REVIEW ARTICLE

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Cardiotoxicity of Histamine and the Possible Role of Histamine in the Arrhythmogenesis Produced by Certain Antihistamines

Jesús Llenas,[1] *Ignasi Cardelús*,[1] *Ascensión Heredia*,[1] *Fernando de Mora*[2] and *Robert W. Gristwood*[3]

1 Department of Pharmacological Development, Research Centre, Almirall Prodesfarma S.A., Barcelona, Spain
2 Department of Pharmacology, Facultad de Veterinaria, Univ. Autónoma de Barcelona, Barcelona, Spain
3 Stevenage Biosciences Ltd, Stevenage, Hertfordshire, England

Abstract

Since 1990 it has repeatedly been reported that some histamine H_1 receptor antagonists (e.g. terfenadine and astemizole) are able to produce ventricular arrhythmias (e.g. torsade de pointes) when they are given at dosages above the therapeutic range and/or administered together with cytochrome P-450 3A4 inhibitors, such as ketoconazole or erythromycin. Although the mechanism by which these arrhythmias are produced remains unclear, the recently reported ability of these drugs to block outward K^+ currents has been suggested as the cause of their arrhythmogenic effects. Alternatively, we have observed that some H_1 antihistamines, including terfenadine and astemizole, are able to release histamine from guinea-pig cardiac mast cells. Thus, we have proposed that the liberated histamine, acting through an H_2 receptor-stimulating mechanism, can prolong the action potential duration and hence induce arrhythmogenic effects. This paper describes experimental observations supporting the hypothesis that some H_1 antihistamines can induce severe cardiac arrhythmias via the local release of histamine.

Dale and Laidlaw[1] first showed in 1919 that histamine had profound effects, including increases in the rate and force of contraction, on isolated cat and rabbit hearts. Subsequent *in vivo* studies demonstrated that intravenous administration of histamine caused tachycardia and changes in coronary blood flow and contractility, together with a variety of arrhythmias, in both animals and humans.[2-4] Such observations raise the question of the possible role of endogenous histamine in drug-induced cardiotoxicity.

In this context, it has recently been shown that some histamine H_1 receptor antagonists (e.g. terfenadine and astemizole), which are able to produce rare but life-threatening arrhythmias in humans by prolonging the action potential duration (APD), can also induce the release of histamine from mast cell stores.[5] Despite suggestions that the effect on APD is mainly related to the blockade

of some delayed rectifier potassium channels, the mechanism by which these arrhythmias are produced remains unclear. The aim of this paper is to discuss the effects of histamine on the heart, the sources of endogenous cardiac histamine, the evidence that endogenous histamine can be released in sufficient quantities to cause arrhythmogenic effects and, finally, the evidence that certain histamine H_1 receptor antagonists can indeed liberate cardiac histamine.

1. The Histamine Release Hypothesis of Antihistamine-Induced Cardiac Arrhythmias

The idea that histamine released from cardiac mast cells by some antihistamines could be related to the reported induction of severe arrhythmias by these drugs followed the description by Tobin et al.[6] of astemizole overdosage in a child. These authors observed cardiotoxic effects that 'resemble more that caused by histamine than by an antihistamine' and arrived at the conclusion that such effects might be produced as a consequence of an activity on the histamine H_3 receptors.

As a consequence of this observation, we tested terfenadine on the isolated guinea-pig ventricular strip preparation and observed that it induced a positive inotropic response through a histamine H_2 receptor-dependent mechanism.[7] We proposed the hypothesis that the cardiac arrhythmias produced by some antihistamines could be mediated through local mast cell histamine release onto cardiac histamine H_2 receptors.

This hypothesis is based on 4 facts:

- Histamine affects cardiac contractility and can increase the ventricular APD in the human heart.[8]
- The amount of histamine present in human cardiac mast cells would be sufficient to produce cardiac arrhythmias if it were released.[2,9,10]
- Cardiac histamine can be released by the two established 'arrhythmogenic antihistamines', terfenadine and astemizole.[5]
- Although therapeutic plasma concentrations of terfenadine and astemizole are much lower than those needed to induce cardiac release of histamine, the extensive accumulation of these drugs, at least in the animal heart, is more than sufficient to produce such release and thereby induce cardiac arrhythmias.[11]

2. Effects of Histamine on Cardiac Contractility and Cardiac Action Potential

A number of histamine effects on the heart have been reported in a variety of animal species. These include increases in the ventricular force of contraction, increases in atrial rate, coronary vasodilation and/or constriction, increased atrioventricular conduction time, and a variety of arrhythmias. There is evidence that both histamine H_1 and H_2 receptors are involved in these effects.[9,12-14]

