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粉防己碱对蟾蜍背根神经节细胞动作电位及后超极化电位的影响

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提要 利用微电极方法记录蟾蜍背根神经节细胞内动作电位。结果表明：Ca^{2+}依浓度地延长 APD 及 AHPD，增大 AHPA。维拉帕米 3 μmol · L^{-1} 缩短 APD_{100} 7%及 $AHPD_{50}$ 13%，减少 AHPA 17%。粉防己碱依浓度地缩短 APD_{100} 及 $AHPD_{50}$，降低 AHPA。当其浓度达 100 μmol · L^{-1} 时，APD_{100}、$AHPD_{50}$、AHPA 分别减少 16%、18%及 20%。提示粉防己碱的作用可能与其阻滞钙通道有关。

关键词 粉防己碱；钙通道；维拉帕米；动作电位；脊神经节 史振蜂

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Effects of exogenous γ-aminobutyric acid on experimental arrhythmias

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ABSTRACT The effects of exogenous γ-aminobutyric acid (GABA) 10 mg · kg^{-1} iv in preventing arrhythmias induced by drugs and ischemia were studied in mice, rats, and guinea pigs. It was found that the threshold dose of aconitine inducing arrhythmia in mice and the recovery rate to normal sinus rhythm increased significantly, ED_{50} of GABA was 5.4 – 5.8 mg · kg^{-1}. The duration of ventricular tachycardia (VT) induced by aconitine in rats was shortened ($P<0.01$). The incidence and the mortality of ventricular fibrillation (VF) in GABA group were decreased to 0/10 *vs* 6/10 and 5/10 in control, respectively ($P<0.05$). The doses of ouabain to induce ectopic beats (EB), VT, VF, and cardiac

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arrest (CA) in guinea pigs were increased ($P<0.01$). The incidence of VF induced by coronary artery ligation in rats was decreased to 0 / 5 in GABA group *vs* 4 / 5 in control group ($P<0.01$). The total amount of EB, total time of VT, and VF were 66%, 41%, and 0% of the control group, respectively. The anti-arrhythmic effects of GABA were dose-dependent and as potent as procainamide (10 or 5 mg · kg^{-1}, iv). The results suggest GABA (10 mg · kg^{-1}, iv) may be useful for the prevention of VT and VF.

KEY WORDS GABA; arrhythmia; aconitine; ouabain; ischemia

GABA icv had anti-arrhythmic effect on ischemic heart by decreasing coronary vessel resistance mediated by sympathetic nerves[1]. We previously reported the effects of the extract of *Angelica pubescens* on experimental arrhythmias[2], and found its effective component contains GABA[3]. The effect of iv GABA on arrhythmias induced by drugs and ischemia was investigated in this paper and compared with that of procainamide.

MATERIALS

GABA, CP, produced by Shanghai Third Pharmaceutical Factory. Procainamide (Pro, 10 mg · ml^{-1}, Lot 780604), Beijing Pharmaceutical Factory. Aconitine(Aco) (E merck) solution pH 7, prepared on the day of experiment. Ouabain, labelled by the National Institute for The Control of Pharmaceutical and Biological Products of P R China. Urethane, $CaCl_2$, and chloroform were of CP. XDH-3 ECG recorder, XB-2B ECG oscilloscope, ZCZ-50 infusion syringe pump and ventilator. Animals were supplied by the Experimental Animal Center of the Academy of Military Medical Sciences.

METHODS AND RESULTS

Effects on arrhythmias induced by Aco in mice Fifty-one Kunming strain mice of either sex, weighing 22 ± *s* 3 g were divided into 4 groups and anesthetized with urethane 2 g · kg^{-1} ip. Three min after GABA (10.0, 5.0, or 2.5 mg · kg^{-1}) or equal volume of NS was injected via the caudal vein, Aco (5 μg · ml^{-1}, 0.22 ml · min^{-1}) was infused till the arrhythmias occurred. The changes of cardiac rhythm were recorded for 30 min by a oscilloscope and ECG. The results showed that the onset time of VT was obviously delayed, the threshold dose of Aco and the rate of recovery to normal sinus rhythm increased significantly in GABA 10 mg · kg^{-1} iv group compared with that of control, respectively. ED_{50} of GABA was 5.4 – 5.8 mg · kg^{-1}. (Tab 1).

