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Synergistic interaction between histamine and ouabain on ventricular fibrillation threshold

Jerome P. Trzeciakowski

Department of Medical Pharmacology & Toxicology, College of Medicine, Texas A&M University, College Station, TX 77843, U.S.A.

1 The interaction between histamine and ouabain on the ventricular fibrillation threshold (VFT) was studied in the isolated, Langendorff-perfused heart of the guinea-pig.

2 When administered separately, histamine and ouabain each reduced the VFT in a concentration-related manner with ED_{50} values of 84.3 and 250 nM, respectively.

3 When perfused in combination the effects of these two drugs on VFT were significantly greater than the sum of their individual contributions.

4 Mepyramine and cimetidine both antagonized the fibrillatory effects of the histamine-ouabain combination. Neither antagonist affected the fibrillation concentration-response curve for ouabain.

5 These results suggest that both classes of histamine receptor may participate in the histamine-ouabain interaction.

Introduction

Cimetidine, a selective antagonist of histamine at H_2-receptors, protects cats (Somerg *et al.*, 1980) and guinea-pigs (Trzeciakowski, 1985) against ouabain cardiotoxicity. In guinea-pigs, this protective effect of cimetidine appears attributable to a decreased sensitivity of the heart to ouabain-induced fibrillation (Trzeciakowski, 1985).

In guinea-pig isolated hearts, non-toxic concentrations of ouabain (3×10^{-9} M) potentiate the arrhythmogenic effects of histamine: the severity of A-V conduction block and the frequency and duration of ventricular arrhythmias are increased (Levi & Capurro, 1975). Histamine has recently been shown to cause dose-dependent decreases in the threshold for ventricular fibrillation (VFT) that are mediated by both classes (H_1 and H_2) of histamine receptor (Trzeciakowski & Levi, 1982). Thus, it is possible that at least part of the protection afforded by cimetidine against ouabain toxicity may result from blockade of myocardial H_2-receptors.

The present study was undertaken to examine the interaction between histamine and ouabain on ventricular fibrillation threshold (VFT). The results indicate that these compounds act in a synergistic manner to reduce VFT and that the effects of the ouabain-histamine combination may be blocked by both H_1- and H_2-receptor antagonists.

Methods

Male Hartley guinea-pigs (300–350 g) were stunned by a blow to the base of the skull and the hearts were quickly removed and mounted on a Langendorff apparatus (Harvard Isolated Heart Perfusion Apparatus, Harvard Apparatus Co., Inc., South Natick, MA) to which an enclosed, water-jacketed Plexiglass chamber had been added to keep the air surrounding the heart moist and warm (37.5°C). Hearts were perfused in a retrograde fashion at a constant pressure of 50 cmH_2O with Ringer-Locke solution (composition mM: NaCl 154.0, KCl 5.6, $CaCl_2$ 2.1, $NaHCO_3$ 5.9 and glucose 5.5). The solution was gassed with 100% O_2 before entering the aorta at 37.5°C. Isometric contractions were measured with a transducer (Myograph F-60, Narco Bio Systems, Houston, TX) attached via a pulley to a clip on the apex of the heart. Bipolar surface electrocardiograms were obtained with platinum electrodes from the right atrium and left ventricle.

The contractions and electrogram were recorded on a Physiograph (Model DMP-4B, Narco Bio-Systems, Inc.). Heart rate and rhythm were determined from the electrocardiogram tracings. Coronary perfusates were collected over intervals of 1–2 min in graduated tubes to determine coronary flow rates. Hearts were per-

fused for a minimum of 30 min before experimentation to allow heart rate, contraction, and coronary flow to attain steady values.

Ventricular fibrillation was produced by a serial shock technique as previously reported (Trzeciakowski & Levi, 1982). Two platinum needle electrodes were inserted into the epicardium: the cathode was placed approximately 2 mm below the left atrial appendage; the anode was placed at a minimum of 10 mm distance, near the apex of the left ventricle. Care was taken to avoid coronary vessels. Square wave pulses (15 Hz frequency, 1–1.5 ms duration) were delivered to the ventricle from a stimulator (Model S44, Grass Instruments, Quincy MA) coupled to a stimulus isolation unit (Model SIU5, Grass Instruments). The intensity of the stimuli were progressively increased until contractions became disordered or ceased and fibrillatory waveforms appeared in the electrogram tracing. The intensity at which these changes were first seen was taken as the ventricular fibrillation threshold (VFT). Because of the small size of these hearts, fibrillation converted spontaneously back to normal rhythm within a few seconds after the stimulator was switched off. The stimulation was repeated several times at 10 min intervals at the start of each experiment to determine a control value of VFT. This value generally fell in the range of 130–145V; in a few cases when it did not, the VFT was brought into this range by making slight adjustments in the pulse width. The currents corresponding to these voltages were determined from measurements of the voltage drop across a 10 KΩ resistor placed in series with the stimulating electrodes; these ranged from 8.4 to 9.5 mA.

