in increasing doses in a volume not exceeding 0.5 ml. The intra-aortic injection of 0.5 ml of Ringer’s solution did not alter any parameters of cardiac function. In some experiments, hearts were continuously perfused with selected concentrations of antihistamines or of a β-adrenergic receptor antagonist. After 20-30 minutes, histamine or norepinephrine was injected intra-aortically in increasing doses.

Drugs
Histamine dihydrochloride and norepinephrine bitartrate were purchased from Sigma Chemical Company. Cimetidine, 4MeH, and ThEA were gifts of Smith Kline & French Laboratories. Chlorpheniramine maleate was a gift of Schering Corporation; pindolol was a gift of Sandoz Pharmaceuticals. All doses of norepinephrine, histamine, 4MeH, and ThEA refer to the free base.

Cardiac Anaphylaxis
Passive sensitization of the guinea pig was induced by the intravenous injection of 0.16 mg of guinea pig anti-dinitrophenyl-bovine γ-globulin (Levi et al., 1978). Twelve hours later the heart was excised and mounted in the Langendorff apparatus. Perfusion of the isolated heart, ligature of the His bundle, and surface electrogram recording were carried out as described above. Antigenic challenge was accomplished by the intra-aortic injection of 1 mg of dinitrophenyl-bovine serum albumin. The histamine content of the coronary venous effluent was determined fluorometrically (Capurro and Levi, 1975).

Results
The Effect of Histamine on Idioventricular Rate
The effects of the administration of a 10 μg dose of histamine to an isolated guinea pig heart with complete atrioventricular conduction block are illustrated in Figure 1. Ligation of the bundle of His resulted in an idioventricular rhythm at 136 beats/min (panel B). Within 15 seconds of the administration of histamine there are independent increases in sinus and idioventricular rates; in D, 1 minute after histamine, there is an abrupt further increase in idioventricular rate, and this coincides with a sudden change in the configuration of the R wave, suggesting a shift in the pacemaker site; in E, 50 seconds later, the new fast rhythm suddenly stops and all ventricular activity ceases for a few seconds until, in F, a new slower idioventricular rhythm appears with a different R wave configuration; in G this rhythm has accelerated, and in H it has been replaced by the rhythm generated in the original pacemaker site. Atrial and ventricular rates are reported at the bottom right of each panel. Times from administration of histamine are reported at the bottom left of each panel. P and R denote atrial and ventricular depolarizations, respectively.
tion of histamine, the idioventricular rate increased to 176 beats/min (panel C). This was followed 45 seconds later by an abrupt increase in idioventricular rate to 260 beats/min. This abrupt increase coincided with a change in the configuration of the R wave, denoting a shift in pacemaker site (panel D). One minute and 50 seconds after the injection of histamine, the fast rhythm suddenly stopped (panel E). Ventricular standstill lasted a few seconds and then was interrupted by the appearance of a slow rhythm with a different R wave configuration (70 beats/min; panel F). In the next minute the idioventricular rate progressively accelerated to 120 beats/min (panel G). By 6 minutes the rate of the ventricles returned to predrug levels (panel H), and the rhythm appeared to be generated in the original pacemaker site (compare R waves in panels B and H).

Thus, in this experiment, histamine increased the idioventricular rate initially by enhancing the firing frequency of the original pacemaker, and subsequently by allowing the emergence of a new pacemaker firing at higher frequency. This pattern of initial gradual acceleration, interrupted by one or more subsequent abrupt increments due to changes in pacemaker site, was common to most of the 14 experiments in which the effects of histamine on idioventricular rate were studied. The acceleration of the idioventricular rate was a dose-related response: the higher the dose of histamine, the greater the acceleration (Fig. 2). The time course of the acceleration of the idioventricular rate also was dose-dependent: the larger the dose of histamine, the longer the duration of its positive chronotropic effect.

It is apparent from Figure 2 that, at all histamine doses except 0.1 μg, greater increments in rate were attained with the emergence of new pacemakers (curve a) than with the acceleration of the original pacemaker (curve b). The incidence of these pacemaker shifts, occurring after each histamine administration in the hearts under study, increased directly with the dose injected (Fig. 3); also, these pacemaker shifts tended to occur progressively ear-
lier with increasing histamine doses. Thus, with increasing histamine doses, the mechanism responsible for the increase in idioventricular rate progressively shifted from a simple acceleration of the original pacemaker to a more complicated pattern in which the original pacemaker was replaced progressively earlier by much faster pacemakers.

