

## Effects of sodium pentobarbital on electric and mechanical activities of guinea pig papillary muscle

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**KEY WORDS** pentobarbital; electrophysiology; action potentials; papillary muscles; potassium channels

**AIM:** To study the effects of sodium pentobarbital (SP) on the action potential (AP) and contraction of guinea pig papillary muscle. **METHODS:** Using conventional glass microelectrode and mechanical recording of myocardium contraction. **RESULTS:** SP ( $\geq 10 \mu\text{mol}\cdot\text{L}^{-1}$ ) prolonged the AP duration (APD) and effective refractory period (ERP), while amplitude (APA) and  $V_{\text{max}}$  of phase 0 showed no changes. The effects of SP were abolished by pretreatment with cromakalim, an agonist of ATP-sensitive  $\text{K}^+$  channel. The maximal isometric tension ( $P_{\text{max}}$ ) and velocity of tension development ( $dT/dt$ ) were decreased to 51% and 48% of control, respectively. The first postrest beat ( $B_1$ ) and second postrest beat ( $B_2$ ) were also depressed. **CONCLUSION:** SP affected the action potential by reducing activities of the  $\text{K}^+$  channels and reduced the contraction of guinea pig myocardium.

Sodium pentobarbital (SP) suppressed sinus node, atrioventricular node, and ventricular function<sup>[1]</sup>. Serious slowing of ventricular conduction frequently occurred in the dogs anesthetized with PB<sup>[2]</sup>. SP anesthesia prolonged the Q-T interval in dogs and prevent the induction of ventricular tachycardia after myocardial infarction<sup>[3]</sup>. SP has direct actions on electrophysiological activity of papillary muscles from guinea pigs and dogs<sup>[4]</sup>. Influence of SP on myocardial contractile function has been studied with conflicting results<sup>[5,6]</sup>. The present study was to observe the effects of SP on electric and mechanical activities of isolated myocardium and to explore the underlying mechanism by simultaneous recording AP and

contraction of preparation.

### MATERIALS AND METHODS

**Action potentials (AP)** In 30 guinea pigs of either sex weighing  $350 \pm 50$  g, the papillary muscle of right ventricle was perfused with modified Tyrode solution containing ( $\text{mmol}\cdot\text{L}^{-1}$ ) NaCl 136.8; KCl 5.4;  $\text{MgCl}_2$  1.05;  $\text{CaCl}_2$  1.08;  $\text{NaHCO}_3$  1.2; glucose 11.0, and Tris 5.0 (pH  $7.4 \pm 0.05$ ). AP was recorded with glass microelectrode<sup>(7)</sup> and fed into a high-impedance microelectrode amplifier (SWF-1). Resting potentials (RP), AP amplitude (APA), overshoot (OS), duration of 50% and 90% repolarization of AP (APD<sub>50</sub> and APD<sub>90</sub>), the maximal rate of phase 0 ( $V_{\text{max}}$ ), and effective refractory period (ERP) were analyzed with the computer using a program designed by our Department<sup>(8)</sup>. After a period of stabilization for 1 h, SP ( $1, 10, 100, 400 \mu\text{mol}\cdot\text{L}^{-1}$ ) was added cumulatively to the bath at 20-min intervals.

#### Effects of cromakalim on myocardial electrophysiology

Twenty preparations were divided into 4 groups: control, solvent (5%  $\text{Me}_2\text{SO}$ ), cromakalim ( $30 \mu\text{mol}\cdot\text{L}^{-1}$ ), cromakalim ( $30 \mu\text{mol}\cdot\text{L}^{-1}$ ) + SP ( $100 \mu\text{mol}\cdot\text{L}^{-1}$ ). AP and ERP were obtained after 15-min perfusion with different drugs. SP: Serva, Germany. Cromakalim: Lipponshoji, Kaisha LTP, Osaka, Japan.

**Myocardial contraction** The preparation were stimulated at 0.1, 0.25, 0.5, and 1 Hz. The maximal isometric tension ( $P_{\text{max}}$ ) 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 first beat ( $B_1$ ), the second beat ( $B_2$ ) after 30-s rest interval, and the time of postrest recovery (RT) were also recorded<sup>(9)</sup>.

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

### RESULTS

**Effects of SP on AP** SP  $1 \mu\text{mol}\cdot\text{L}^{-1}$  had little action on AP. At  $\geq 10 \mu\text{mol}\cdot\text{L}^{-1}$ , it prolonged APD<sub>50</sub>, APD<sub>90</sub>, and ERP ( $P < 0.05 - 0.01$ ) in a concentration-dependent manner. However, SP did not produce obvious changes in RP, OS, APA, and  $V_{\text{max}}$  (Tab 1).