Drugs to be tested were dissolved in the solution perfusing the hearts. For histamine, fibrillation thresholds were determined 5 min after perfusion with each new concentration when effects on rate, contractility and coronary flow reached maximal, stable levels (Trzeciakowski & Levi, 1982). Because of the slower onset of action of ouabain, maximal effects (as evidenced by increases in contractile force) required 20–30 min to develop. Thus, effects of ouabain on VFT were not tested until 30 min after perfusion with each new concentration was begun. For experiments in which histamine antagonists were used, hearts were perfused with cimetidine (1×10^{-5} M) or mepyramine (4×10^{-8} M) for 30 min before the addition of histamine or ouabain; responses to the latter two drugs were then measured in the presence of either cimetidine or mepyramine.

Values of VFT obtained in the presence of drugs were expressed as a percentage of the control VFT for each preparation. To insure that alterations in VFT were caused only by the actions of the drugs and not by damage to the heart, all drugs were washed from the heart following the completion of each experiment and VFT was redetermined. Preparation in which this value differed more than 5–7% from the initial control value were disregarded.

To determine whether the effects of the histamine-ouabain combinations were additive or synergistic, theoretical additive concentration-response curves were constructed as described by Poch & Holzmann (1980). The observed responses of the drug combinations were then compared with those predicted on the basis of summation of individual drug actions. For these calculations the data, expressed in Figure 1 as % of control VFT (ranging from 100 to 0), were converted to fractions of the maximal response (ranging from 0 to 1), by dividing each value by 100 and subtracting the quotient from 1.0. Ariens' equation (Ariens *et al.*, 1956) was used to calculate the additive dose-response curve for two drugs acting on independent receptor systems:

$$E_{H+O} = E_H + E_O - (E_H E_O)$$

where E_H and E_O are the fractional responses of histamine and ouabain determined separately and E_{H+O} is the predicted response of the combination, expressed as a fraction of the maximal response (1.0) (Poch & Holtzmann, 1980).

Analysis of variance with repeat observations was used for multigroup comparisons of dose-response data. Differences among several means were tested with Duncan's multiple range test.

Drugs were obtained from the following sources:

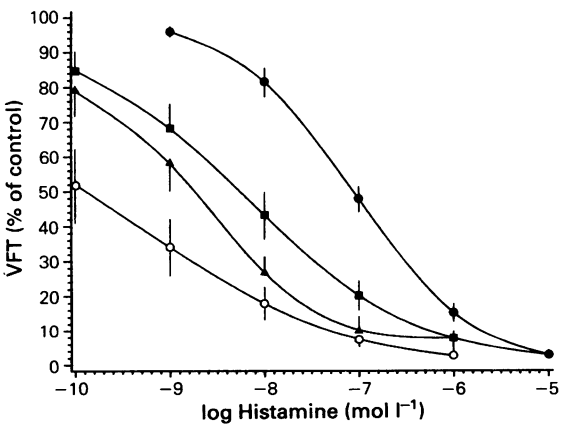

Figure 1 Potentiation of the VFT-lowering effect of histamine in the guinea-pig isolated heart by ouabain in concentrations of 10^{-9} M (■), 10^{-8} M (▲) and 10^{-7} M (○). The control histamine curve is indicated by (●). Ordinate scale: % of control VFT, which was 137.2 ± 3.2 V in the control group, and 136.2 ± 2.6 V, 135.6 ± 3.7 V, and 139.2 ± 2.8 V for the groups treated with ouabain at 10^{-9} M, 10^{-8} M and 10^{-7} M, respectively. Points are means of 6 observations and bars represent s.e.means.