The brief period of ventricular standstill that followed the sudden arrest of the faster pacemaker (Fig. 1E), and the subsequent emergence of a new pacemaker firing at a slower rate (Fig. 1F), were observed in most of the experiments at the higher doses of histamine (3–30 μg). This pattern probably resulted from overdrive suppression (see Discussion).

The Effect of Norepinephrine on Idioventricular Rate

Norepinephrine, like histamine, accelerated the idioventricular rate of the isolated guinea pig heart with complete atrioventricular conduction block. The acceleration of idioventricular rate was dose-dependent, and the mechanism appeared to be similar to that of histamine, since it involved an increase in firing frequency of the original pacemaker (Fig. 5B) followed by a further increase in rate (Fig. 4) associated with abrupt shifts in pacemaker site. Norepinephrine was more potent than histamine, but the maximum effect was the same for both amines (Fig. 4).

Effects of Antihistamines on the Histamine-Induced Acceleration of Idioventricular Rhythms

The histamine H2 receptor antagonist cimetidine (3 × 10⁻⁶ and 10⁻⁵ M) antagonized the increase in idioventricular rate induced by histamine in the isolated guinea pig heart with complete atrioventricular conduction block. Cimetidine antagonized both the histamine-induced increase in firing rate of the original pacemaker (Fig. 5A) and the further increase in idioventricular rate resulting from pacemaker shifts (Fig. 6A). As a function of its concentration, cimetidine progressively shifted to the right the dose-response curve for the histamine-induced increase in idioventricular rate (Fig. 6A). The incidence of the histamine-induced pacemaker shifts that coincided with abrupt increases in rate was also reduced by cimetidine as a function of its concentration (Fig. 3A).

On the contrary, the histamine H1 receptor antagonist chlorpheniramine (10⁻⁷–10⁻⁶ M) failed to oppose the histamine-induced acceleration of idio-
Chlorpheniramine did not antagonize either component of the action of histamine: neither the histamine-induced increase in rate of the original pacemaker nor the acceleration resulting from pacemaker shifts was inhibited by chlorpheniramine (Figs. 5A and 6B). In the presence of chlorpheniramine the dose-response curve for the histamine-induced acceleration of the original pacemaker was shifted to the left (Fig. 5A). Chlorpheniramine did not modify the incidence of pacemaker shifts caused by histamine (Fig. 3B).

Prior to histamine administration, neither cimetidine nor chlorpheniramine modified the idioventricular rate.

Effects of Selective Histamine H₁ and H₂ Receptor Agonists on Idioventricular Rate

In Figure 7 the effects of two selective histamine receptor agonists are compared with the effects of histamine on the idioventricular rate of the isolated guinea pig heart with complete atrioventricular conduction block. Both the H₂ receptor agonist 4MeH and the H₁ receptor agonist ThEA accelerated the idioventricular rate as a function of dose; but whereas the dose-response curve for 4MeH was in close proximity to the curve for histamine, the dose-response curve for ThEA fell far to the right. Thus ThEA failed to accelerate the idioventricular rate in the dose range (i.e., below 30 μg) in which ThEA selectively activates histamine H₁ receptors (Durrant et al., 1975; Levi et al., 1975b). Histamine and 4MeH were equally effective in causing pacemaker shifts, whereas ThEA was much weaker in this respect; at the lower doses (1–30 μg, H₁-selective), ThEA did not cause any pacemaker shift.

Effect of β-Adrenergic Blockade on the Acceleration of Idioventricular Rhythms by Histamine and Norepinephrine

The β-adrenergic receptor antagonist pindolol, in a concentration of 7 × 10⁻¹⁰ M, antagonized the norepinephrine-induced increase in idioventricular rate. Pindolol antagonized both the norepinephrine-induced enhancement in the firing rate of the original pacemaker (Fig. 5B) and the further increase in idioventricular rate resulting from pacemaker shifts (Fig. 8A). The incidence of norepinephrine-induced pacemaker shifts was also reduced by pindolol. On the other hand, pindolol failed to modify the histamine-induced acceleration of idioventricular rhythms.

