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Effects of sex hormones on action potential and contraction of guinea pig papillary muscle[1]

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AIM: To study the effects of sex hormones, estradiol (Est), progesterone (Pro) and testosterone (Tes) on the action potential (AP) and contraction of guinea pig papillary muscle. **METHODS:** Using conventional glass microelectrode and mechanical recording of myocardial contraction. **RESULTS:** Est slowed down the maximal rate of rise of phase 0 (V_{max}) of AP at low concentration (1 $\mu mol \cdot L^{-1}$). At 10 $\mu mol \cdot L^{-1}$ and above, Est also prolonged AP duration (APD_{50} and APD_{90}), effective refractory period (ERP) and decreased the maximal isometric tension (P_{max}) and velocity of tension development (dT/dt) of contraction. Tes (100 $\mu mol \cdot L^{-1}$ – 1 $mmol \cdot L^{-1}$) prolonged APD_{90} and ERP with decreased P_{max} and dT/dt. But Pro (1 $\mu mol \cdot L^{-1}$ – 1 $mmol \cdot L^{-1}$) had no effects on both AP and contraction. **CONCLUSION:** Est prolonged AP and depressed contraction of guinea pig papillary muscle.

There are pronounced sex differences in the occurrence and manifestation of coronary disease. Estrogen has many effects on cardiovascular system[1-3]. Estrogen receptor has been found in heart, which implies heart to be an estrogen target organ[4]. Some proposed that estrogen had a protecting action on coronary diseases, but others considered that increase of blood estrogen was a coronary risk factor[5-7]. Estrogen inhibited contraction of isolated rabbit heart[8] and antagonized experimental arrhythmia[2]. The present study was to observe the influences of estradiol (Est), as well as methyl testosterone (Tes), and progesterone (Pro) on electric and mechanical activities of guinea pig papillary muscle.

MATERIALS AND METHODS

Action potentials (AP) Guinea pigs, Grade I, bred by Experimental Animal Center Hebei Medical University, Certificate № 04040, ♂, weighing 320 ± *s* 41 g were used, the papillary muscle of right ventricle was perfused with modified Tyrode's solution (37 ℃) containing NaCl 136.8, KCl 5.4, $MgCl_2$ 1.05, $CaCl_2$ 1.08, $NaHCO_3$ 1.2, glucose 11.0, and Tris 5.0 $mmol \cdot L^{-1}$ (pH 7.4 ± 0.05). AP was recorded with glass microelectrode[9] and fed into a high-impedance microelectrode amplifier (SWF-1). Resting potential (RP), AP amplitude (APA), duration of 50 % and 90% repolarization of AP (APD_{50} and APD_{90}), the maximal rate of phase 0 (V_{max}), and effective refractory period (ERP) were analyzed with the program designed by our Department[10]. After a period of stabilization for 1 h, Est (1, 10, 100 $\mu mol \cdot L^{-1}$), Tes (1, 10, 100, 1000 $\mu mol \cdot L^{-1}$), or Pro (1, 10, 100, 1000 $\mu mol \cdot L^{-1}$) was added cumulatively to the bath at 20-min intervals. The hormone was dissolved in ethyl alcohol absolute and added to the perfusate, where the maximal concentration of alcohol was 0.1 %.

Myocardial contraction The preparation was stimulated at 1 Hz. The maximal isometric tension (P_{max}) and velocity of tension development (dT/dt) were recorded with a tension transducer connected to a two-channel physiograph (LMS-2B) and the microcomputer. The dose-response curve was made according to the percentage changes of contraction in different concentrations of sex hormones.

Statistics Statistical analysis was made using the paired *t*-test.

Drugs Est (E Merck, Germany), Tes and Pro (Shanghai № 2 Chemical Reagent Plant, China).

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RESULTS

AP At 1 μmol·L^{-1}, Est diminished the speed of depolarization in AP, slowing down V_{max} ($P<0.05$). At $\geq$10 μmol·L^{-1}, it prolonged APD_{50}, APD_{90} and ERP ($P<0.05$, $P<0.01$) in a concentration-dependent manner, but it had no action on RP or APA ($P>0.05$, Tab 1).

