

# 11种人参皂甙单体对心肌细胞动作电位的影响

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## Influence of 11 ginsenoside monomers on action potentials of myocardiocytes

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**ABSTRACT** Eleven ginsenoside monomers were added to cultured myocardiocytes of neonatal Wistar rats in a concentration of  $20 \mu\text{g} \cdot \text{ml}^{-1}$ . And the action potentials (AP) were led with microelectrodes. Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, R<sub>c</sub>, Rg<sub>1</sub>, Rg<sub>2</sub>, R<sub>e</sub>, and Rh<sub>1</sub> inhibited AP, decreasing APA by 20%, 13%, 5%, 18%, 30%, 37%, 28%, and 23%, respectively. The potency of the most effective monomer Rg<sub>2</sub>  $20 \mu\text{g} \cdot \text{ml}^{-1}$  was similar to that of the calcium channel blocker nimodipine  $1.25 \mu\text{g} \cdot \text{ml}^{-1}$ . R<sub>d</sub>, R<sub>f</sub>, and R<sub>o</sub> had no significant influence on AP. The average potency of the panaxatriol saponin (PTS) monomers were greater than that of the panaxadiol saponin (PDS) monomers. The above demonstrate the reason why the calcium channel blockade action of PTS is stronger than that of PDS results from the summation of monomer drug effects.

**KEY WORDS** ginseng; saponins; cultured cells; myocardium; action potentials; nimodipine

**摘要** 培养 Wistar 大鼠乳鼠的心肌细胞。分别加入 11 种人参皂甙单体，浓度均为  $20 \mu\text{g} \cdot \text{ml}^{-1}$ 。用微电极引导动作电位。Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, R<sub>c</sub>, Rg<sub>1</sub>, Rg<sub>2</sub>, R<sub>e</sub>, Rh<sub>1</sub> 抑制 AP，分别使 APA 降低 20%，13%，5%，18%，30%，37%，28%，23%。作用最强的单体 Rg<sub>2</sub> 的药效与钙通道阻滞剂尼莫地平  $1.25 \mu\text{g} \cdot \text{ml}^{-1}$  相似。R<sub>d</sub>, R<sub>f</sub>, R<sub>o</sub> 对 AP 无明显影响。提示人参三醇组皂甙的钙通道阻滞作用比人参二醇组皂甙强，是其所属单体综合合作用的结果。

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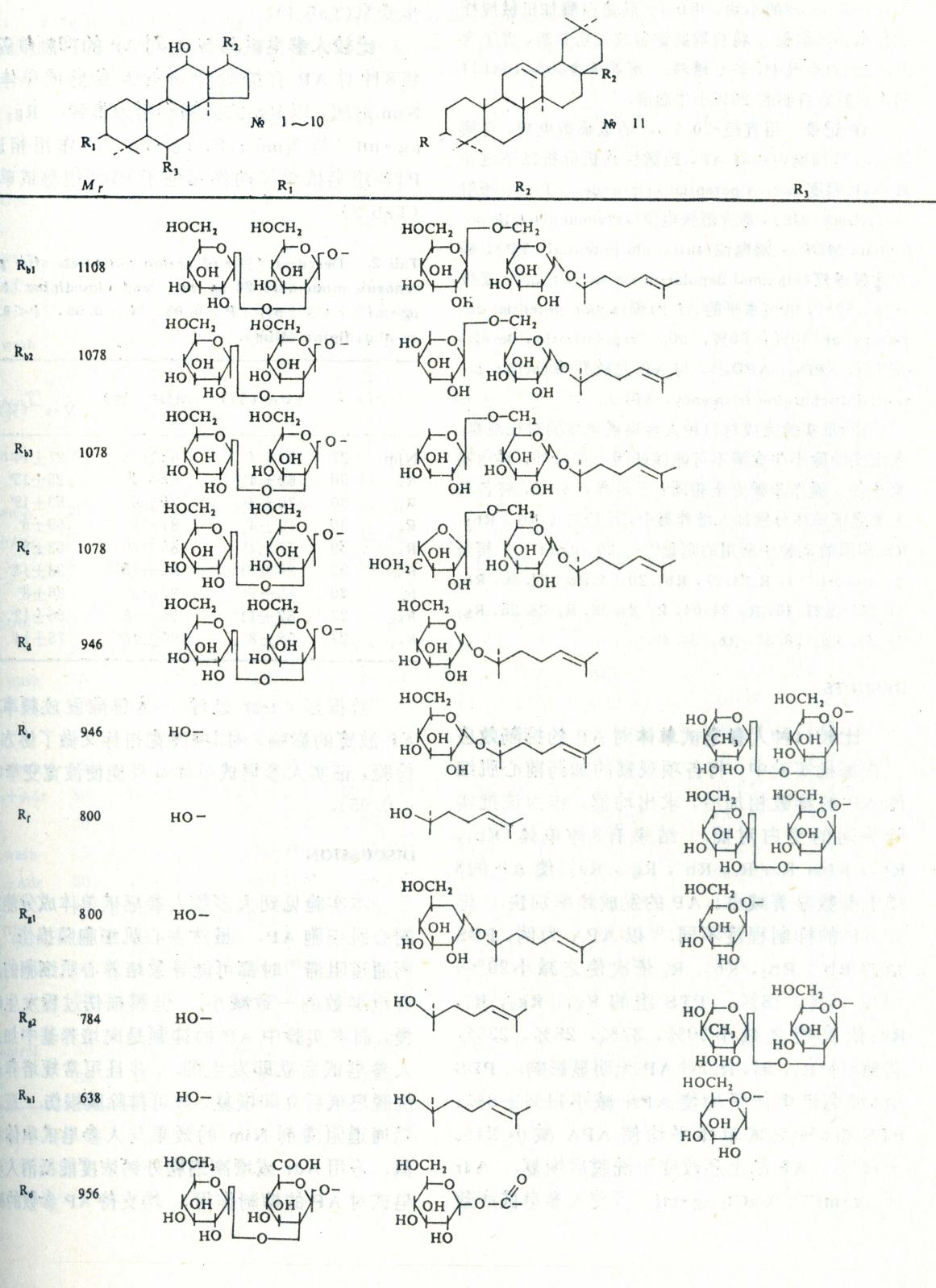
**关键词** 人参；皂甙；培养的细胞；心肌；动作电位；尼莫地平