The contractile effects of histamine on the heart are very species dependent (table I), and this has obvious relevance when animal models are used to predict cardiotoxicity involving endogenous histamine. Thus, guinea-pig and human heart are both very sensitive to histamine, whereas the cat heart shows an atrial, but not a ventricular, response, and the dog heart is completely insensitive to the direct effects of histamine.[15] In the rat, histamine produces a decrease rather than an increase in ventricular contractility.[15] In terms of receptors, histamine H_2 receptors are involved in these effects in human and guinea-pig heart,[16] whereas H_1 receptors are involved in the ventricular response in the pig and rabbit.[3,15]

In addition to the effects of histamine on contractility in human ventricular preparations, its

Table I. Species dependence of cardiac effects of histamine[3,15,16]

Species	Effect/histamine receptor	
	ventricle Fc	atrial rate
Human	↑ H_2	↑ H_2
Guinea-pig	↑ H_2	↑ H_2
Cat	No effect	↑ H_2
Dog	No effect	No effect
Pig	↑ H_1	↑ H_2
Rat	↓ ?	
Rabbit	↑ H_1	↑ H_1

Fc = force of contraction. ↑ = increase; ↓ = decrease; ? = receptor unknown.

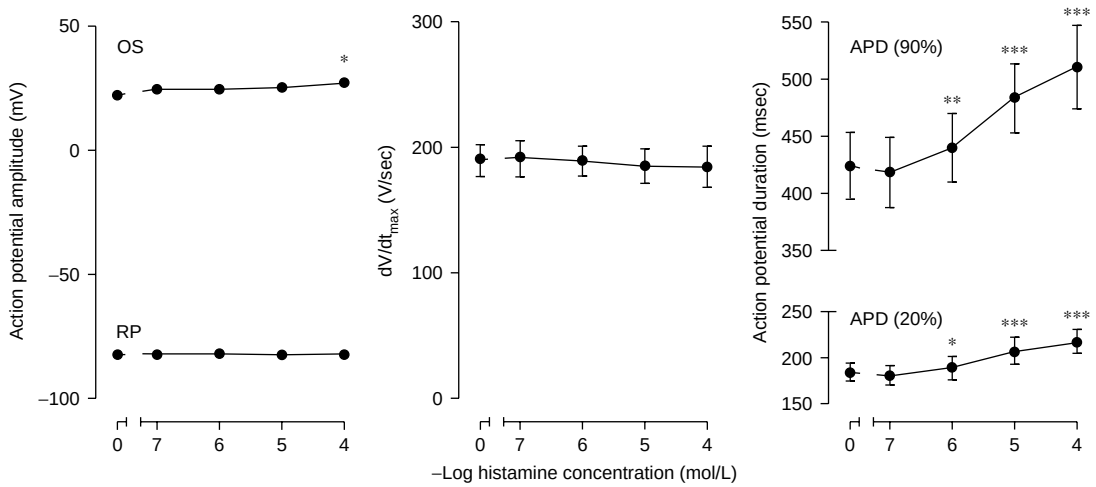

Fig. 1. Concentration-response curves for the effect of histamine on action potential in human papillary muscles (R.W. Cristwood, unpublished data).[8] For each parameter, mean absolute control values (0) and mean values obtained after equilibration with histamine (10^{-4} mol/L, n = 11; other values, n = 13) ± SEM are shown. **APD** (90% and 20%) = action potential duration at 90% and 20% repolarisation, respectively; **RP** = resting potential; **OS** = overshoot. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* baseline values.

effects on action potential have also been investigated. At a threshold concentration of 0.1 μmol/L, histamine produced concentration-dependent increases in the force of contraction and reductions in time to peak tension and relaxation time. At the same time, marked changes in action potential configuration, such as an elevation of the plateau height and an increase in the duration of the action potential, reflected in the increase in APD at 20% of repolarisation (ADP 20%) and APD at 90% of repolarisation (APD 90%), respectively, was found (fig. 1). However, no effect on dV/dt_{max} or resting potential has been reported. The largest effect seems to be on APD, with a mean increase of 30% at the 10^{-4} mol/L concentration.[8,17] All effects of histamine on the human heart were H_2 receptor mediated.

