Antiarrhythmic Properties of Estrogens

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Estrone, estriol, and estradiol valerate exhibited antiarrhythmic activity in rats with aconitine-induced arrhythmia. Estrone was most effective in this respect.

Key words: *estrogens; rat heart; antiarrhythmic activity*

Sex hormones in physiological and therapeutic doses can produce a direct effect on the heart. Published data show that 17β-estradiol decreases contractility of the isolated heart and myocardial strip [8]. Estrogens cause coronary vasodilatation. Estradiol possesses antianginal and antiischemic properties [6]. Previous studies with reperfusion of postischemic heart revealed an antiarrhythmic effect of estrogens. Intravenous treatment with this hormone significantly decreases the incidence of ectopic rhythms and critical tachyarrhythmias. These changes were accompanied by the improvement of coronary perfusion under ischemic conditions [10].

Female sex hormones contribute to spontaneous defibrillation of a fibrillating heart in females or males with hormonal imbalance [3,7].

Little is known about antiarrhythmic properties of female sex hormones and their synthetic analogues.

We previously studied the antiarrhythmic properties of some estrogens, including estradiol valerate and estradiol nitrate. Estradiol valerate is used in clinical practice as an estrogen substitute. Estradiol nitrate is a new promising donor of NO [5].

Here we compared antiarrhythmic activity of female sex hormones estrone and estriol with that of estradiol valerate and commonly used antiarrhythmics lidocaine and Ethmozine.

MATERIALS AND METHODS

Antiarrhythmic activity of estrone and estriol was studied on conscious rats with aconitine-induced arrhythmia [2]. Aconitine hydrochloride in doses of 40-50 μg/kg was injected into the caudal vein of conscious male rats (160-190 g). Further experiments were performed with aconitine hydrochloride in a dose, which induced moderate arrhythmia (polytopic extrasystoles). ECG recording in standard lead II was performed 3, 5, 10, 15, and 20 min after aconitine administration. Mixed atrial-ventricular arrhythmias were recorded.

Estrone or estriol in doses of 1.0, 0.5, 0.25, and 0.125 mg/kg was injected into the caudal vein 1-2 min before aconitine treatment.

Activity of drugs was estimated by the ability to prevent aconitine-induced arrhythmias. The effective dose of the test drug producing the antiarrhythmic effect in 50% animals (ED_{50}) was determined by the Miller—Tainter method [1].

RESULTS

The model of aconitine-induced cardiac fibrillation [2] allows studying the effect of drugs on mixed atrial-ventricular arrhythmias. Aconitine causes polytopic extrasystoles that are comparable with arrhythmia in patients.

Estrone and estradiol have high antiarrhythmic activity during aconitine-induced arrhythmia.

The test drugs had a dose-dependent antiarrhythmic effect. Estrone in a dose of 0.1 mg/kg had the highest antiarrhythmic activity (75% animals). The antiarrhythmic effect of estrone became less significant with increasing or decreasing its dose (Fig. 1). Estrone in a dose of 0.5 mg/kg produced the antiarrhythmic effect only in 35% animals.

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The maximum antiarrhythmic effect of estriol was observed upon treatment with a higher dose of this drug (0.5 mg/kg, 75% animals). A decrease or increase in the dose of estrone was accompanied by the reduction of antiarrhythmic activity (25-30% animals). Estrone and estriol in doses of 0.15 and 0.32 mg/kg, respectively, prevented arrhythmia in 50% animals (Table 1).

Estradiol valerate also produced a dose-dependent antiarrhythmic effect. This drug in a dose of 0.125 mg/kg produced an antiarrhythmic effect in 33% animals. Antiarrhythmic activity of estradiol valerate increased to 37% with increasing its dose to 0.25 mg/kg. The antiarrhythmic effect was most significant upon treatment with estradiol valerate in a dose of 0.5 mg/kg (75% animals). ED_{50} of estradiol valerate was 0.32 mg/kg.

Estrone was 52 times more potent then lidocaine. The effectiveness of estriol and estradiol valerate 24-fold exceeded that of lidocaine (Table 1). Estriol, estradiol valerate, and Ethmozine had similar ED_{50} (0.32, 0.32, and 0.28 mg/kg, respectively). ED_{50} of estrone (0.15 mg/kg) was much lower.

The development of aconitine-induced arrhythmia is associated with changes in activity of fast sodium channels in the excitable membrane and increase in their conductivity. Some substances (*e.g.*, class I antiarrhythmics and tetrodotoxin) are specific blockers of fast sodium channels.

Estrogens and class I antiarrhythmics have pronounced antiarrhythmic activity during aconitine-induced arrhythmia. These data suggest that the mechanism for antiarrhythmic activity of estrone, estriol, and estradiol valerate is similar to that of class I antiarrhythmic drugs.

It cannot be excluded that the antiarrhythmic effect of estrogens is partly due to modulation of calcium cannels. Estradiol and synthetic estrogen diethylstilbestrol can induce fast inhibition of sodium L-channels in cardiomyocytes. Estradiol in micromolar concentrations decreases the calcium current in isolated myocytes by 80% [9].

TABLE 1. Antiarrhythmic activity (ED_{50}) of Estrone and Estriol *vs.* Estradiol Valerate, Lidocaine, and Ethmozine

Name	ED_{50}, mg/kg	Relative activity
Estrone	0.15 (0.12-0.18)	52
Estriol	0.32 (0.23-0.41)	24
Estradiol valerate	0.32 (0.26-0.38)	24
Lidocaine	7.80 (5.60-10.80)	1
Ethmozine	0.28 (0.17-0.38)	27

Note. Antiarrhythmic activity of lidocaine serves as a unit of activity.

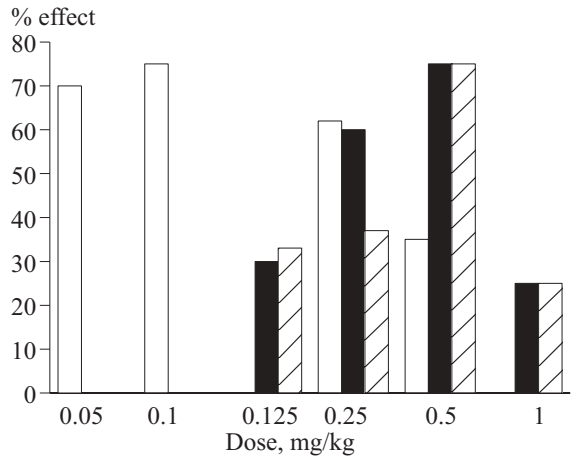

Fig. 1. Antiarrhythmic activity of estrone (light bars), estriol (dark bars), and estradiol valerate (shaded bars) in rats with aconitine-induced arrhythmia. Ordinate: prevention of aconitine-induced arrhythmia with test drugs, percentage of animals.

Previous autoradiographic studies suggest that the heart is a target organ for estrogens and androgens [11,12].

The effect of estrogens on the heart can be realized via cytoplasmic receptors. Our results show that membrane processes play an important role in the action of these hormones. This hypothesis is supported by our findings that estradiol produces a direct effect on membranes of ventricular cardiomyocytes and modulates the duration of action potentials [4].

Estrone has the highest antiarrhythmic activity. Estradiol valerate and estriol produce a less significant antiarrhythmic effect.

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