三七总皂甙<sup>[1,2]</sup>及其皂甙单体成分 Rb<sub>1</sub><sup>[3]</sup>能抑制心肌细胞动作电位(AP)和慢内向电流。人参二醇组皂甙(panaxadiol saponins, PDS)和人参三醇组皂甙(panaxatriol saponins, PTS)能抑制心肌细胞 AP, PTS 比 PDS 的作用强<sup>[4]</sup>。我们用连细胞斑片钳技术记录了心肌细胞钙通道的单通道活动，证明了 PDS 及其单体成分 Rb<sub>1</sub> 有钙通道阻滞作用<sup>[5]</sup>，与上述以动作电位为指标的观察结果完全吻合。考虑到 PDS 和 PTS 均为数种皂甙单体的混合物，本实验拟在单体水平上进行比较：在培养的心肌细胞上，对比观察 11 种人参皂甙单体对 AP 的影响。旨在分析 PTS 比 PDS 钙通道阻滞作用强的原因，并筛选出此项作用最强的人参皂甙单体。

## MATERIALS AND METHODS

**人参皂甙单体** 11 种人参皂甙单体均为本校有机化学教研室自吉林人参(*Panax ginseng* C A Mey)茎、叶中提取，纯度 >95%。人参皂甙的甙元分为原人参二醇、原人参三醇、与齐墩果酸，齐墩果酸与糖结合形成的人参皂甙只有一种即 R<sub>e</sub>，属齐墩果烷型五环三萜皂甙。Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, R<sub>c</sub>, R<sub>d</sub> 属于人参二醇组皂甙。R<sub>e</sub>, R<sub>f</sub>, Rg<sub>1</sub>, Rg<sub>2</sub>, Rh<sub>1</sub> 属于人参三醇组皂甙，这两组人参皂甙均为达玛烷型四环三萜皂甙。11 种人参皂甙的结构式及 Mr 如下：

肾上腺素  $1 \text{ mg} \cdot \text{ml}^{-1}$  (adrenaline, Adr, 上海天丰制药厂)。CaCl<sub>2</sub> CP (北京红星化工厂)。尼莫地平 (nimodipine, Nim, 天津市中央制药厂)。Dulbeco's modified Eagle medium (DMEM, Life Technologies Inc, USA)。



**心肌细胞培养** 取生后24—48 h的Wistar大鼠心室，剪成 $1\text{ mm}^3$ 的小块，用0.1%胰蛋白酶加机械搅拌法分离心肌细胞。将获取的细胞放入培养瓶，置于含5% CO<sub>2</sub>的空气中，37℃培养。培养基含80% DMEM和本实验室自制的20%小牛血清。