Effects on ventricular arrhythmias induced by Aco in rats Thirty-two Wistar male rats weighing 238 ± 24 g were divided into 4 groups and anesthetized with urethane 1.2 g · kg^{-1} ip. Aco (18 μg · kg^{-1}) was injected in 20 s three min after injection GABA (10.0 or 7.5 mg · kg^{-1}), Pro (10.0 mg · kg^{-1}), or qual volume of NS via sublingual vein. ECG was monitored and recorded for 30 min. The

Tab 1. Effects of GABA on arrhythmias induced by aconitine. $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control.**

GABA mg · kg^{-1}, iv	Mice	Onset of VT / min	Threshold dose of Aco / μg · kg^{-1}	Recovery to sinus rhythm in 30 min
0	21	1.75 ± 0.19	83 ± 11	1 / 21
2.5	10	1.72 ± 0.17*	83 ± 12*	1 / 10*
5.0	10	2.03 ± 0.47**	98 ± 19**	0 / 10*
10.0	10	1.99 ± 0.35**	94 ± 15**	5 / 10**

results indicated that the onset time of ventricular arrhythmias induced by Aco was delayed, the duration of VT shortened, and the incidence of VT, VF, and the mortality decreased significantly in GABA 10.0 or 7.5 mg · kg^{-1} iv group compared with that of control, respectively. (Tab 2).

Effects on arrhythmias induced by ouabain in guinea pigs Twenty-five guinea pigs of either sex weighing 367 ± 47 g were divided into 4 groups and anesthetized with urethane 1.2 g · kg^{-1} ip. Ouabain (10 μg · ml^{-1}, 3.3 ml · min^{-1}) was infused in a constant rate after iv GABA, Pro, or equal volume of NS. Lead II ECG was monitored and recorded. Ten min later, the same dose of GABA, Pro, or NS was injected again by the same way. The results showed that the increased dose of ouabain inducing ectopic beats (EP), VT, VF, and cardiac arrest (CA) in GABA 10 mg · kg^{-1} iv twice group, and the increased dose of ouabain inducing EB and VT in GABA 7.5 mg · kg^{-1} iv twice group had significant differences with that of the control. The effect was similar to that of Pro 10 mg · kg^{-1} iv twice. (Tab 3).

Effects on arrhythmias induced by myocardial ischemia Thirty Wistar ♂ rats weighing 483 ± 48 g were divided into 6 groups randomly. Three min after GABA, Pro, or equal volume of NS injected via sublingual vein, surgical ligation of the left coronary artery was performed. ECG was recorded for 30 min[2]. The results indicated that in GABA 10 mg · kg^{-1} iv group the incidence of VF decreased significantly and the total amount of EB, total time of VT and VF decreased to 66%, 41%, and 0%, respectively compared with control. In GABA 5 mg · kg^{-1} iv group, the incidence and mortality of VF decreased, but no significant differenses with that of control, and the total amount of EB, total time of VT and VF decreased to 77 %, 67 %, and 10 %, respectively compared with control. (Tab 4).

Effects on VF induced by $CaCl_2$ in rats Sixteen ♂ Wistar rats weighing 232 ± 22 g were devided into 2 groups randomly. VT

Tab 2. Effects of GABA and procainamide (Pro) on arrhythmias induced by aconitine. $\bar{x} \pm s$, $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

	Dose / mg · kg^{-1}, iv	Rats	Onset of ectopic beat / min	Ventricular tachycardia Incidence	Ventricular tachycardia Duration / min	Ventricular fibillation Incidence	Ventricular fibillation Mortality
Control		10	2.23 ± 0.82	10 / 10	25.40 ± 2.83	6 / 10	5 / 10
Pro	10.0	6	3.69 ± 0.82**	6 / 6*	18.53 ± 3.95**	4 / 6*	0 / 6**
GABA	10.0	10	9.01 ± 8.44**	7 / 10*	14.50 ± 9.77**	0 / 10**	0 / 10**
GABA	7.5	6	8.91 ± 4.96*	6 / 6*	15.61 ± 6.02**	1 / 6*	0 / 6**

Tab 3. Effects of GABA and procainamide (Pro) on arrhythmias induced by ouabain. $\bar{x} \pm s$, $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

	Dose / mg · kg^{-1}, iv	Guinea pigs	Dose of ouabain inducing arrhythmias / μg · kg^{-1} Ectopic beats	VT	VF	Cardiac arrest
Control		10	99 ± 26	148 ± 31	202 ± 52	230 ± 52
Pro	10.0 × 2	5	159 ± 41**	200 ± 27**	200 ± 40*	274 ± 34*
GABA	10.0 × 2	5	171 ± 34***	217 ± 34***	261 ± 13***	288 ± 19***
GABA	7.5 × 2	5	147 ± 19***	187 ± 23**	234 ± 24*	267 ± 26*

Tab 4. Effects of GABA and procainamide (Pro) on arrhythmias induced by coronary artery ligation in rats. $\bar{x} \pm s$, $^{*}P > 0.05$, $^{**}P < 0.05$, $^{***}P < 0.01$ **vs control.**

Group	Dose / mg · kg^{-1}, iv	Vertricular tachycardia			Ventricular fibrillation		
		Ectopic beats	Incidence	Total time / s	Incidence	Death	Total time / s
Control		6919	5 / 5	645	4 / 5	2 / 5	805
Pro	5	3914	4 / 5	179	0 / 5**	0 / 5*	0
GABA	10	4576	5 / 5	264	0 / 5**	0 / 5*	0
Control		8279	4 / 5	1726	4 / 5	2 / 5	600
Pro	2	4570	4 / 5	1195	1 / 5*	1 / 5*	305
GABA	5	6415	4 / 5	1161	1 / 5*	1 / 5*	60

was induced by $CaCl_2$ [2], VT occured in 8 / 8 of control and 7 / 8 in GABA 10 mg · kg^{-1} iv group ($P > 0.05$).

