PHYSIOLOGY

The Effect of 17-β-Estradiol Sulfate on the Transmembrane Potentials of Guinea Pig Cardiomyocytes

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It is demonstrated that 17-β-estradiol sulfate increases the electrical homogeneity of the myocardium as a result of reducing the differences in the duration of cardiomyocyte action potentials.

Key Words: *myocardium; transmembrane potentials; estradiol*

On the basis of autoradiography data it has been hypothesized that the heart is a target organ for both estrogens and androgens [7,8]. Although the cytosolic reception of estrogens predominates, it has been assumed that the membrane processes play an important role in the mechanism of action of steroid hormones [4,5].

The heart of animals with transformed hormonal status (males treated with estrogens) is more resistant to arrhythmogenic factors and is more capable of spontaneous defibrillation [1,2,6]. Since it is difficult to distinguish between direct and indirect effects of estrogens on cardiomyocytes *in vivo*, the present study was carried out on isolated myocardial stripes.

MATERIALS AND METHODS

Eighteen experiments were performed on isolated myocardial stripes excised from the left ventricle of guinea pig heart. The stripes were perfused with warm (33°C, pH 7.3) oxygenated (95% O_2/5% CO_2) Ringer solution containing (in mM): KCl 4, NaCl 137, $CaCl_2$ 2, $NaHPO_4$ 1.8, $MgCl_2$ 2.7, $NaHCO_3$ 1.75 g/liter, and glucose 2 g/liter. An aqueous solution of 17-β-estradiol sulfate (10^{-6} g/liter, 17-β-ES, Sigma) was employed as an estrogen. The solution was changed every 3 min.

The electrical activity of endocardial and epicardial cells was continuously recorded with a Tektronix 5103N oscilloscope, photocamera, and glass electrodes filled with 3 M KCl. The resting potential (RP), and the amplitude and duration of the action potential (AP) at 20, 50, and 80% repolarization were measured by the standard methods; the first derivative of the front of AP growth was determined.

Statistical analysis was performed using PSI-PLOT software.

RESULTS

In order to suppress sources of automaticity, the stripes were stimulated with a frequency of 1.4-2 Hz for 25-30 min. Under a light microscope, a microelectrode was inserted in cells of the trabecular muscles located on the endocardial surface. It was found

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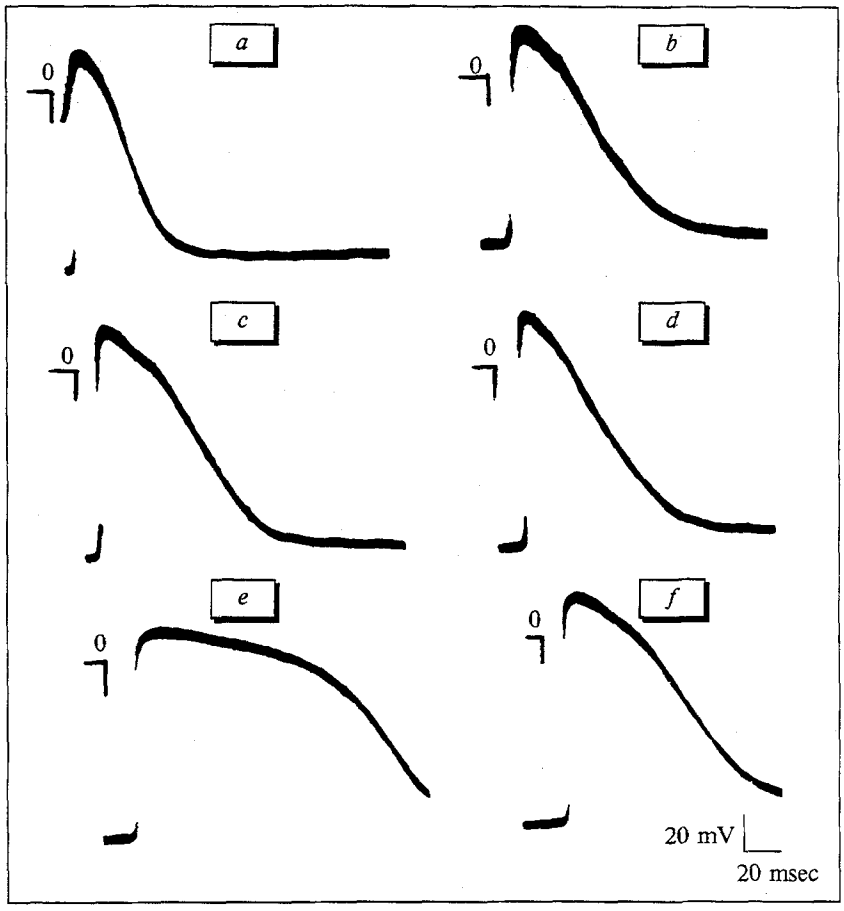