**AP记录** 用直径<0.5 μm的玻璃微电极，自搏动的心肌细胞内引导AP，经微机连机分析以下电参数：AP幅度(action potential amplitude, APA)，超射(overshoot, OS)，最大舒张电位(maximal diastolic potential, MDP)，阈电位(threshold potential, TP)，最大除极速度(maximal depolarization rate, V<sub>max</sub>)，复极10%，50%，90%水平的AP时程(action potential durations at 10%，50%，90% repolarization levels, APD<sub>10</sub>, APD<sub>50</sub>, APD<sub>90</sub>)，与AP发放频率(action potential discharging frequency, APF)。

经4批实验完成对11种人参皂甙单体的对比观察。各批实验除小牛血清不可能保证同一批号外，其他实验条件、操作步骤完全相同：于培养d 4—5，将各种人参皂甙单体分别加入培养基中，沿用对比Rb<sub>1</sub>，Rb<sub>2</sub>，Rb<sub>3</sub>作用的实验中所用的剂量<sup>(6)</sup>—20 μg·ml<sup>-1</sup>。相当于(μmol·L<sup>-1</sup>)：R<sub>e</sub> 24.27, Rb<sub>1</sub> 20.94, Rb<sub>2</sub> 21.46, Rb<sub>3</sub> 21.23, R<sub>c</sub> 21.46, R<sub>d</sub> 24.04, R<sub>f</sub> 24.33, R<sub>t</sub> 28.25, Rg<sub>1</sub> 28.25, Rg<sub>2</sub> 28.57, Rh<sub>1</sub> 34.42。

## RESULTS

### 比较11种人参皂甙单体对AP的抑制效应

在每批实验中，将各项观察的加药前心肌细胞AP的参数相加后，求出均值，作为该批实验共同的空白对照。结果有8种单体(Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, R<sub>c</sub>, R<sub>e</sub>, Rh<sub>1</sub>, Rg<sub>1</sub>, Rg<sub>2</sub>)使AP的8项电参数显著减小、AP的发放频率加快。但对AP的抑制程度不同。以APA为例，PDS组的Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, R<sub>c</sub>依次使之减小20%，13%，5%，18%。PTS组的Rg<sub>1</sub>, Rg<sub>2</sub>, R<sub>e</sub>, Rh<sub>1</sub>依次使之减小30%，37%，28%，23%。其他3种(R<sub>d</sub>, R<sub>f</sub>, R<sub>t</sub>)对AP无明显影响。PDS组5种皂甙单体平均使APA减小11%±8%；PTS组5种皂甙单体平均使APA减小24%±15%。AP的上述改变于洗脱后恢复。Adr 10 μg·ml<sup>-1</sup>、CaCl<sub>2</sub> 1 μg·ml<sup>-1</sup>可使人参皂甙所致

的AP抑制逆转，但对AP的波宽则使之进一步变窄(Tab 1)。

### 比较人参皂甙与Nim对AP的抑制效应

将8种对AP有抑制作用的人参皂甙单体与Nim对照，以Rg<sub>2</sub>的抑制作用为最强。Rg<sub>2</sub> 20 μg·ml<sup>-1</sup>与Nim 1.25 μg·ml<sup>-1</sup>的作用相近。PTS组皂甙单体的作用强于PDS组皂甙单体(Tab 2)。

Tab 2. Decrease (%) of action potentials after ginsenoside monomers 20 μg·ml<sup>-1</sup> and nimodipine (1.25 μg·ml<sup>-1</sup>) ( $\bar{x}\pm s$ ). <sup>a</sup>P>0.05, <sup>b</sup>P<0.05, <sup>c</sup>P<0.01 vs nimodipine (Nim).

	n	APA (%)	MDP (%)	V <sub>max</sub> /V·s <sup>-1</sup> (%)
Nim	27	62±4	63±13	27±14
R <sub>g2</sub>	30	63±4 <sup>a</sup>	68±4 <sup>b</sup>	25±15 <sup>a</sup>
R <sub>g1</sub>	30	70±3 <sup>c</sup>	75±6 <sup>c</sup>	63±19 <sup>c</sup>
R <sub>e</sub>	30	72±4 <sup>c</sup>	81±6 <sup>c</sup>	69±6 <sup>c</sup>
R <sub>h1</sub>	30	77±4 <sup>c</sup>	85±7 <sup>c</sup>	63±6 <sup>c</sup>
R <sub>b1</sub>	30	80±11 <sup>c</sup>	93±13 <sup>c</sup>	38±13 <sup>c</sup>
R <sub>c</sub>	30	82±7 <sup>c</sup>	83±9 <sup>c</sup>	86±8 <sup>c</sup>
R <sub>b2</sub>	27	87±11 <sup>c</sup>	96±18 <sup>c</sup>	56±12 <sup>c</sup>
R <sub>b3</sub>	27	95±8 <sup>c</sup>	100±16 <sup>c</sup>	75±14 <sup>c</sup>

