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Prophylactic effects of taurine and diltiazem, alone or combined, on reperfusion arrhythmias in rats[1]

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KEY WORDS taurine; diltiazem; myocardial reperfusion injury; combination drug therapy; arrhythmia; malondialdehyde; superoxide dismutase

AIM: To study the effects of taurine (Tau) and diltiazem (Dil), alone or in combination, on reperfusion arrhythmias in anesthetized rats. **METHODS**: The arrhythmias were produced by coronary artery ligation for 15 min followed by reperfusion. Malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were measured by thiobarbituric acid fluorescence assay and colorimetric determination. **RESULTS**: Tau 70 mg·kg^{-1} in combination with Dil 1 mg·kg^{-1} were more effective on prevention of the reperfusion arrhythmias than each drug alone. The combination of both drugs not only decreased the content of MDA, but also increased the activity of SOD in reperfusion myocardium. **CONCLUSION**: The inhibition of lipoperoxides formation as well as the inhibition of the calcium influx was involved in the anti-arrhythmic effect of both Tau and Dil.

The generation of ischemia-reperfusion arrhythmias has been suggested to involve in the formation of oxygen-derived free radicals and the development of "Ca^{2+} overload"[1,2]. We have proved that taurine (Tau) was able to prevent many kinds of arrhythmias and to regulate the intracellular calcium concentration[3,4]. In present study, we examined the effects of Tau or diltiazem (Dil) and combined administration of both on ischemia-reperfusion arrhythmias in anesthetized rats. We also studied the relationship between the anti-arrhythmic activity of Tau and Dil in myocardial oxygen-derived free radicals production.

MATERIALS AND METHODS

Ischemia-reperfusion arrhythmias Wistar rats of either sex (n = 62, 243 ± s 30 g) were anesthetized with sodium pentobarbital (50 mg·kg^{-1}, ip). The femoral artery and jugular vein were cannulated for measurement of arterial blood pressure (BP) and for drug injection, respectively. Standard lead Ⅱ electrocardiogram (ECG) and BP were monitored by polygraph (Hellige Co, German).

The arrhythmias were produced by coronary artery ligation for 15 min followed by reperfusion[2] and the arrhythmic scores were evaluated[5]. The rats with a sustained low mean BP (< 10.7 kPa) or ventricular premature contractions (VPC) after the thoracic operation were discarded. Lead Ⅱ ECG was continuously monitored by an inputed video tape recorder (TE AC R-71, Japan).

Drugs and normal saline (NS) were administered iv 5 min prior to coronary artery occlusion. Rats were randomly divided into 6 groups: NS; Tau (Shanghai Second Pharmaceutical Factory) 70 mg·kg^{-1}; Tau 140 mg·kg^{-1}; Dil (Sigma) 1 mg·kg^{-1}; Dil 2 mg·kg^{-1}; Tau 70 mg·kg^{-1} plus Dil 2 mg·kg^{-1}. All volumes were 20 mL·kg^{-1}.

Measurement of malondialdehyde (MDA) and superoxide dismutase (SOD) activity MDA content and SOD activity were measured by thiobarbituric acid fluorescence assay[6] and colorimetric determination[7], respectively. The content of myocardial protein was measured colorimetrically[8].

Statistical analysis All data were expressed as $\bar{x} \pm s$, χ^2 test was used to analyze differences in the incidences of arrhythmias between control and pretreated groups. Group t test was made for comparison.

RESULTS

Ischemia-reperfusion arrhythmia After Tau 70 mg·kg^{-1}, the duration of reperfusion-induced ventricular tachycardia (VT) and time required to sinus rhythm were shorter than those of NS group, the mortality was reduced. In rats pretreated with Tau 140 mg·kg^{-1}, the number of ventricular premature counts (VPC), the incidence and the duration of VT, and ventricular fibrillation (VF) were decreased ($P > 0.05$, $P < 0.01$ *vs* NS). None of the treated rats died, time to gain sinus rhythm was reduced (Tab 1).

The duration of VT and mortality were decreased by pretreatment with Dil 1 mg·kg^{-1}.

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Tab 1. Effects of diltiazem (Dil) and taurine (Tau), alone or in combination of both on reperfusion arrhythmias in rats. $\bar{x} \pm s$. $^bP<0.05$, $^cP<0.01$ *vs* saline; $^dP>0.05$, $^eP<0.05$ *vs* Dil.