3. Cardiac Histamine Content, its Release by Anaphylaxis and the Role of Cardiac Histamine H_2 Receptors

Clinical evidence indicates that cardiac histamine H_2 receptors do not have a physiological role. This evidence is based on findings that, at doses blocking the cardiovascular effects of the H_2 agonist impromidine, cimetidine has no effect on car-

Table II. Histamine content of guinea-pig and human hearts

Species	Region	Histamine content (mg/kg fresh weight)	n	Reference
Guinea-pig	Right atrium	18.10 ± 2.40	17	18
	Right ventricle	9.80 ± 1.30	17	18
	Left ventricle	5.10 ± 0.60	17	18
Human	Right atrium	1.04 ± 0.07	3	9
	Right ventricle	5.30 ± 0.50	25	19
	Left ventricle	0.71 ± 0.10	4	8
		5.40 ± 0.60	25	19

Table III. Effects of the mast cell histamine releaser compound 48/80 on human right atrium *in vitro*[9]

Parameter	Untreated	+ Cimetidine pretreatment
Histamine EC_{50}	4.3 μmol/L (range 2.6-7.5 μmol/L)	4.7 μmol/L (range 3.7-7.6 μmol/L)
Histamine equivalent response of comp. 48/80	4.1 μmol/L	No response

EC_{50} = concentration releasing 50% of the total histamine content.

diovascular parameters in humans at rest or during exercise. However, histamine is present in various tissues within the body, including the heart, and can be released under certain circumstances.[18,19]

When considering a myocardial response to released endogenous histamine, release of both cardiac and extracardiac histamine could be important. However, localised myocardial release would be expected to result in much higher localised levels within the heart.

Histamine is present in the heart, and is largely contained within mast cells. Table II compares the histamine content in human and guinea-pig heart. Although the histamine content of guinea-pig right atrium is much higher than that of human right atrium, the contents of the ventricles are more similar.

In order to examine the consequences of released histamine, a number of studies have used the anaphylactic response in the isolated guinea-pig heart: Animals were sensitised to ovalbumin and, 2 weeks later, the hearts were removed and perfused. They responded strongly when challenged with ovalbumin, with resulting increases in sinus rate, left ventricular contractility, aortic flow and cardiac output.[4,20-24] Coronary flow was decreased and there were severe arrhythmias. These effects occurred soon after the challenge and coincided with histamine release, which peaked at 30 seconds after challenge. The majority of the effects, including the arrhythmias, were histamine H_2 receptor mediated.

Effects similar to those seen during anaphylaxis were produced by the potent mast cell histamine releaser compound 48/80 in the guinea-pig heart. In human right atrium *in vitro*, compound 48/80 elicited an inotropic response, which was blocked by pretreatment with cimetidine (table III). The magnitude of the 48/80 response was equivalent to the 50% maximal histamine response.[9]

During a severe anaphylactic response in the guinea-pig, up to 70% of the endogenous histamine was released from the heart.[9]

4. H_1 Antihistamines and Cardiac Histamine Release

Histamine release is not generally observed with H_2 receptor antagonists. Histamine release by H_1 receptor antagonists was first described in 1946, when Pellerat and Murat[25] reported that the blood histamine level was increased after administration of various antihistamines. In 1952, Arunlaksh-

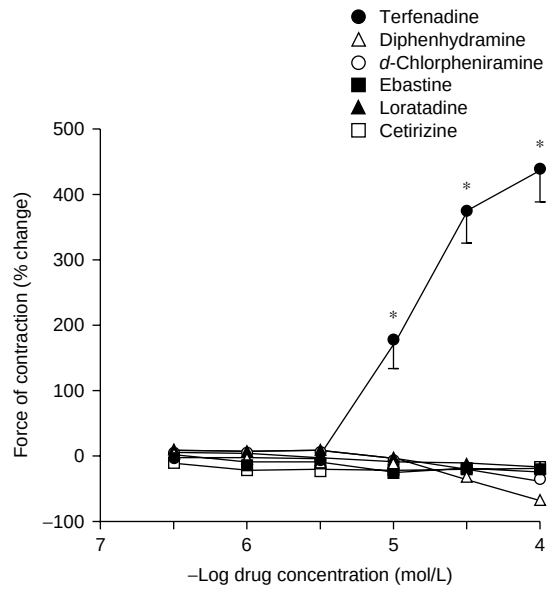

Fig. 2. Comparative effects of terfenadine, diphenhydramine, *d*-chlorpheniramine, ebastine, loratadine and cetirizine on ventricular strips (n = 10 to 21) from reserpinised guinea-pigs. Values are expressed as mean ± SEM. * $p < 0.05$ *vs* basal values.[7]

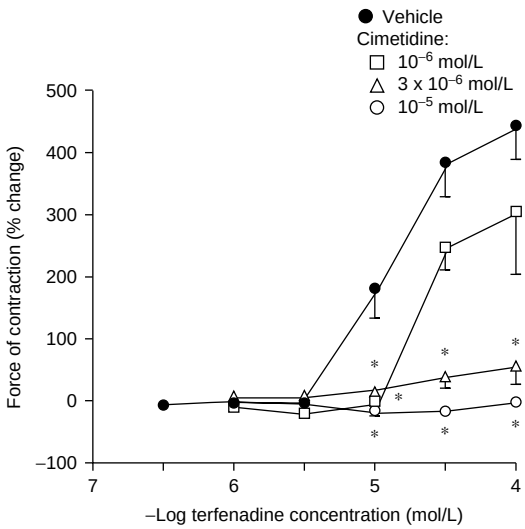

Fig. 3. Effects of terfenadine on guinea-pig ventricular strips pretreated with vehicle or cimetidine at 10^{-6} mol/L, 3×10^{-6} mol/L and 10^{-5} mol/L (n = 7 to 21).[7] Values are expressed as mean ± SEM. * $p < 0.05$ *vs* vehicle.

ana[26] reported that diphenhydramine was similar to compound 48/80 in its ability to release histamine from human lung tissue (releasing up to 36% of the endogenous histamine).