Fig. 1. Effect of 17-β-estradiol (17-β-ES) on the transmembrane potentials of cardiomyocytes isolated from the ventricles of guinea pig heart. *a, e*) control; *b*) 30 min of the 17-β-ES effect; *c, f*) 45 min; *d*) washing from 17-β-ES for 10 min; 0) zero line.

that the duration of AP varies from cardiomyocyte to cardiomyocyte. All cells were arbitrarily divided into two groups: with an indistinct (group 1) and a distinct (group 2) plateau phase. The resting potential and the amplitude of AP did not differ significantly in these groups, the mean values being -84.6±1.3 mV (RP) and 102.1±4.4 mV (AP). There were no significant differences between RP and AP of various cells localized on the epicardial surface.

A 35-45-min perfusion of cardiac preparations with a 17-β-ES-containing solution led to a progressive increase in the duration of AP from group 1 cells (Fig. 1, *a-c*) and a decrease in the duration of AP from group 2 cells (Fig. 1, *e, f*). These changes were

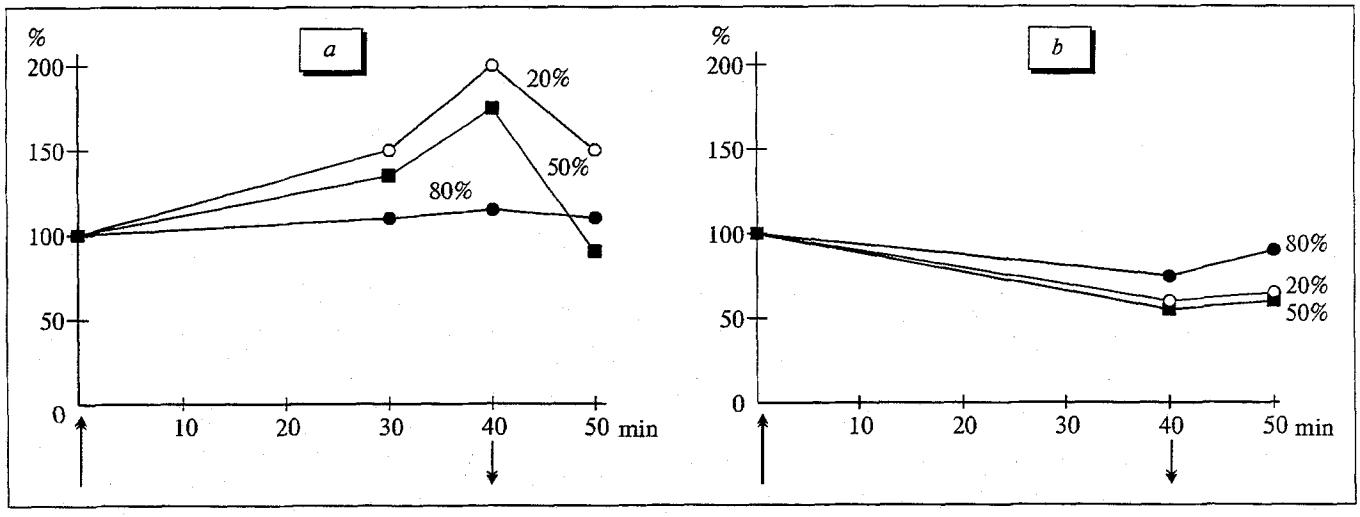

Fig. 2. Kinetics of duration of action potential from cardiomyocytes at different levels of repolarization (20, 50, and 80%) under the action of 17-β-estradiol (up arrow) and washing from it (down arrow). The initial value of each phase is taken as 100%. *a*) group 1; *b*) group 2.