数据经t test处理。为排除发放频率对AP波宽的影响，对3项波宽指标又做了协方差检验，证实人参皂甙单体本身能使波宽变窄( $P<0.05$ )。

## DISCUSSION

本实验见到大多数人参皂甙单体成分能抑制心肌细胞AP。虽然在心肌细胞膜损伤<sup>(7)</sup>与钙通道阻滞<sup>(8)</sup>时都可能导致培养心肌细胞的所有电参数的一致减小。但膜损伤过程发生较慢，而本实验中AP的抑制是向培养基中加入人参皂甙后立即发生的。并且用常规培养基洗脱皂甙后立即恢复，故可排除膜损伤。应用钙通道阻滞剂Nim的效果与人参皂甙单体相似、应用Adr或增高细胞外钙浓度能抵消人参皂甙对AP的抑制作用，均支持AP参数的减

Tab 1. Effects of 11 ginsenoside monomers on action potentials ( $\bar{x} \pm s$ ).  $^aP > 0.05$ ,  $^bP < 0.05$ . $^cP < 0.01$  vs control;  $R_x$ :  $20 \mu\text{g} \cdot \text{ml}^{-1}$ ;  $\text{CaCl}_2$ :  $80 \mu\text{g} \cdot \text{ml}^{-1}$ ; adrenalin (Adr):  $10 \mu\text{g} \cdot \text{ml}^{-1}$ ;  $n$ : penetrations.