In 1995, Cardelús and colleagues[7] studied the effects of several histamine H_1 receptor antagonists: diphenhydramine, *d*-chlorpheniramine, loratadine, ebastine, cetirizine and terfenadine on ventricular strips from reserpinised guinea-pigs.

The results showed that terfenadine, with a threshold concentration between 3 and 10 μmol/L, produced concentration-related increases in the force of contraction. By contrast, none of the other antihistamines studied had this effect. The maximum observed effect with terfenadine at 100 μmol/L represented an increase of 441 ± 42% (fig. 2).

Pretreatment of preparations with cimetidine inhibited the effects of terfenadine (fig. 3), showing that these are H_2 receptor mediated. Since terfenadine is not a histamine H_2 ligand, the effects of terfenadine must be due to the liberation of histamine.[7]

These findings with terfenadine prompted further studies using guinea-pig isolated cardiac mast cells. The results were reported by Heredia et al.[5]

Figure 4 shows the release of histamine from guinea-pig cardiac mast cells produced by antihistamines. The result for terfenadine confirms the previous evidence for histamine release in the heart. Terfenadine was the most potent compound, with a steep dose-response curve and an EC_{50} (concentration that releases 50% of the total histamine content) value of 13.5 μmol/L and virtually total release at 30 μmol/L. Terfenadine was not alone in producing this effect, and both astemizole (EC_{50} = 21.9 μmol/L) and descarboethoxyloratadine (EC_{50} = 43.5 μmol/L), the main metabolite of loratadine, also caused the virtual complete release of histamine at 100 μmol/L. Loratadine, fexofenadine and carebastine were without effect up to 100 μmol/L and ebastine (EC_{50} >100 μmol/L) induced only partial release of histamine and showed a very shallow dose-response curve.[5]

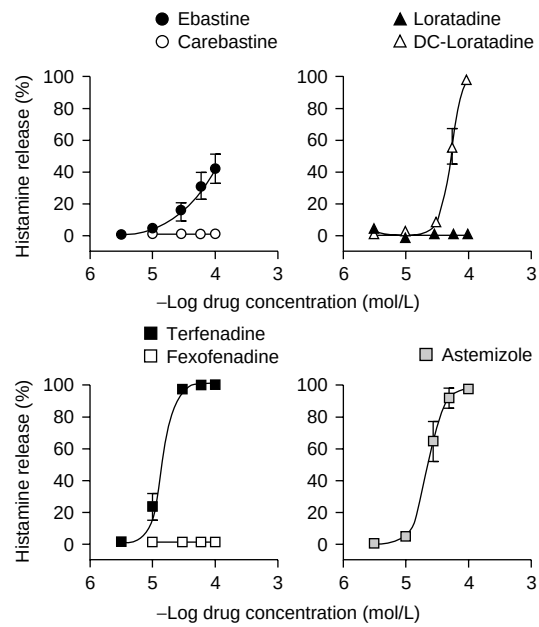

Fig. 4. Comparative effects of several antihistamines on spontaneous histamine release from guinea-pig heart mast cells.[5] Values are expressed as mean ± SEM. **DC-Loratadine** = descarboethoxyloratadine.

5. Accumulation of Antihistamines in the Heart

Concentrations of antihistamines inducing the release of cardiac histamine *in vitro* exceed plasma concentrations seen in humans even under conditions of overdose or metabolic inhibition. Nevertheless, some of these agents, particularly astemizole and terfenadine, accumulate in cardiac tissue and can achieve histamine-releasing concentrations. Furthermore, certain pathological conditions, e.g. myocardial ischaemia or dilated cardiomyopathy, could facilitate the release *in vivo* at even lower concentrations. In fact, Patella et al.[27] have recently reported that the release of histamine was significantly higher in human heart mast cells from cardiomyopathy patients than from healthy controls.

6. Conclusions

The data presented support the hypothesis that cardiac histamine release could, at least in part, contribute to the adverse cardiac effects of some antihistamines, such as terfenadine and astemizole.

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Correspondence and reprints: Dr *J. Llenas,* Department of Pharmacological Development, Research Centre, Almirall Prodesfarma S.A., Cardener, 68-74, 08024 Barcelona, Spain.