Table 1 Effect of histamine on rate, contraction and coronary flow, alone and in combination with ouabain in guinea-pig isolated heart

Ouabain (M)	*Control*	*After ouabain**	*Histamine* (M) 10^{-9}	10^{-8}	10^{-7}	10^{-6}
			Heart rate (beats min^{-1})			
0	200 ± 14†	—	221 ± 13	219 ± 12	251 ± 7	298 ± 10
10^{-9}	220 ± 14	224 ± 7	247 ± 13	238 ± 12	253 ± 12	304 ± 14
10^{-8}	209 ± 9	212 ± 7	216 ± 9	228 ± 7	224 ± 9	334 ± 7
10^{-7}	209 ± 11	228 ± 17	228 ± 21	232 ± 20	228 ± 20	319 ± 16
			Contractile force (g)			
0	13.3 ± 1.5	—	14.5 ± 1.5	13.9 ± 1.1	15.5 ± 1.8	12.5 ± 2.2
10^{-9}	13.8 ± 1.2	16.3 ± 1.5	17.8 ± 2.2	17.3 ± 2.4	17.0 ± 2.4	15.9 ± 2.4
10^{-8}	11.1 ± 1.0	15.3 ± 1.0	16.8 ± 2.0	15.3 ± 2.8	10.7 ± 2.8	12.7 ± 2.1
10^{-7}	12.6 ± 1.8	18.9 ± 1.1	20.1 ± 2.8	19.9 ± 2.7	16.8 ± 4.4	23.9 ± 6.3
			Coronary flow (ml min^{-1})			
0	3.7 ± 0.7	—	6.6 ± 0.6	6.3 ± 0.6	6.3 ± 0.4	6.4 ± 0.5
10^{-9}	3.9 ± 0.7	3.9 ± 0.3	6.8 ± 0.6	6.4 ± 0.6	6.3 ± 0.6	6.5 ± 0.7
10^{-8}	3.8 ± 0.4	3.8 ± 0.6	6.5 ± 0.4	6.3 ± 0.3	6.0 ± 0.4	6.8 ± 0.3
10^{-7}	3.8 ± 0.5	4.0 ± 0.8	6.6 ± 1.0	6.4 ± 1.0	6.0 ± 1.0	6.6 ± 0.8

*Ouabain was perfused for 30 min before testing histamine responses.
†Values are means ± s.e.mean of 6 observations.

cimetidine (Smith Kline & French), histamine dihydrochloride (Sigma), mepyramine maleate (Sigma), and ouabain octahydrate (Sigma).

Results

Histamine lowered VFT in a concentration-related fashion from 10^{-8} to 10^{-5} M (Figure 1). In concentrations between 10^{-9} and 10^{-7} M, ouabain potentiated the effects of histamine on VFT. This is seen as a shift downward and to the left in the concentration-response curves for each histamine-ouabain combination as compared with the control curve for histamine (Figure 1). When tested alone, ouabain reduced VFT to 99.7 ± 0.21%, 96.3 ± 1.5%, and 73.3 ± 4.6% of

