Histamine modification of spontaneous rate and rhythm in infarcted canine ventricle

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Abstract

1. Histamine (10^{-3} M) increased the spontaneous rate similarly in isolated preparations of normal left ventricular tissue from control, i.e. normal and sham-operated, dogs (control preparations) and in preparations consisting of normal and contiguous infarcted left ventricular tissue from dogs with subacute, i.e. 24 hours after left coronary artery ligation, myocardial infarction (infarcted preparations).

2. Histamine (10^{-3} M) markedly enhanced the irregular rhythm of infarcted preparations.

3. The H_{1}-receptor antagonist, chlorpheniramine (10^{-4} M), and the H_{2}-receptor antagonist, cimetidine (10^{-3} M), antagonized the effects of histamine (10^{-3} M) on the spontaneous rate of both control and infarcted preparations.

4. The H_{1}-receptor agonist, 2-pyridyl ethylamine (PEA, 10^{-4} M), increased the spontaneous rate of control and infarcted preparations; these effects were antagonized by chlorpheniramine (10^{-4} M). The H_{2}-receptor agonist, dimaprit, had no effect.

5. Similar to histamine (10^{-3} M), PEA (10^{-4} M) enhanced the irregular rhythm of infarcted preparations; dimaprit had no effect.

6. High local concentrations of histamine may occur in poorly perfused ischemic tissue. The enhancement of irregular rhythm produced by histamine, and the specific H_{1}-receptor agonist, PEA, leads us to suggest its involvement in arrhythmias associated with subacute myocardial infarction.

Introduction

Arrhythmias have been characterized in the well-studied Harris model of experimental myocardial infarction in dog [1]. More recent electrophysiologic studies have clarified the cellular bases for arrhythmias occurring during the subacute (~24 hours after permanent coronary artery ligation) phase of myocardial infarction in this model (see [2], for review); the role of enhanced automaticity in this phase has been emphasized.

HARRIS [1] hypothesized that 'unidentified substances' such as histamine might be formed or released during injury and necrosis in regional myocardial ischemia and might serve as an excitatory factor in the genesis of ectopic impulses. Histamine causes arrhythmogenic alterations in impulse formation (automaticity) in normal guinea-pig ventricular myocardium [3] and in diseased human atrial muscle [4] via stimulation of cardiac H_{1}-receptors. On the other hand, arrhythmogenic alterations in impulse propagation (i.e. atrio-ventricular conduction) appear to be mediated through H_{2}-receptor stimulation (see [5], for review). While numerous agents and substances have been studied with respect to their role in infarction-related arrhythmias, there are no reports of the effects of histamine on the rate and rhythm of infarcted ventricular myocardium.

The present study evaluated the effects of histamine and H_{1}- and H_{2}-receptor agonists on left ventricular preparations from dog hearts with subacute myocardial infarction. While transmembrane action potentials recorded in control and infarcted canine myocardium were not appreciably affected by histamine (Gaide et al., unpublished observations), its enhancement of irregular rhythms of infarcted preparations suggests that it is associated with arrhythmias in vivo in this model of myocardial infarction.

Methods

Adult dogs (15–26 kg) were anesthetized with sodium pentobarbital (30 mg/kg, i.v. and supplemental doses) during surgical procedures and prior to removal of their hearts for tissue bath studies. After incubation and initiation of ventilation (Harvard Respirator), left thoracotomy and reflection of the pericardium exposed the left atrium and anterior surface of the left ventricle. A short segment of the
left anterior descending coronary artery (LAD) was carefully freed from surrounding tissue at a point just proximal to the last major branch of the LAD and ligated [11]. This technique produced an infarction located on the anterior and apical aspects of the left ventricular free wall, including the base of the anterior papillary muscle and lower 2/3 of the septum, and usually extending transmurally from the endocardium to the epicardium [6]. The same procedure was followed for sham-operated hearts except that non-occlusive ties were used. A Lead II electrocardiogram (ECG) was recorded (Electronics for Medicine DR-12) before, during and after surgery. The chest was closed and each dog was maintained in a colony for 24 hours.

At the time of study, each dog was anesthetized as described above and the ECG was recorded. The heart was excised and placed in Tyrode's solution gassed with 95% O₂:5% CO₂. The atria and right ventricle were removed, and the left ventricular free wall was divided between the anterior and posterior papillary muscles. The epicardial area of the anterior portion was trimmed, and the preparation was mounted, endocardial surface up, in a tissue bath and superfused (15 ml/min) with 36.5°C Tyrode's solution containing the following (in mM): KCl, 4.0; NaCl, 129; NaHCO₃, 20; NaH₂PO₄, 1.8; dextrose, 5.5; CaCl₂, 2.7; MgCl₂, 0.5. Each preparation from a LAD-ligated heart included both normal (non-infarcted) and contiguous infarcted areas.

Preparations were stimulated with pulses (1 msec; 1.2 x threshold voltage) delivered through Teflon-coated bipolar silver wire electrodes (cycle lengths: 800–1000 msec). Identical electrodes were used to record surface electrograms which were differentially amplified and displayed on an oscilloscope (Tektronix 565 Dual-Beam). Spontaneous activity was monitored with glass microelectrodes (1.0 μm tip diameter; 15–20 megohms resistances) filled with 3 M KCl [6, 7]. Intracellular signals were amplified (WPI Dual Microprobe, Model KS-700), displayed on the oscilloscope and recorded on a polygraph (Grass Model 79).

Gross visual inspection and surface electrograms were used to identify non-infarcted and infarcted (pale color and abnormal activation areas, [7]). Stimulation was ceased after a 30-min equilibration period and each preparation was allowed to beat spontaneously for the remainder of the experiment. The spontaneous rates were monitored for 1 hour prior to initiation of drug exposure. Mean pre-drug spontaneous rate (beats/min) was calculated from the 10-min interval just prior to initiation of drug exposure. Mean spontaneous rate for drug effect was calculated from the 10-min interval beginning 20 min after initiation of drug exposure. This latter interval corresponded to the peak response of the preparation to the drug or drug combinations.

Histamine dihydrochloride, dimaprit dihydrochloride, 2-pyridyl ethylamine dihydrochloride (PEA) and chlorpheniramine maleate (Smith Kline and French Laboratories, Philadelphia, PA), nadolol (E. R. Squibb and Sons, Princeton, NJ) and phentolamine hydrochloride (Ciba, Summit, NJ), were dissolved in Tyrode's solution. Cimetidine (Smith Kline and French Laboratories, Philadelphia, PA) was dissolved in Tyrode's solution with a small amount of lactic acid. Drug solutions were prepared fresh prior to each experiment.

Data are expressed as mean ± standard deviation (SD) and were evaluated for statistical significance by analyses of variance with repeated measures [8]. Duncan's Multiple Range Test was used to make comparisons among means when the analyses of variance indicated significant differences [8]. Differences between means were considered significant at p < 0.01.

Results

All hearts with 24-hour myocardial infarction (MI) displayed ventricular ectopic activity in vivo prior to excision. Arrhythmias consisted of multifocal single or repetitive premature ventricular depolarizations and occasionally nodal rhythms or ventricular tachycardia. Arrhythmias in vivo were never observed in any normal or sham-operated dog. All preparations from MI hearts also displayed arrhythmic spontaneous activity in vitro; the activity was irregular and occurred in bursts interspersed with periods of tissue quiescence (Fig. 1). The spontaneous activity of control (normal and sham-operated) hearts was more uniform and did not display