At 1 – 10 μmol·L^{-1}, Tes had no obvious action on both RP and AP. At $\geq$100 μmol·L^{-1}, it prolonged APD_{90} and ERP significantly ($P<0.05$, Tab 1).

Pro, at 1, 10, 100, 1000 μmol·L^{-1}, had little effects on all parameters of RP and AP ($P>0.05$, Tab 1).

Myocardial contraction Est (1 – 10 μmol·L^{-1}), Tes (1 – 100 μmol·L^{-1}) and Pro (1 – 1000 μmol·L^{-1}) had no remarkable effects on P_{max} and dT/dt. But by perfusion of Est ($\geq$100 μmol·L^{-1}) or Tes ($\geq$1000 μmol·L^{-1}), P_{max} and dT/dt were greatly reduced ($P<0.05$, Fig 1).

Perfused with 0.1 % alcohol-Tyrode's solution for 80 min, the papillary muscle had no significant changes on electrophysiologic and mechanical events ($P>0.05$, Tab 1).

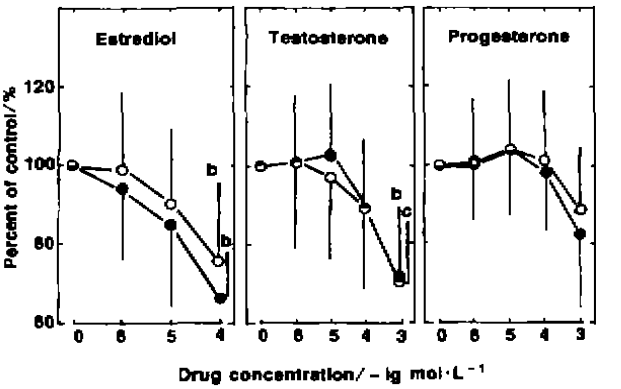

Fig 1. Effects of Est, Tes, and Pro on contraction of papillary muscle ● P_{max} ○ dT/dt n = 30 guinea pigs. $^bP<0.05$, $^cP<0.01$ *vs* control. The control value of P_{max} in Est, Tes, and Pro were 0.49 ± 0.09, 0.5 ± 0.08, 0.49 ± 0.08 g, respectively, dT/dt, 1.12 ± 0.02, 1.11 ± 0.03, and 1.12 ± 0.02 g/s, respectively.

DISCUSSION

The present study first observed the influence of 3 kinds of sex hormones on electrophysiologic and mechanical activities of guinea pig papillary muscle. Among 3 sex hormones used, Est is the most effective, affecting myocardial electrical activity at a low concentration (1 μmol·L^{-1}) and also inhibiting contraction at a high one (100 μmol·L^{-1}). Tes is effective only at a high concentration ($\geq$100 μmol·L^{-1}). Pro is not effective whatever concentration is administered. These results suggest that Est may play a definite role in the sexual differences of occurrence, manifestation and pathological process of coronary disease. The prolongation of APD and ERP in AP may be the electrophysiologic basis of the anti-arrhythmic of Est.

Tab 1. Effects of sex hormones on AP and ERP of guinea pig papillary muscle. n = 35 guinea pigs, $\bar{x} \pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

