PHYSIOLOGY

Effects of Epinephrine and 17β-Estradiol Sulfate on Transmembrane Potentials of Guinea Pig Cardiomyocytes

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Changes in the transmembrane potentials of guinea pig cardiomyocytes caused by epinephrine and 17β-estradiol sulfate are studied. It is shown that 17β-estradiol attenuates the effect of epinephrine on these cells.

Key Words: *epinephrine, myocardium, microelectrodes, estrogens*

The reuptake of catecholamines (CA) (for example, epinephrine) in the heart is inhibited by estrogens [5,8,9], which may promote accumulation of CA in this organ. Catecholamines may contribute to the development of cardiac arrhythmias. It was hypothesized that increased concentration of CA is one of the major causes of arrhythmia [10]. However, activation of the sympathetic control over cardiac activity may have an antifibrillatory significance [7]. Estrogens increase cardiac resistance to fibrillation-inducing agents [1,4,8]. On the other hand, hyperestrogenemia potentiates the damaging effect of CA on the heart [6]. Considering these data, we decided to examine the effects of CA and estrogen on the transmembrane potentials of cardiomyocytes.

MATERIALS AND METHODS

Ten series of experiments were performed on isolated myocardial strips from the left ventricle of the heart of a guinea pig. The strips were perfused with warm (33°C, pH 7.3) oxygenated (95% O_2/5% CO_2) Ringer solution containing 4 mM KCl, 137 mM NaCl, 2 mM $CaCl_2$, 1.8 mM $NaHPO_4$, 2.7 mM $MgCl_2$, 1.75 g/liter $NaHCO_3$, and 2 g/liter glucose. The solution was replaced every 3 min. Aqueous solutions of 17β-estradiol sulfate (10^{-6} g/ml, Sigma) and epinephrine (10^{-7} g/ml) were used. The electrical activity of endo- and epicardial cells was measured using glass microelectrodes filled with 3 M KCl solution and recorded continuously from a Tektronix 5103N two-channel oscilloscope at a constant rhythm of electrostimulation from a GRASS-S88 stimulator.

The following protocol was employed. Each myocardial strip was placed in a thermostated chamber and stimulated with electric current for 15-20 min at a frequency range 1.4-2 Hz. Some strips were then perfused for 15 min with epinephrine-containing Ringer solution and washed for 10 min. Other strips were perfused with the same solution, washed, perfused for 30 min with Ringer solution containing 17β-estradiol sulfate and then for 10 min with epinephrine-containing solution, and washed.

The resting potential (RP) as well as the amplitude and duration of action potential (AP) were measured by the standard method at 10, 20, 50, and 80% repolarization.

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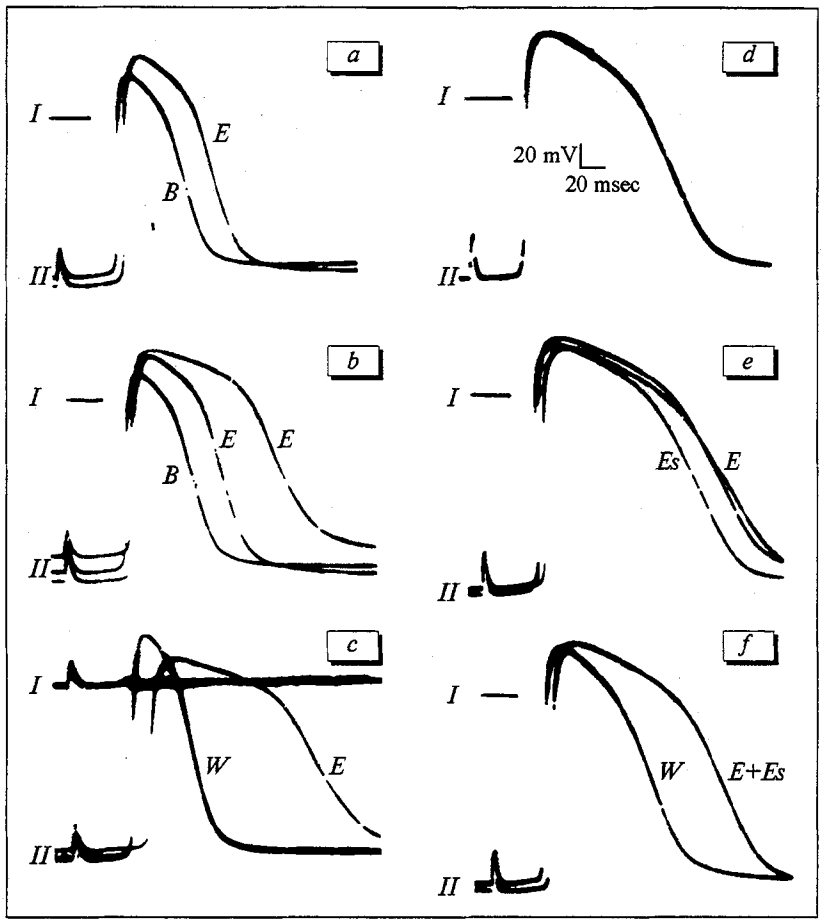