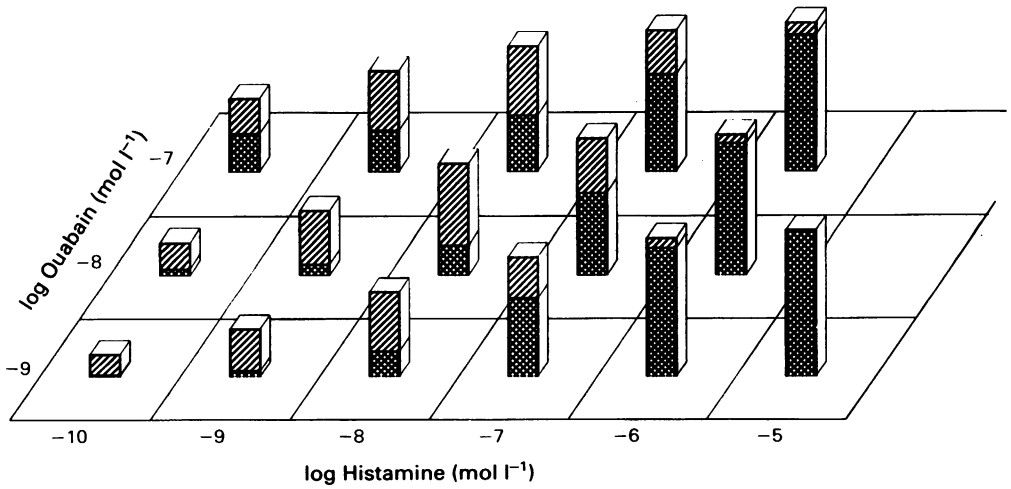

Figure 2 Comparison of actual effects of histamine-ouabain combinations on VFT with responses predicted on the assumption that the drugs interact in an additive fashion. The bars represent a superposition of the actual responses given right-handed shading with predicted responses given left-handed shading. Cross-hatched areas represent the extent of overlap of these responses. With the exception of the one bar (ouabain = 10^{-9} M; histamine = 10^{-5} M) in which the actual and predicted responses are equal, the experimental effects are all larger than the theoretical additive effects.

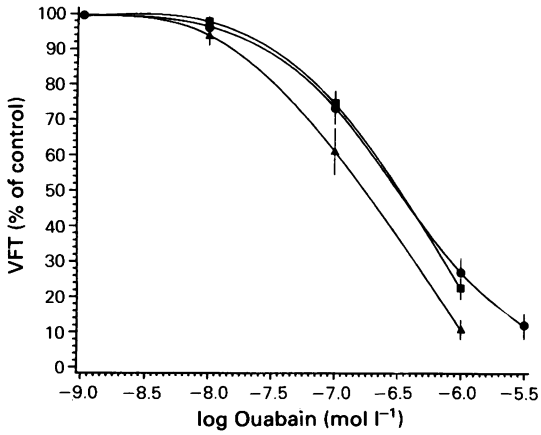

Figure 3 Lack of effect of mepyramine (■, 4×10^{-8} M) and cimetidine (▲, 1×10^{-5} M) on the VFT-lowering effect of ouabain. The control ouabain curve is indicated by (●). Ordinate scale: % of control VFT which was 137.6 ± 3.3 V, 137.7 ± 4.1 V, and 137.9 ± 4.0 V for the control, mepyramine, and cimetidine groups, respectively. Points are means of 7 observations and bars represent s.e.means.

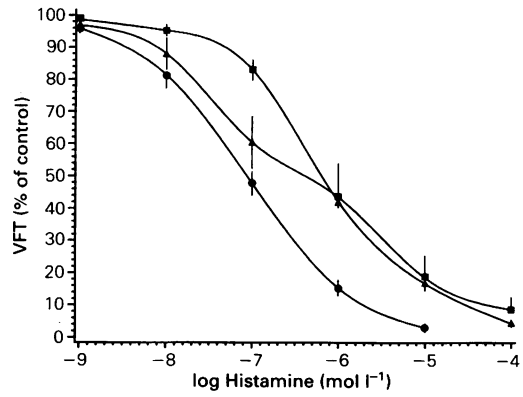

Figure 4 Antagonism of histamine-induced decreases in VFT by 4×10^{-8} M mepyramine (■, $n = 5$) and 1×10^{-5} M cimetidine (▲, $n = 7$). The control histamine curve ($n = 5$) is indicated by (●). Ordinate scale: % of control VFT, which was 137.2 ± 3.2 V, 131.0 ± 4.6 V, and 142.0 ± 3.3 V for the control, mepyramine and cimetidine groups, respectively. Bars represent s.e.means.

control at 10^{-9} M, 10^{-8} M and 10^{-7} M, respectively. Only the last value represents a significant decrease from control.

The effects of histamine on heart rate, force of contraction and coronary flow in the absence and presence of ouabain are listed in Table 1. Ouabain did not alter the action of histamine on any of these parameters of cardiac function.

Theoretical additive concentration-response curves were constructed from the individual effects of histamine and ouabain as described under Methods. Bars depicting the predicted values for histamine-ouabain combinations were given leftward-slanting (bottom to top) shading and superimposed on bars representing the actual values of those combinations, given rightward-slanting shading (Figure 2). Cross-hatched areas thus represent the degree of overlap between the actual and predicted values. Predicted values in excess of actual values would be represented by areas of leftward-slanting shading: actual values in excess of predicted values would be represented by areas of rightward-slanting shading. With the exception of the fully-crosshatched bar (at ouabain = 10^{-9} M; histamine = 10^{-5} M) where the actual and predicted values were equal, experimental effects were all found to be greater than the theoretical additive effects (Figure 2). Ouabain and histamine, therefore, appear to be acting synergistically to lower VFT.