Agents/ mg·kg^{-1}	Rats	VPC		VT		VF		Time to sinus rhythm/ min	Mean scores	Mortality/ %
		Number of VPC in 10 min	Incidence/ %	Duration/ s	Incidence/ %	Duration/ s	Incidence/ %			
Saline	16	81 ± 72	94	78 ± 33	88	51 ± 36	56	6.1 ± 2.6	161 ± 67	44
Dil										
1	10	50 ± 36	70	32 ± 7^b	60	14 ± 8	40	3.6 ± 2.6	94 ± 92	0
2	6	34 ± 28	67	8 ± 5^c	33^b	5.0 (1 case)	17^b	3.1 ± 1.7^b	67 ± 58	0
Tau										
70	10	47 ± 24	80	23 ± 13^c	70	21 ± 8	20	3.4 ± 1.7^b	106 ± 68	0
140	10	19 ± 14^b	82	9 ± 4^c	36^c	2.0 (1 case)	9^b	3.7 ± 2.6^b	82 ± 56^c	0
Dil 1 + Tau 70	10	15 ± 11^b	30^{ce}	13.0 ± 0.8^{ce}	30^{ce}	0	0	2.5 ± 2.0^b	34 ± 32^c	0

After administration of Dil 2 mg·kg^{-1}, the number of VPC, the incidence and the duration of VT and VF were reduced. None of the rats died, and the recovery time to sinus rhythm was shortened.

The combined administration of Tau 70 mg·kg^{-1} and Dil 1 mg·kg^{-1} not only reduced both the number of VPC and VT, but also shortened the duration of VT. None of rats presented VF. Above values were significant *vs* control. However, the number of VPC and the duration of VT were less than those of pretreated rats with Dil 1 mg·kg^{-1} alone. The indices were not significantly different *vs* pretreated rats given Tau 140 mg·kg^{-1} or Dil 2 mg·kg^{-1} (Tab 2).

Myocardial MDA content and SOD activity

In the reperfused myocardium, the content of MDA was higher and the activity of SOD was lower than those in normal or ischemic myocardium. Tau 70 mg·kg^{-1} or Dil 1 mg·kg^{-1} reduced the content of MDA in reperfused myocardium ($P < 0.05$ *vs* normal).

The combined administration of Tau 70 mg·kg^{-1} and Dil 1 mg·kg^{-1} decreased the content of MDA and increased the activity of SOD in reperfused myocardium ($P<0.05$ or $P<0.01$ *vs* normal, respectively). The mean arrhythmic scores presented the positive correlative tendency to myocardial content of MDA and the negative correlative tendency to myocardial activity of SOD (Tab 2).

Tab 2. Effects of diltiazem or taurine alone and their combination on the content of MDA and activity of SOD in rat myocardium. Saline: saline plus reperfusion. $\bar{x} \pm s$. $^bP<0.05$, $^cP<0.01$ *vs* normal; $^fP<0.05$ *vs* ischemia; $^gP>0.05$, $^hP<0.05$, $^iP<0.01$ *vs* saline.

Group	Rats	SOD, U/ mg protein	MDA, nmol/ g wet weight
Normal	8	1.62 ± 0.25	212 ± 74
Ischemia	8	1.45 ± 0.19	198 ± 109
Reperfusion	12	1.20 ± 0.27^{ce}	313 ± 64^{be}
Saline	10	1.22 ± 0.28^{ce}	310 ± 59^{be}
Diltiazem 1 mg·kg^{-1}	5	1.42 ± 0.15^g	215 ± 73^h
Taurine 70 mg·kg^{-1}	5	1.42 ± 0.06^g	230 ± 50^h
Taurine 70 mg·kg^{-1} plus Diltiazem 1 mg·kg^{-1}	5	1.52 ± 0.11^h	175 ± 97^i

DISCUSSION

Results obtained in our study indicated that reperfusion arrhythmias were associated with a large increase in the content of MDA of myocardium. Tau 140 mg·kg^{-1} and Dil 2 mg·kg^{-1} protected against reperfusion arrhythmias. Tau 70 mg·kg^{-1} in combination with Dil 1 mg·kg^{-1} were more effective than the low dose of either drug alone on reperfusion arrhythmias.

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The combination of both Tau and Dil improved the cardiac function, which was attenuated by Dil alone (to be published). It was apparent that the anti-arrhythmic effects of Tau and Dil were related to the inhibition of lipoperoxides formation as well as the inhibition of the calcium influx.

The mechanism of the enhanced anti-arrhythmic efficiency by the combined administration of both Tau and Dil was based on their suppression of lipid peroxidation and blockade of myocardial calcium channels, so the "calcium overload" was attenuated.

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牛磺酸、硫氮革酮单用及合用对大鼠再灌心律失常的预防作用

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心肌缺血

关键词 牛磺酸; 硫氮革酮; 心肌再灌注损伤; 联合药物疗法; 心律失常; 丙二醛; 超氧化物歧化酶

目的: 研究牛磺酸(70 mg·kg^{-1}), 硫氮革酮(1 mg·kg^{-1})合用对麻醉大鼠再灌注心律失常的影响. **方法**: 冠脉结扎 15 min 后再灌诱发心律失常. 硫代巴比妥酸法和分光光度法分别测定 MDA 和 SOD. **结果**: 两药合用的效果优于各药小剂量单用. 联合用药后不仅更显著降低缺血/再灌心肌的 MDA 含量, 尚可增加 SOD 活性. **结论**: 牛磺酸与硫氮革酮合用通过抑制脂质过氧化物的产生和防止心肌细胞内"钙超负荷"发挥抗缺血/再灌心律失常作用.

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