Tab 1. Effects of pentobarbital and cromakalim on AP and ERP of guinea pig papillary muscle.  $n = 30$ ,  $\bar{x} \pm s$ .  
<sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs control.

$\mu\text{mol} \cdot \text{L}^{-1}$	RP/mV	OS/mV	APA/mV	$V_{\text{max}}/V \cdot \text{s}^{-1}$	APD <sub>50</sub> /ms	APD <sub>90</sub> /ms	ERP/ms
SP 0	71 ± 4	37 ± 3	108 ± 4	160 ± 62	178 ± 25	218 ± 27	217 ± 24
1	71 ± 5 <sup>a</sup>	38 ± 4 <sup>a</sup>	108 ± 6 <sup>a</sup>	157 ± 62 <sup>a</sup>	188 ± 28 <sup>a</sup>	226 ± 28 <sup>a</sup>	227 ± 22 <sup>a</sup>
10	63 ± 9 <sup>a</sup>	34 ± 7 <sup>a</sup>	104 ± 8 <sup>a</sup>	151 ± 61 <sup>a</sup>	189 ± 22 <sup>b</sup>	230 ± 26 <sup>b</sup>	230 ± 19 <sup>a</sup>
100	70 ± 4 <sup>a</sup>	37 ± 4 <sup>a</sup>	107 ± 5 <sup>a</sup>	150 ± 53 <sup>a</sup>	203 ± 14 <sup>c</sup>	254 ± 20 <sup>c</sup>	249 ± 18 <sup>c</sup>
400	68 ± 3 <sup>a</sup>	37 ± 4 <sup>a</sup>	105 ± 4 <sup>a</sup>	144 ± 54 <sup>a</sup>	206 ± 27 <sup>c</sup>	280 ± 33 <sup>c</sup>	269 ± 21 <sup>c</sup>
Control	69 ± 4	39 ± 4	108 ± 4	165 ± 42	190 ± 33	230 ± 40	220 ± 36
Solvent	70 ± 4 <sup>a</sup>	38 ± 6 <sup>a</sup>	109 ± 4 <sup>a</sup>	154 ± 56 <sup>a</sup>	194 ± 37 <sup>a</sup>	232 ± 34 <sup>a</sup>	229 ± 32 <sup>a</sup>
Cromakalim 30	67 ± 4 <sup>a</sup>	36 ± 9 <sup>a</sup>	107 ± 4 <sup>a</sup>	151 ± 54 <sup>a</sup>	182 ± 32 <sup>a</sup>	218 ± 41 <sup>a</sup>	220 ± 37 <sup>a</sup>
Cromakalim 30 + SP 100	71 ± 6 <sup>a</sup>	41 ± 6 <sup>a</sup>	108 ± 3 <sup>a</sup>	149 ± 60 <sup>a</sup>	187 ± 30 <sup>a</sup>	229 ± 34 <sup>a</sup>	229 ± 36 <sup>a</sup>

**Effects of cromakalim on myocardial electrophysiology** Transmembrane potentials obtained in solvent were not significantly different from control. In cromakalim group, APD<sub>50</sub>, APD<sub>90</sub>, and ERP tended to shorten ( $P > 0.05$ ). After 15-min pretreatment with cromakalim, the effect of SP on AP was almost abolished (Tab 1).

**Effects of SP on myocardial contraction** SP 1  $\mu\text{mol} \cdot \text{L}^{-1}$  had no remarkable effects on  $P_{\text{max}}$  and  $dT/dt$ . By perfusion of SP ( $\geq 10 \mu\text{mol} \cdot \text{L}^{-1}$ ),  $P_{\text{max}}$  and  $dT/dt$  were greatly reduced in a concentration-dependent manner.  $P_{\text{max}}$  and  $dT/dt$  were decreased to 50 % and 48.4 % of control, respectively. At the same concentration, changes of  $P_{\text{max}}$  and  $dT/dt$  caused by low rate of stimuli were more obvious than those by high rate of stimuli.

After 30-s rest, the  $B_1$  was smaller than pre-rest beat (control) and then gradually recovered. In the lower rate (0.1 or 0.25 Hz) of stimulation,  $B_1$  was smaller than  $B_2$ , but  $B_2$  was smaller than  $B_1$  as stimulation rate increased (0.5 or 1 Hz). SP ( $\geq 10 \mu\text{mol} \cdot \text{L}^{-1}$ ) markedly inhibited both  $B_1$  and  $B_2$  in a concentration-dependent manner. Post-rest recovery time (RT) was not affected by SP (Tab 2).

## DISCUSSION

In accordance with reference 4, SP mainly prolonged APD and ERP, indicating the reduction of repolarization process. It may be an important reason why SP increases Q-T interval and prevents ventricular tachycardia after myocardial infarction<sup>[3]</sup>. Cromakalim, an agonist of ATP-sensitive

Tab 2. Effects of pentobarbital on contraction of guinea pig papillary muscle.  
 $n = 10$ ,  $\bar{x} \pm s$ . <sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs control.