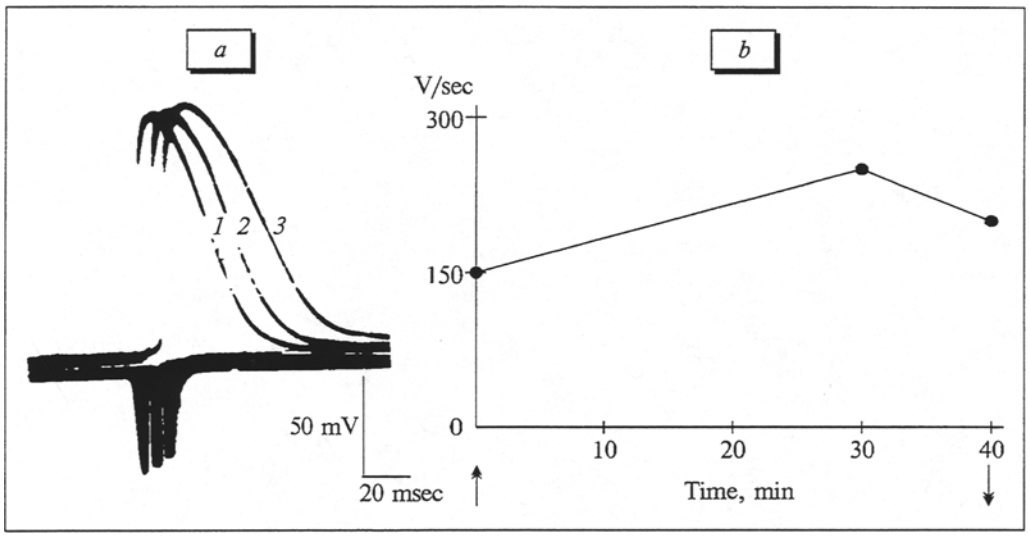

Fig. 3. Effect of 17-β-estradiol (17-β-ES) on first derivative of action potential (AP). *a*) superposition of three AP during washing from 17-β-ES. The first AP was recorded after 40 min of perfusion with 17-β-ES-containing solution, the second and the third AP after 5 and 10 min of washing, respectively; *b*) dynamics of the first derivative. The start of perfusion is indicated with an arrow pointing up; the arrow pointing down indicates 10 min after washing.

recorded at all measuring points of AP duration. The duration of AP was restored during reperfusion of the preparation with 17-β-ES-free solution (Fig. 1, *d*).

At the same time, the cells displayed different degrees of sensitivity to estradiol and reperfusion with estradiol-free solution. The smallest changes were recorded in group 1 cells at 80% repolarization; they were almost the same as those occurring at 50 and 20% repolarization. The same sensitivity for various levels of depolarization was observed in group 2 cells. During washing of myocardial stripes from 17-β-ES, the greatest changes in group 1 cells were recorded at 50% repolarization and in group 2 at 80% repolarization (Fig. 2, *a, b*).

These findings indicate that 17-β-ES has different effects on the outward potassium current, which is responsible for the repolarization of AP, and probably affects the calcium current, which is responsible for the plateau phase. The significantly high rate of washing and restoration of the original electrical activity implies that 17-β-ES is weakly bound to the cardiomyocyte membrane.

During perfusion with 17-β-ES-containing solution, the RP of cardiomyocytes changed insignificantly by 5-8 mV. If the original RP ranged from 72 to 76 mV, a hyperpolarization of the plasma membrane to 78-82 mV was observed. By contrast, if the RP ranged from 82 to 86 mV, there was no change or a slight (several mV) depolarization occurred. In all cardiomyocytes, the amplitude of AP increased by 6-8 mV; however, this increase was statistically insignificant.

17-β-ES significantly increased the rate of rapid depolarization of AP, the effect being reversible during reperfusion with a 17-β-ES-free solution. Fig. 3, *a* shows superposition of three AP during washing of the preparation with an estradiol-free Ringer solution and Fig. 3, *b* shows the dynamics of the first derivative of the rapid depolarization phase during the experiment. It can be hypothesized that 17-β-ES activates Na channels.

Our results indicate that 17-β-ES has a direct effect on the plasma membranes of ventricular cardiomyocytes. This compound decreases electrical heterogeneity of the myocardium by reducing the differences in the duration of the AP of endocardial cardiomyocytes and, consequently, by reducing the heterogeneity in refractoriness. A higher heterogeneity of refractoriness is known to lead to electrical instability of the heart and the development of arrhythmias [3]. Thus, an increase in the electrical homogeneity of the myocardium may be one of the mechanisms underlying the antiarrhythmic effect of estradiol.

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