The complete concentration-response curve for the effect of ouabain on VFT is shown in Figure 3. The effects of ouabain on VFT were not accompanied by significant alterations in heart rate or coronary flow (Table 2). The force of contraction, however, was increased in a concentration-related fashion. Addition

Table 2 Effects of ouabain on heart rate, contraction, and coronary flow in guinea-pig isolated heart

Ouabain (M)	*Heart rate* (beats min^{-1})	*Contractile force* (g)	*Coronary flow* (ml min^{-1})
0	175 ± 8*	10.2 ± 1.1	3.3 ± 0.4
10^{-10}	192 ± 14	16.8 ± 1.4	3.5 ± 0.7
10^{-9}	183 ± 11	17.4 ± 0.8	3.4 ± 0.5
10^{-8}	189 ± 15	20.3 ± 1.1	3.5 ± 0.7
10^{-7}	186 ± 15	22.9 ± 1.6	3.4 ± 0.8
10^{-6}	195 ± 20	25.6 ± 1.3	3.5 ± 0.9

*Measurements were taken after 30 min perfusion with each concentration of ouabain.
Values are means ± s.e.mean of 7 observations.

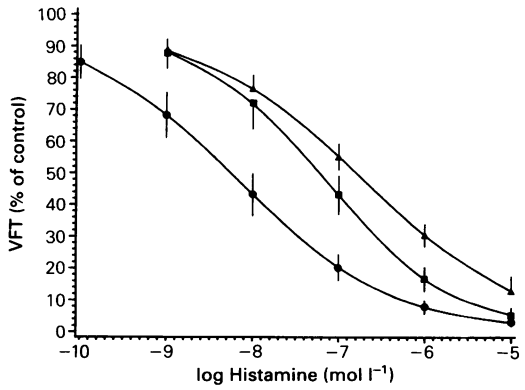

Figure 5 Effect of 4×10^{-8} M mepyramine (■, $n = 5$) and 1×10^{-5} M cimetidine (▲, $n = 8$) on the VFT dose-response curve of histamine combined with 1×10^{-9} M ouabain (●, $n = 6$). Ordinate scale: % of control VFT, which was 136.2 ± 2.6 V for hearts treated with histamine and ouabain, 126.7 ± 2.3 V for those treated with histamine, ouabain and mepyramine, and 135.9 ± 3.5 V for hearts given histamine, ouabain and cimetidine. Bars represent s.e.means.

of the H_1-receptor antagonist, mepyramine (4×10^{-8} M), to the perfusion fluid did not alter the effect of ouabain on VFT (Figure 3). Cimetidine (10^{-5} M), an H_2-receptor antagonist, slightly increased the response to 10^{-6} M ouabain but was otherwise devoid of effect (Figure 3). Neither antagonist significantly affected heart rate, force of contraction or coronary flow at these concentrations.

In contrast to their lack of effect on ouabain, both cimetidine and mepyramine antagonized the action of histamine on VFT (Figure 4). Mepyramine and cimetidine also produced significant shifts to the right of the VFT concentration-response curve for histamine combined with 10^{-9} M ouabain (Figure 5). The histamine receptor blockers did not affect the control value of VFT in the concentrations tested (VFT was 136.6 ± 1.8V before and 132.5 ± 3.5 V after treatment with mepyramine, $n = 17$; in other hearts, VFT was 137.1 ± 1.5 V before and 138.7 ± 2.0 after treatment with cimetidine, $n = 22$).

Discussion

This investigation demonstrated that histamine and ouabain, when perfused in combination, lowered VFT to a greater extent than would be expected from the pharmacological sum of their individual effects. As a result, low concentrations of ouabain and histamine, that individually had no effect on the heart, produced quite dramatic decreases in VFT when tested in combination.

The VFT-lowering effects of the histamine-ouabain combinations could be inhibited by antagonists selective for either class of histamine receptor. A number of H_1-receptor antagonists, mepyramine included, possess antiarrhythmic properties that are unrelated to their actions at histamine receptors (Dews & Graham, 1946; Dutta, 1949; Weidman, 1955). Nevertheless, it is unlikely that antiarrhythmic effects were a major factor in the inhibitory action of mepyramine shown in Figures 4 and 5. Quinidine-like effects of mepyramine on cardiac conduction occur at concentrations ranging from 3.1 to 6.6 μM (Dews & Graham, 1946); whereas the mepyramine concentration used in the present study was only 0.04 μM. Quinidine and related drugs are known to elevate VFT in antiarrhythmic concentrations (Vaughan Williams & Szekeres, 1961). In contrast, mepyramine and cimetidine had no effect on the basal level of VFT in these experiments. Finally, the concentration-response curve for the effect of ouabain on VFT was unaltered by either mepyramine or cimetidine. Thus, the ability of cimetidine and mepyramine to antagonize the effects of histamine and histamine-ouabain combinations on VFT was probably mediated by histamine receptor blockade, and not by nonspecific or generalized antiarrhythmic actions.