Effects of VF induced by chloroform in mice Thirty ♂ mice of Kunming strain weighing 33 ± 1 g were devided into 2 groups randomly. VF was induced by chloroform[2], VF was found in 80 % in control and 60 % in GABA 10 mg · kg^{-1} iv group ($P > 0.05$).

Effects on ECG of anesthetized rats Lead II of ECG was recorded in 10 Wistar ♂ rats (253 ± 38 g). Ten min after urethane 1.2 g · kg^{-1} ip. GABA 10 mg · kg^{-1} was injected via sublingual vein. ECG at the third and fifth min showed that the R–R intervals prolonged 20 ± 12 % and 18 ± 11 %, respectively compared with premedication ($P < 0.01$). It recovered in 10 min and maintained to 30 min after administration of GABA. No significant changes were seen on P–R interval in 30 min.

Acute toxicity Sixty ♂ Kunming mice (19 ± 3 g) were tested. It was proved by the sequential method that LD_{50} of procainamide was 107 – 222 mg · kg^{-1} iv, but none of 10 mice in GABA 2.5 g · kg^{-1} iv group died in 72 h.

DISCUSSION

The results of our experiments proved that GABA 10 mg · kg^{-1} iv prevented arrhythmias induced by Aco. ouabain, and acute myocardial ischemia. GABA and diazepam inhibited arrhythmias induced by stimulating the hypothalamus[4,5], and anticonvulsent sodium valproate counteracted the ischemic and reperfusive arrhythmias by accumulation of GABA in brain[6], but the antiarrhythmic mechanism of iv GABA in our experiments especially those caused by acute myocardial ischemia is not sure and worth further study.

In addition, the results in our experiments proved that the acute toxicity of exogenous GABA is lighter than that of procainamide. Therefore, investigation of the receptors and analogues of GABA and diazepam may become a fruitful approach in the clinical treatment of cardiac arrhythmias.

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外源性 γ-氨基丁酸对实验性心律失常的作用

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提要 本实验证明 GABA 10 mg · kg^{-1} iv 使乌头碱诱发的 VT 由对照组的 6/10 减少至 0/10 ($P<0.05$)，VT 持续时间由 25.4 ± 2.8 min 缩短到 14.5 ± 9.8 min ($P<0.01$)。冠状动脉结扎诱发的 VF 由 4/5 减少到 0/5 ($P<0.01$)，哇巴因诱发 VT 和 VF 的阈剂量显著增加。以上作用呈剂量依赖性并与普鲁卡因胺 10 或 5 mg · kg^{-1} iv 作用相同。提示 GABA iv 可预防 VT 和 VF。

关键词 γ-氨基丁酸；心律失常；乌头碱；哇巴因；缺血

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Scavenging effects of phenylpropanoid glycosides on superoxide and its antioxidation effect[1]

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ABSTRACT The antioxidative activities of six phenylpropaniod glycosides (PPG) extracted from *Pedicularis striata* and *Pedicularis lasiophrys* for inhibiting the lipid peroxidation induced by Fe^{2+} / ascorbic acid in mouse liver microsome may be related to the number and steric position of phenolic hydroxyl groups (PHG) they possess (32.5 μmol · L^{-1} to 65.0 μmol · L^{-1}). The scavenging effects of PPG for superoxide produced by NBT / PMS / NADH system may be related to both the number of PHG and their conjugated system (16.0 μmol · L^{-1} to 65.0 μmol · L^{-1}).

KEY WORDS phenylpropanoid glycosides; superoxide; free radical scavengers; antioxidants

Pedicularis is used in folk medicine as cardi–tonics for treatment of collapse, exhaustion and senility[1], and is usually called "pseudo–ginseng" by local inhabitants of northwestern China. PPG, a class of constituents of *Pedicularis*, showed antiviral[2] and antiplatelet properties[3], inhibited leukotriene B_4 formation[4], but had little effect on blood pressure, heart rate, microbial growth, or prostaglandin biosynthesis[4]. Phenolic compounds possess both antiradical and antioxidative properties. We have reported the antioxidative and scavenging activities of 7 natural hydroxylated flavonoids[5] and 6 phenols[6]. Since PPG are polyphenols, we investigated the superoxide–scavenging and antioxidative effects of the 6 natural PPG.

MATERIALS AND METHODS

Agents Isoverbascoside, verbascoside, echinacoside and pedicularioside A (new compound) were extracted from *Pedicularis striata*, and cistanoside D

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