	<i>n</i>	APA/mV	OS/mV	MDP/mV	$V_{\max}/\text{V} \cdot \text{s}^{-1}$	APD <sub>50</sub> /ms	APD <sub>90</sub> /ms	F/bpm
Control	27	64 ± 6	20 ± 8	45 ± 9	16 ± 6	82 ± 9	130 ± 8	168 ± 18
R <sub>b1</sub>	30	51 ± 7 <sup>c</sup>	9 ± 6 <sup>c</sup>	42 ± 6 <sup>a</sup>	6 ± 5 <sup>c</sup>	80 ± 14 <sup>b</sup>	123 ± 10 <sup>c</sup>	190 ± 22 <sup>c</sup>
R <sub>b1</sub> wash	27	62 ± 7 <sup>a</sup>	20 ± 4 <sup>a</sup>	42 ± 7 <sup>a</sup>	16 ± 8 <sup>a</sup>	83 ± 8 <sup>a</sup>	129 ± 9 <sup>a</sup>	192 ± 15 <sup>a</sup>
R <sub>b1</sub> + Ca <sup>2+</sup>	27	63 ± 7 <sup>a</sup>	21 ± 6 <sup>a</sup>	42 ± 6 <sup>a</sup>	14 ± 6 <sup>a</sup>	80 ± 6 <sup>a</sup>	122 ± 5 <sup>c</sup>	214 ± 19 <sup>c</sup>
R <sub>b2</sub>	27	56 ± 7 <sup>c</sup>	13 ± 5 <sup>c</sup>	43 ± 8 <sup>a</sup>	9 ± 4 <sup>c</sup>	81 ± 12 <sup>a</sup>	125 ± 5 <sup>c</sup>	187 ± 20 <sup>c</sup>
R <sub>b2</sub> wash	27	68 ± 3 <sup>a</sup>	20 ± 4 <sup>a</sup>	49 ± 5 <sup>a</sup>	16 ± 3 <sup>a</sup>	67 ± 10 <sup>c</sup>	95 ± 23 <sup>c</sup>	268 ± 31 <sup>c</sup>
R <sub>b3</sub>	27	61 ± 5 <sup>c</sup>	16 ± 5 <sup>b</sup>	45 ± 7 <sup>b</sup>	12 ± 4 <sup>c</sup>	84 ± 11 <sup>b</sup>	127 ± 5 <sup>c</sup>	179 ± 20 <sup>c</sup>
R <sub>b3</sub> wash	27	63.1 ± 1.5 <sup>a</sup>	22 ± 4 <sup>a</sup>	41 ± 4 <sup>a</sup>	14.1 ± 0.8 <sup>a</sup>	82.7 ± 1.8 <sup>a</sup>	99 ± 22 <sup>c</sup>	191 ± 6 <sup>b</sup>
Control	30	72 ± 4	19.2 ± 0.8	53 ± 3	14.4 ± 1.6	79.4 ± 2.1	111 ± 4	194 ± 8
R <sub>c</sub>	30	60 ± 5 <sup>c</sup>	15.1 ± 2.2 <sup>c</sup>	44 ± 5 <sup>c</sup>	12.4 ± 1.3 <sup>c</sup>	70 ± 5 <sup>c</sup>	101 ± 10 <sup>c</sup>	218 ± 14 <sup>c</sup>
R <sub>c</sub> wash	25	72.3 ± 1.5 <sup>a</sup>	18.5 ± 0.9 <sup>a</sup>	54 ± 2 <sup>a</sup>	14.1 ± 1.1 <sup>a</sup>	78.8 ± 2.2 <sup>a</sup>	109 ± 4 <sup>a</sup>	192 ± 6 <sup>a</sup>
R <sub>c</sub> + Adr	30	81 ± 9 <sup>c</sup>	26 ± 5 <sup>c</sup>	55 ± 8 <sup>b</sup>	17.7 ± 1.9 <sup>c</sup>	68 ± 4 <sup>c</sup>	97 ± 11 <sup>c</sup>	249 ± 8 <sup>c</sup>
R <sub>d</sub>	30	72.2 ± 1.5 <sup>a</sup>	18 ± 3 <sup>a</sup>	54 ± 4 <sup>a</sup>	15 ± 5 <sup>a</sup>	78.1 ± 1.7 <sup>a</sup>	107.2 ± 2.8 <sup>a</sup>	197 ± 12 <sup>a</sup>
Control	50	75 ± 3	22 ± 3	53 ± 3	15.5 ± 2.3	84 ± 8	121 ± 10	209 ± 12
R <sub>e1</sub>	30	52.5 ± 1.5 <sup>c</sup>	12.6 ± 2.6 <sup>c</sup>	39.9 ± 2.8 <sup>c</sup>	14.9 ± 2.7 <sup>c</sup>	81 ± 5 <sup>b</sup>	115 ± 13 <sup>b</sup>	220 ± 15 <sup>c</sup>
R <sub>e1</sub> wash	25	75 ± 4 <sup>a</sup>	21 ± 4 <sup>a</sup>	55 ± 3 <sup>a</sup>	14.4 ± 1.0 <sup>a</sup>	83 ± 4 <sup>a</sup>	119 ± 13 <sup>a</sup>	207 ± 9 <sup>a</sup>
R <sub>e1</sub> + Adr	30	79 ± 6 <sup>b</sup>	24 ± 4 <sup>b</sup>	55 ± 5 <sup>b</sup>	17.7 ± 1.8 <sup>b</sup>	70 ± 5 <sup>c</sup>	108 ± 4 <sup>b</sup>	238 ± 10 <sup>c</sup>
R <sub>e2</sub>	30	47 ± 3 <sup>c</sup>	12.2 ± 2.7 <sup>c</sup>	35.7 ± 2.1 <sup>c</sup>	4 ± 4 <sup>c</sup>	79 ± 4 <sup>b</sup>	109 ± 6 <sup>c</sup>	223 ± 5 <sup>c</sup>
R <sub>e2</sub> wash	25	75 ± 5 <sup>a</sup>	22 ± 4 <sup>a</sup>	54 ± 4 <sup>a</sup>	16 ± 5 <sup>a</sup>	83 ± 5 <sup>a</sup>	119 ± 8 <sup>a</sup>	210 ± 7 <sup>a</sup>
R <sub>e2</sub> + Adr	30	76 ± 3 <sup>a</sup>	24.6 ± 2.2 <sup>c</sup>	53.8 ± 2.3 <sup>a</sup>	18 ± 3 <sup>c</sup>	78 ± 3 <sup>c</sup>	105 ± 6 <sup>c</sup>	220 ± 7 <sup>c</sup>
R <sub>e</sub>	30	54 ± 3 <sup>c</sup>	11.5 ± 2.3 <sup>c</sup>	43 ± 4 <sup>c</sup>	10.6 ± 1.3 <sup>c</sup>	79 ± 6 <sup>b</sup>	113 ± 5 <sup>c</sup>	227 ± 14 <sup>c</sup>
R <sub>e</sub> wash	25	74.9 ± 1.5 <sup>a</sup>	22 ± 4 <sup>a</sup>	53 ± 4 <sup>a</sup>	14.8 ± 1.3 <sup>a</sup>	83.2 ± 2.5 <sup>a</sup>	127 ± 4 <sup>a</sup>	213 ± 9 <sup>a</sup>
R <sub>e</sub> + Adr	30	78 ± 6 <sup>a</sup>	23 ± 2.5 <sup>a</sup>	54 ± 4 <sup>a</sup>	16.8 ± 2.3 <sup>a</sup>	62 ± 8 <sup>c</sup>	93 ± 13 <sup>c</sup>	231 ± 9 <sup>c</sup>
R <sub>h1</sub>	30	57.8 ± 2.5 <sup>c</sup>	12.8 ± 1.4 <sup>c</sup>	45 ± 3 <sup>c</sup>	10.0 ± 0.5 <sup>c</sup>	62 ± 2 <sup>c</sup>	113 ± 5 <sup>c</sup>	233 ± 5 <sup>c</sup>
R <sub>h1</sub> wash	25	75 ± 3 <sup>a</sup>	21.7 ± 1.6 <sup>a</sup>	54 ± 4 <sup>a</sup>	14.8 ± 0.7 <sup>a</sup>	82 ± 2.9 <sup>a</sup>	120 ± 4 <sup>a</sup>	221 ± 10 <sup>a</sup>
R <sub>h1</sub> + Adr	30	87 ± 5 <sup>c</sup>	29 ± 3 <sup>c</sup>	59 ± 5 <sup>c</sup>	20.5 ± 1.3 <sup>c</sup>	64 ± 5 <sup>c</sup>	100 ± 10 <sup>c</sup>	262 ± 16 <sup>c</sup>
R <sub>f</sub>	30	76 ± 6 <sup>a</sup>	21 ± 3 <sup>a</sup>	55 ± 4 <sup>a</sup>	15.5 ± 2.7 <sup>a</sup>	82 ± 7 <sup>a</sup>	120 ± 8 <sup>a</sup>	213 ± 10 <sup>a</sup>
Control	30	73 ± 4	20.1 ± 2.4	53 ± 3	14.6 ± 1.4	87 ± 8	127 ± 10	214 ± 17
R <sub>o</sub>	30	72 ± 4 <sup>a</sup>	19 ± 4 <sup>a</sup>	52 ± 4 <sup>a</sup>	14.5 ± 1.3 <sup>a</sup>	85 ± 7 <sup>a</sup>	124 ± 8 <sup>a</sup>	210 ± 24 <sup>a</sup>

