H$_1$- and H$_2$-receptors in the guinea-pig heart: an electrophysiological study

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Abstract

The mechanical and electrophysiological effects of 2-pyridylethylamine (PEA) and 4-methylhistamine (4MeH) in different sections of guinea-pig heart were examined.

4MeH produced a dose-dependent increase in contractility in the right ventricle and the right atrium, and a decrease in functional refractory period (FRP) in all the sections studied; the action potential duration was decreased and the plateau phase was usually heightened in both atria and the ventricle. These effects were consistently antagonized by cimetidine.

PEA-induced changes in contractility, FRP and the action potential profile were studied in the presence of cimetidine. Triprolidine antagonized PEA effects on FRP and the action potential profile only in the left atrium.

The results obtained are discussed in terms of the functional role of both H$_1$ and H$_2$ receptors in the various guinea-pig heart sections.

Introduction

A great amount of experimental data demonstrating direct cardiac actions of histamine is available [1-3]. From some of these studies it appears that in guinea-pig heart the distribution of H$_1$ and H$_2$ receptors is not homogeneous: only H$_2$ receptors are present in the right atrium, only H$_1$ receptors in the left atrium and both H$_1$ and H$_2$ receptors in the right ventricle [4-7]. We previously reported that histamine induced changes in guinea-pig ventricular action potential profile, resulting in either a decrease or an increase in action potential duration [8, 9]. These effects were antagonized by burimamide and by triprolidine respectively [8], thus suggesting that H$_1$ and H$_2$ receptors could modify the electrophysiological characteristics of cardiac cells in opposite directions. The availability of the H$_1$- and H$_2$-specific histamine agonists, 2-pyridylethylamine (PEA) and 4-methylhistamine (4MeH) [11], and of the H$_2$ antagonist, cimetidine [12], convinced us to reconsider the electrophysiological effects mediated by specific stimulation of cardiac H$_1$ and H$_2$ receptors more carefully, since to our knowledge only few and conflicting data have been published [13, 14]. However, in order to clarify whether the proposed distribution of H$_1$ and H$_2$ receptors has a general functional significance, we extended our study to different cardiac sections (right atrium, left atrium, right ventricle), looking at the effects of PEA and 4MeH on contractility, functional refractory period (FRP) and intracellular action potential (AP).

Methods

Male guinea-pig of weight range 300-400 g were killed by a blow on the head. The heart was rapidly removed and dissected; the right and left atria and a ventricular strip about 10 mm long x 2-3 mm wide were obtained. All the experiments were carried out using a Tyrode solution of the following composition (mM): NaCl 115; KCl 4.7; MgSO$_4$ 1.2; KH$_2$PO$_4$ 1.2; NaHCO$_3$ 25; CaCl$_2$ 3.6; glucose 10. The solution was gassed with a mixture of 97% O$_2$ and 3% CO$_2$. The pH of the aerated solution was 7.4; the temperature was kept constant at 32°C.

Extracellular studies

The preparations were vertically mounted in a 10 ml double-walled chamber; the bottom was pinned to the stimulating electrodes and the apex was connected to an isometric transducer. The preparations were paced at constant rate (as indicated in the text); in the same preparation the force of contraction was recorded and the functional refractory period was determined according to Govier [15]. The effects of each drug concentration were followed for 10 min, measurements of FRP were carried out at 5- and 10-min intervals. Cumulative dose-response curves were obtained according to Van Rossom [16].

Intracellular studies

The preparations were pinned by means of silver wires to the bottom of a 2 ml tissue bath; two wires were
completely insulated except for the tip and were used as stimulating electrodes. The preparations were paced at constant rate, and the transmembrane action potentials were recorded by conventional microelectrodes filled with 3 M KCl (resistance between 5–10 megaohms). Experiments in which it was impossible to follow the effects of the drug in the same cells were discarded.

Statistical analysis
For testing the statistical significance of drug-induced changes in action potential characteristics, a paired t-test was used.

Drugs used
2-Pyridylethylamine dihydrochloride (PEA), 4-methylhistamine hydrochloride (4MeH), and cimetidine (kindly supplied by SKF Laboratories); triprolidine (Wellcome Research Laboratories). All the solutions were freshly prepared and the concentrations referred to in the text are expressed as the salt.

Results
Effects of 4MeH on FRP and contractility
4MeH caused a dose-dependent increase in contractility in the right ventricle and in both right and left atria. As shown in Figure 1, the maximal effect was reached in the right ventricle, as expected; the effect of 4MeH was stronger in the right than in the left atrium. All the dose-response curves were shifted to the right by cimetidine $10^{-5}$ M, confirming that the inotropic effect of 4MeH was due to H2-receptor stimulation. It was worth noting that $10^{-6}$ M of 4MeH, which had practically no effect on the atria, was able to increase ventricular contractility by as much as 50%. Similar results were obtained on the FRP: the maximal net changes in FRP were obtained in the right ventricle; the effect in the right atrium was greater than in the left atrium. Again 4MeH $10^{-6}$ M did not have any effect on the atrial FRP, but caused a reduction in ventricular FRP of about 50% of the maximal effect. The effects were again antagonized by cimetidine ($10^{-5}$ M). It appears that H2-receptor stimulation is important not only in modulating contractility but also in regulating FRP.

![Figure 1](image-url)

Cumulative dose-response curves of 4MeH alone and in the presence of cimetidine ($10^{-5}$ M) on FRP (upper row) and contractility (lower row) of different guinea-pig heart preparations. Each point represents the mean value of 5 experiments (right ventricle), of 4–7 experiments (right atrium) and of 4–9 experiments (left atrium). Vertical bars indicate standard errors.