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Changes in Electrical Activity of Working Myocardium under Condition of I_f Current Inhibition

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The study examined the effect of ZD7288, a blocker of hyperpolarization-activated "funny" current I_f, on electrical activity in working atrial and ventricular myocardium in rats. In concentrations range from 3×10^{-6} to 3×10^{-5} M, the agent significantly increased the duration of action potentials at 50 and 90% repolarization levels in both atrial and ventricular myocardium at the fixed stimulation rate of 5 Hz. The blocker affected neither resting potential nor the upstroke velocity of action potential. In patch-clamp experiments, ZD7288 selectively inhibited I_f current, but produced no effect on delayed rectifier potassium currents that determine the rate of repolarization. The described effects of ZD7288 are not related to its non-specific effects on the ionic currents except I_f.

Key Words: *I_f current; atrium; action potential; ionic currents*

The currents activated by hyperpolarization and baptized by the generic name of "funny currents" (I_f) play a crucial role in generation of automatic activity in mammalian cardiac pacemaker cells. According to modern views, these currents are responsible for the development of initial, linear, and slow diastolic depolarization in cells of the sinoatrial node [6]. Inhibition of I_f with cesium ions or selective organic blockers such as ivabradin, zatebradin, and ZD7288 down-regulates HR due to deceleration of diastolic depolarization [7], although it does not completely arrest pacemaker activity. At the same time, a rather small I_f current was revealed not only in atypical, but also in working atrial and ventricular cardiomyocytes [3]. Functional role of I_f in these cells possessing no intrinsic automaticity was questionable for a long time.

Recently, new data were obtained indicating possible involvement of I_f in performance of working cardiomyocytes. Specifically, the experiments carried out on the strips of working atrial and ventricular myocardium isolated from rats demonstrated the positive inotropic effect resulted from inhibition of I_f with selective blocker ZD7288 [8]. In contrast, the development of cardiac failure in rats was paralleled by an increase in I_f current density in the ventricular cardiomyocytes [2], which attested to the pathophysiological role of this current and its involvement in the development of ventricular tachyarrhythmias aggravating cardiac failure. It remains unclear how I_f participates in shaping electrical activity of normal working cardiomyocytes in the atria and ventricles.

This work was designed to study changes in the shape of action potential (AP) of atrial and ventricular cardiomyocytes in rats induced by specific inhibition of I_f current with organic blocker ZD7288.

MATERIALS AND METHODS

Experiments were performed on random-bred male albino rats (n=17) weighing 300-350 g and random-bred male albino mice (n=6) weighing 20-30 g. The experiments with intracellular recording of electrical activity in working myocardium were carried out on rats. The animals were decapitated, the chest was ra-

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