Pentobarbital/ $\mu\text{mol} \cdot \text{L}^{-1}$	Cycle length	$P_{\text{max}}/\text{mg}$	$dT/dt/\text{mg} \cdot \text{s}^{-1}$	$B_1/\text{mg}$	$B_2/\text{mg}$	RT/s
0	10 s	20 ± 11	211 ± 122	17 ± 11	18 ± 10	2.1 ± 0.9
	1 s	44 ± 18	467 ± 192	32 ± 15	22 ± 12	16 ± 8
1	10 s	18 ± 9 <sup>a</sup>	178 ± 89 <sup>a</sup>	14 ± 6 <sup>a</sup>	15 ± 7 <sup>a</sup>	2.6 ± 1.0 <sup>a</sup>
	1 s	44 ± 19 <sup>a</sup>	463 ± 187 <sup>a</sup>	31 ± 15 <sup>a</sup>	21 ± 10 <sup>a</sup>	17 ± 6 <sup>a</sup>
10	10 s	15 ± 7 <sup>b</sup>	154 ± 68 <sup>b</sup>	12 ± 6 <sup>b</sup>	13 ± 7 <sup>b</sup>	1.9 ± 0.6 <sup>a</sup>
	1 s	42 ± 18 <sup>b</sup>	453 ± 185 <sup>b</sup>	28 ± 13 <sup>b</sup>	18 ± 7 <sup>b</sup>	16 ± 6 <sup>a</sup>
100	10 s	13 ± 5 <sup>b</sup>	128 ± 52 <sup>b</sup>	11 ± 5 <sup>b</sup>	12 ± 5 <sup>b</sup>	2.1 ± 0.9 <sup>a</sup>
	1 s	35 ± 16 <sup>c</sup>	347 ± 154 <sup>c</sup>	25 ± 11 <sup>b</sup>	16 ± 7 <sup>b</sup>	14 ± 5 <sup>a</sup>
400	10 s	10 ± 6 <sup>b</sup>	102 ± 57 <sup>b</sup>	9 ± 5 <sup>b</sup>	9 ± 6 <sup>b</sup>	2.0 ± 0.9 <sup>a</sup>
	1 s	25 ± 17 <sup>c</sup>	244 ± 154 <sup>c</sup>	20 ± 10 <sup>c</sup>	11 ± 7 <sup>c</sup>	13 ± 5 <sup>a</sup>

K<sup>+</sup> channel<sup>[10]</sup>, can abolish effects of SP, implying that electrophysiological effects of SP may be related to inhibition of K<sup>+</sup> channel. However, the concrete mechanism remains to be studied. In high rate of stimulation, SP may influence not only repolarization, but also depolarization<sup>[4]</sup>. It exhibited that the effects of SP on myocardial electrical activities was dependent on the stimulation rate.

Postrest recovery of muscle can reflect Ca release from sarcoplasmic reticulum (SR) and Ca influx. After a rest interval, B<sub>1</sub> evoked by resuming stimulation principally reflects SR Ca release, but B<sub>2</sub> and subsequent contractions reflect Ca influx<sup>[9,12]</sup>. Our results obtained implied that SP might inhibit both SR Ca release and Ca influx<sup>[12]</sup>.

Up to date, SP is a most commonly used anesthetic for *in vivo* cardiovascular studies. Normal anesthetic concentration of SP ranges between 100 and 200 μmol·L<sup>-1</sup><sup>[4]</sup>. Our findings showed that SP at anesthetic concentration affected electric activity and contractile function of myocardium.

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戊巴比妥钠对豚鼠乳头状肌电活动和机械收缩的影响

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关键词 戊巴比妥<sup>钠</sup>; 电生理学; 动作电位;  
乳头状肌; 钾通道 R 77  
R P6

**目的:** 研究戊巴比妥钠 (SP) 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:** SP ( $\geq 10 \mu\text{mol}\cdot\text{L}^{-1}$ ) 明显延长 AP 复极化时程 (APD) 和有效不应期 (ERP) 但对 AP 幅度 (APA)、动作电位 0 期最大除极速率 ( $V_{\text{max}}$ ) 无明显影响。 K<sup>+</sup> 通道激活剂 cromakalim 可阻断 SP 上述作用。 SP 使收缩最大张力和张力上升速率 (dT/dt) 分别降至正常值的 51% 和 48%, 对休息后刺激引发的第一次收缩 (B<sub>1</sub>) 和第二次收缩 (B<sub>2</sub>) 也有明显抑制作用。 **结论:** SP 对心肌细胞电生理活动和机械收缩具明显影响, 其作用与 K<sup>+</sup> 通道抑制有关。