In Figure 6 the effects of the histamine H₂ receptor antagonist cimetidine (A) and of the H₁ receptor antagonist chlorpheniramine (B) on the acceleration by histamine of the spontaneous idioventricular rate of isolated guinea pig hearts with complete atrioventricular conduction block. Points (means ± se) represent the maximum increase in idioventricular rates due either to enhanced firing of the original pacemaker or to a pacemaker shift. Rates were 136 ± 11 beats/min (n = 6) after cimetidine, 10⁻⁶ M, and 149 ± 18 (n = 6) after chlorpheniramine 10⁻⁷ M. All other control idioventricular rates were the same as in Figure 5.
Effects of Histamine and Norepinephrine on the Sinus Rate and Force of Ventricular Contraction

In the isolated guinea pig heart with complete atrioventricular conduction block, histamine (0.1–30 μg) and norepinephrine (0.03–10 μg) increased sinus rate and force of ventricular contraction in a dose-dependent fashion. Pindolol, but not the antihistamines, antagonized the positive chronotropic and inotropic effects of norepinephrine. The effects of histamine were unaffected by pindolol or chlorpheniramine but were antagonized by cimetidine. Like histamine, the H2 agonist 4MeH increased the sinus rate and the force of ventricular contraction. ThEA caused only moderate increases in sinus rate and in force of ventricular contraction but only at high doses, at which ThEA loses its selectivity for histamine H1 receptors (Durant et al., 1975; Levi et al., 1975b).

Prior to histamine or norepinephrine administration, sinus rate and ventricular contraction amplitude were unmodified by cimetidine, chlorpheniramine, or pindolol.

The Effect of Anaphylaxis on Idioventricular Rate

The time course of the effects of antigen administration to a previously sensitized isolated guinea pig heart with complete atrioventricular conduction block is shown in Figure 9. After ligation of the
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bundle of His, the atrial rate was 308 beats/min (Fig. 9A) and the idioventricular rate was 141 beats/min (Fig. 9B). Within 30 seconds of the antigenic challenge (Fig. 9B) the idioventricular rate gradually increased to 187 beats/min and it increased to about 200 beats/min by 2 minutes. Fifteen seconds later, the idioventricular rate abruptly increased to 261 beats/min, and this coincided with a change in the configuration of the R wave, suggesting a shift in the pacemaker site. The rate remained constant at about 260 beats/min until 3 minutes and 45 seconds after antigen, when this fast rhythm was replaced by a much slower rhythm characterized by a different R wave configuration. This rhythm accelerated from 130 to 180 beats/min in the next 15 seconds, remained constant for about 1 minute, and was replaced by a slower rhythm with the same R wave configuration as that of the original pacemaker. This rhythm slowly accelerated from about 130 to 160 beats/min in the next 2 minutes and 30 seconds and slowly decelerated to preantigen levels over the following 6 minutes. Also (Fig. 9A), the atrial rate increased very rapidly from 308 to 428 beats/min within 45 seconds of antigenic challenge, remained at or about 400 beats/min until 4 minutes after antigen, and then gradually declined over the next 10 minutes. These changes in atrial and idioventricular rates were accompanied by release of histamine into the coronary perfusate (Fig. 9C). The release of histamine reached a peak at 2 minutes and ceased about 8 minutes after challenge.

Discussion

Our results clearly demonstrate that histamine is capable of accelerating the spontaneous idioventricular rate of the guinea pig heart with complete atrioventricular conduction block. This action is dose-dependent: the degree of acceleration varies directly with the dose administered. Two components are recognizable in the ventricular chronotropic effect of histamine. The first component involves an acceleration of the original pacemaker established after the ligation of the bundle of His. This causes an acceleration in the rate of firing of the original pacemaker which results in an increase in ventricular rate. The second component probably results from changes in pacemaker site, with the sudden appearance of faster pacemakers; this causes further abrupt increases in idioventricular rate. The second component could involve one or more recognized mechanisms for arrhythmias, such as reentry secondary to circus movement of excitation (Wit et al., 1972; Cranefield, 1975) or triggered activity secondary to the presence of depolarizing afterpotentials (Cranefield, 1977). In any event, our data clearly indicate that, whatever the mechanism, both components of the ventricular chronotropic action of histamine must involve receptors of the H2 type. This assertion is based on the findings that the ventricular chronotropic action of histamine is selectively antagonized by the H2 blocker cimetidine, but not by the H1 blocker chlorpheniramine, while it is mimicked by the selective H2 agonist 4MeH, but not by ThEA at doses selective for H1 receptor activation. Moreover, our view is strengthened by the finding that, in the same hearts and within the same dose range in which histamine accelerates the idioventricular rate, it also enhances the sinus rate and the force of ventricular contraction; these effects, which are known to be mediated by H2 receptors (Levi et al., 1975a; Levi et al., 1976), are antagonized or mimicked in the same order of relative potency as is the increase in idioventricular rate.