	μmol·L^{-1}	RP/mV	APA/mV	V_{max}/V·s^{-1}	APD_{50}/ms	APD_{90}/ms	ERP/ms
Solvent		– 81 ± 4^a	113 ± 6^a	114 ± 24^a	242 ± 29^a	300 ± 26^a	297 ± 31^a
Est	0	– 84 ± 4	114 ± 4	120 ± 21	241 ± 24	296 ± 26	295 ± 27
	1	– 84 ± 4^a	114 ± 5^a	109 ± 24^b	246 ± 26^a	303 ± 24^a	300 ± 27^a
	10	– 84 ± 4^a	114 ± 6^a	101 ± 25^b	263 ± 24^b	315 ± 19^b	309 ± 28^b
	100	– 84 ± 3^a	115 ± 6^a	98 ± 21^c	270 ± 24^c	324 ± 21^c	319 ± 27^c
Tes	0	– 83 ± 6	111 ± 5	114 ± 24	242 ± 20	292 ± 21	287 ± 23
	1	– 81 ± 6^a	112 ± 6^a	112 ± 28^a	242 ± 22^a	294 ± 22^a	293 ± 23^a
	10	– 82 ± 5^a	112 ± 4^a	113 ± 31^a	247 ± 21^a	298 ± 23^a	297 ± 27^a
	100	– 83 ± 6^a	111 ± 5^a	113 ± 30^a	250 ± 25^a	304 ± 23^a	304 ± 25^a
	1000	– 84 ± 7^a	112 ± 4^a	111 ± 30^a	263 ± 19^b	317 ± 22^b	316 ± 22^b
Pro	0	– 81 ± 4	111 ± 4	115 ± 24	238 ± 27	293 ± 23	291 ± 30
	1	– 80 ± 4^a	111 ± 5^a	109 ± 22^a	237 ± 32^a	293 ± 23^a	295 ± 29^a
	10	– 80 ± 4^a	111 ± 5^a	107 ± 20^a	243 ± 26^a	299 ± 28^a	300 ± 34^a
	100	– 80 ± 3^a	109 ± 3^a	107 ± 19^a	248 ± 28^a	300 ± 30^a	298 ± 37^a
	1000	– 81 ± 4^a	109 ± 4^a	106 ± 24^a	249 ± 31^a	304 ± 32^a	301 ± 36^a

Myocardial AP depolarization mainly involves Na^+ channel and repolarization relates with different K^+ channels and Ca^{2+} channels[11]. Est affects both depolarization and repolarization of AP in cultured rat myocardial cells, decreasing APA, OS, MDP, V_{max}, and APD markedly in a dose-dependent manner[12]. Furthermore, Est reduces Ca^{2+} inward current (I_{Ca}) and delays recovery time of I_{Ca} inactivation in isolated ventricular myocytes of guinea pig without affecting the current-voltage relationship[13]. Our work indicated that Est influenced V_{max}, APD, and ERP and suppressed myocardial contraction, which implies that Est affects the activities of Na^+ channels and K^+ channels besides blocking Ca^{2+} channels and inhibiting Ca^{2+} influx.

Estrogen caused a negative inotropic action, either in isolated rabbit heart[5], guinea pig isolated ventricular cells[13] or in guinea pig papillary muscle in our experiment. So did Tes in high concentration. Under our experimental condition, the electrophysiologic changes manifested earlier than contraction, suggesting sex hormones are prone to affect the electric activity of myocardial cell.

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性激素对豚鼠心室乳头状肌动作电位和收缩的影响[1]

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关键词 雌二醇; 睾酮; 孕酮; 乳头状肌; 电生理学; 动作电位; 心肌收缩

目的: 研究雌二醇(Est)、睾酮(Tes)和孕酮(Pro)对豚鼠心室乳头状肌动作电位(AP)和收缩活动的影响. **方法**: 经典的玻璃微电极方法和心肌收缩描记方法. **结果**: Est 在较低浓度(1 μmol·L^{-1})即明显减慢动作电位 0 期最大除极速率(V_{max}). 随着浓度增加, 还可延长动作电位时程(APD_{50}, APD_{90})和有效不应期(ERP). 并呈现负性肌力作用, 使最大收缩张力(P_{max})降低, 张力产生速率(dT/dt)减慢. Tes 在较高浓度(100 μmol·L^{-1} – 1 mmol·L^{-1})可延长 APD_{90}、ERP, 降低 P_{max} 和 dT/dt. 而 Pro 对心肌电生理活动及收缩均无明显影响. **结论**: 雌激素延长豚鼠乳头状肌动作电位, 抑制其收缩活动.