In these experiments cimetidine appeared to block responses to higher histamine concentrations (above 10^{-7} M) more effectively than responses to lower histamine concentrations. This is in accord with other data indicating that decreases in VFT are mediated primarily by H_1-receptors at histamine concentrations below 10^{-7} M, whereas H_2-mediated responses predominate at higher histamine levels (Trzeciakowski & Levi, 1982).

The method used to determine VFT was based on the serial shock technique described by Szekeres & Papp (1971) for measurement of flutter thresholds in cats. This method has since been adapted for VFT determinations in rabbits (Almotrefi & Baker, 1980), rats (Marshall *et al.*, 1981) and guinea-pigs (French & Scott, 1978; Trzeciakowski & Levi, 1982). The use of serial shocks has several advantages over the single shock method for induction of fibrillation in that artificial pacing is not required, the vulnerable period does not have to be located, and VFT determinations can be made more frequently (Winslow, 1984). However, the electrophysiological basis for the induction of arrhythmias by serial shocks or high frequency trains of stimuli applied during the vulnerable period is uncertain. Asynchrony in the recovery of excitability and spread of excitation during the period of stimulation may contribute to the development of re-entrant rhythms and, ultimately, to fibrillation if the current intensity is sufficient (Szekeres & Papp, 1971; Han, 1973; Winslow, 1984).

The electrophysiological basis for the observed synergistic interaction between histamine and ouabain

is also not known. Both substances produce similar arrhythmogenic actions such as increases in the slope of phase 4 depolarization and spontaneous rate of ectopic pacemakers (Vassale *et al.*, 1962; Senges *et al.*, 1977; Levi & Zavecz, 1979), and generation of delayed afterdepolarizations and triggered activity (Davis, 1973; Rosen *et al.*, 1973; Cranefield, 1977; Levi *et al.*, 1981). Ouabain and histamine also share the ability to increase the intracellular level of Ca^{2+} in the myocardium; ouabain via inhibition of Na^+ K^+ ATPase and subsequent Na^+-Ca^{2+} exchange (Smith *et al.*, 1984), and histamine via cyclic AMP-dependent activation of slow channels, mediated by H_2-receptors (Watanabe & Besch, 1974; Innui & Imamura, 1976; Sperelakis, 1984). Histamine may, in addition, increase transsarcolemmal Ca^{2+} influx through an H_1-mediated, cyclic AMP-independent process (Yao *et al.*, 1984). Application of serial shocks may have contributed to the increase in intracellular Ca^{2+} through the combined influence of the increase in rate (positive staircase phenomenon), local release of neurotransmitters (Euler, 1980; Winkle *et al.*, 1980), and cellular damage (Tanz & Opie, 1978). Data supporting an association between Ca^{2+} influx and development of ventricular fibrillation have recently been reported (Opie & Thandroyen, 1983). Nevertheless, the exact nature of the relationship between Ca^{2+} and fibrillation is unknown, and evidence of enhanced intracellular Ca^{2+} levels in the presence of ouabain and histamine remains to be established.

In summary, histamine and ouabain have been found to lower VFT in a synergistic fashion in the guinea-pig isolated heart. The fibrillatory effects of the histamine-ouabain combination were antagonized by both H_1- and H_2- receptor blockers in an apparently specific manner. Because of this synergy, extremely low concentrations of histamine might greatly increase the cardiotoxic effects of ouabain. Histamine is present in the heart and can be released by antigen-antibody reactions (Feigen & Prager, 1969; Levi, 1972), drugs (Lorenz, 1975; Levi *et al.*, 1982), and nerve stimulation (Blandina *et al.*, 1983; Gross *et al.*, 1984) in quantities sufficient to interact with cardiac glycosides. Further studies are required to assess the clinical significance of this synergistic interaction.

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