The histamine-induced acceleration of the origi-
nal idioventricular pacemaker, which we attribute to the selective activation of H₂ receptors, appears to be potentiated by the H₁ blocker chlorpheniramine (see Fig. 5A). This finding is not surprising, since chlorpheniramine is known to potentiate other histamine H₂ responses such as the positive inotropic and chronotropic effects of histamine (Levi and Capurro, 1973; Levi and Kuye, 1974). Histamine receptors of both classes coexist in the heart (Levi et al., 1976; Levi et al., 1979). Thus selective occupation of one type of receptor by an antagonist would allow for increased availability of histamine toward the other type of receptor, resulting in an increased pharmacological activity at this receptor site, which is manifest as potentiation (Levi et al., 1976).

The acceleration of idioventricular rhythms by histamine is similar to the action of norepinephrine. Therefore we determined the possible contribution of adrenergic mechanisms to the response of ventricular rhythmicity to histamine. Since catecholamines enhance idioventricular rates via β-adrenergic receptor activation (Pearle and Gillia, 1974), we used the β-blocker pindolol (Hill and Turner, 1969) to evaluate possible catecholamine participation. Clearly, pindolol antagonizes the action of norepinephrine but fails to influence that of histamine. This confirms that, although it is similar to norepinephrine, the action of histamine on idioventricular rhythmicity is direct and independent of possible catecholamine release from intracardiac stores.

Thus our findings clearly show that histamine can enhance idioventricular pacemaker activity through specific receptors. It is intriguing to speculate that, beyond the activation of specific and separate receptors, histamine and norepinephrine might enhance idioventricular rhythmicity via a final common pathway, as proposed for the stimulation of the sinoatrial node by these two biogenic amines (Levi and Pappano, 1978). A final common mechanism operative at the Purkinje cell membrane could enhance repetitive activity either by an action on pacemaker potassium current (iK) (Noble, 1975) or by an action on triggered activity secondary to depolarizing afterpotentials (Cranefield, 1977), or both.

It is significant that histamine stimulates idioventricular rate within the same dose range in which it impairs atrioventricular conduction (Levi, 1972; Levi et al., 1976). The combination of these two actions may explain the frequent occurrence of idioventricular tachyarrhythmias when cardiac histamine is released by immediate hypersensitivity reactions in the guinea pig (Capurro and Levi, 1975; Zavec and Levi, 1977). In fact, when histamine is immunologically released in a heart with atrioventricular conduction block, the idioventricular rate is greatly accelerated (see Fig. 9B). The time course of this ventricular chronotropic effect and of that caused by exogenous histamine are almost identical. In both cases the sequence involves a gradual acceleration of the original pacemaker, an abrupt increase in rate coinciding with changes in pacemaker site, and a discontinuous deceleration suggestive of overdrive suppression. Since in these experiments the effects of anaphylaxis and of exogenous histamine are superimposable, and since the time course of histamine release parallels the time course of the ventricular chronotropic effect (compare panels B and C in Figure 9), it is most probable that cardiac histamine release is responsible for the idioventricular tachyarrhythmias of cardiac anaphylaxis. A net amelioration of these arrhythmias is obtained with the histamine H₂ receptor antagonists burimamide (Levi and Capurro, 1973) and cimetidine (Levi et al., 1979). Thus in all likelihood activation of H₂ receptors is relevant to the induction of ventricular rhythm disturbances due to immunological histamine release.

In the course of systemic anaphylactic reactions in humans, severe cardiac dysfunction and fatal arrhythmias often occur as a primary event, not secondary to respiratory distress (Berneriter, 1959; James and Austen, 1964; Booth and Patterson, 1970; Criep and Woehler, 1971; Austen, 1974; Wegmann and Renker, 1976). Although cardiac histamine release has not been measured under these circumstances, it is conceivable that histamine mediates these arrhythmias, since released histamine appears to be the cause of severe arrhythmias and cardiac arrest following a variety of therapeutic and diagnostic procedures in man (Lorenz, 1975; Witten, 1975).

In the experimental animal, ventricular dysrhythmias caused by histamine, either exogenously administered or immunologically released, can be corrected by histamine H₂ receptor antagonists (Levi and Capurro, 1973; Capurro, 1974; Levi et al., 1975a; Levi et al., 1979). Thus our findings suggest new approaches in the pharmacological treatment of ventricular tachyarrhythmias where histamine release could be a suspected causative mechanism.

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