Fig. 1. Superposition of transmembrane potentials of guinea pig ventricular cardiomyocytes. *a*) baseline (*B*) + 5-min perfusion with epinephrine-containing solution (*E*); *b*) baseline (*B*) + 5- and 15-min perfusion with epinephrine-containing solution (*E*); *c*) 15-min perfusion with epinephrine-containing solution (*E*) + 10-min washing (*W*); *d*) 30-min perfusion with estradiol-containing solution; *e*) 15-min perfusion with epinephrine-containing solution (*E*) after exposure to estradiol (*Es*); *f*) 10-min washing (*W*) from epinephrine (*E*) and estradiol (*Es*); *a-f*) continuous recording; *I*) zero line; *II*) action potential.

The results were statistically processed using a PSIPLOT software.

RESULTS

Previously, we showed that according to electrophysiological properties the strips of guinea pig ventricular cardiomyocytes can be divided into two groups: with short (first group) and long (second group) plateau phase [3].

As Fig. 1, *a*, *b* shows, perfusion of a myocardial strip with epinephrine-containing solution progressively increased more than twofold the duration of AP in cells of the first group. However, this increase varied with the repolarization level, being the greatest (2.8-fold) at 10% and the smallest (2.2-fold) at 80% repolarization. Washing led to a 10-15% decrease in the AP duration compared with the baseline level (Fig. 1, *c*).

In cardiomyocytes with a long (second group) plateau phase, AP were shorter and regained the initial parameters after washing. In all studied cardiomyocytes, changes in the AP amplitude were biphasic and time-dependent. The AP amplitude increased by 10-12 mV after 5 min of perfusion and returned to baseline level by the 15th min. During washing it increased to 110-114 mV (14-18 mV over the baseline). It should be stressed that variations in the AP amplitude resulted from alterations of the overshoot (recharging of the cell membrane), since there were no significant changes in RP.

Epinephrine also prolonged delay of the excitation conduction by 12-15% after 5 min and by 20-25% after 15 min of perfusion. These changes disappeared after a 10-min washing.

So far, the effects of epinephrine on the transmembrane potentials of cardiomyocytes are debatable. It was suggested that the effect is species-specific and is determined by individual characteristics and functional state of the heart [2]. Our findings confirm that RP of cardiomyocytes is influenced by epinephrine. The amplitude of AP is determined by two components of the incoming ionic current: the "fast" sodium flux with low sensitivity to epinephrine and the "slow" calcium flux which is highly sensitive to epinephrine [2]. An increase in the AP amplitude resulting from overshoot and prolongation of AP at the expense of the plateau phase is consistent with this mechanism.

Perfusion of myocardial strips with 17β-estradiol sulfate-containing solution for 30 min progressively

prolonged AP (Fig. 1, *d*), while RP and amplitude of AP changed insignificantly ($p>0.05$) by 6-8 mV. However, the rate of fast depolarization increased significantly ($p<0.05$).

Perfusion of myocardial strips with epinephrine after perfusion with 17β-estradiol sulfate led to an insignificant prolongation of AP, predominantly due to prolongation of the plateau phase, while the slope of the terminal repolarization phase remained virtually unchanged (Fig. 1, *e*). The transmembrane potentials were restored by washing; however, the AP duration was 90-120% above the baseline (Fig. 1, *f*).

Thus, we showed that against the background of 17β-estradiol sulfate epinephrine produces a weak effect on the transmembrane potential of the guinea pig cardiomyocytes. In other words, 17β-estradiol sulfate strongly inhibits the effect of epinephrine on these cells. This may account for the antiarrhythmic effects of estrogens [1,4,8].

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