小是钙通道阻滞的可能性。至于加 Adr 或增高细胞外钙浓度时 AP 的波宽变窄，可能是钙内流增多使  $[Ca^{2+}]_i$  增高，增高的  $[Ca^{2+}]_i$  继之又使钙通道失活<sup>[9]</sup>、使钙依赖性钾通道激活<sup>[10]</sup>的结果。

PTS 组中各单体成对 AP 的平均抑制程度比 PDS 组者大，证明 PTS 比 PDS 组作用强<sup>[4]</sup>，是其各自的单体成分对 AP 抑制程度不同的综合结果。

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## 青藤碱对大鼠离体心脏再灌注损伤的预防作用

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#### Prevention of sinomenine on isolated rat myocardial reperfusion injury

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**ABSTRACT.** Acute myocardial ischemia and reperfusion injury of rats were produced by ligating the left coronary artery for 15 min and reopening. The myocardial calcium contents were increased from 3.53  $\pm 0.58 \mu\text{mol/g}$  dry wt in sham operation group to 6.02

$\pm 1.19 \mu\text{mol/g}$  dry wt with reducing SOD/MDA ratio and showing ventricular extrasystole (VE), ventricular tachycardia (VT), and ventricular fibrillation (VF). Sinomenine (Sin) and verapamil (Ver) infusion 15 min before ischemia attenuated the elevated calcium contents to the level of the sham operation group, increased SOD/MDA ratio, and produced antagonistic effects on VE, VT, VF. These improvements indicated that Sin, similar to Ver, prevented myocardial injury by lowering intracellular  $Ca^{2+}$  accumulation.

**KEY WORDS** sinomenine; verapamil; myocardial reperfusion injury; free radicals

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