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Depressant effect of taurine on triggered activity induced by cesium chloride in rabbit hearts *in vivo*[1]

KANG Yi, LI Ping, WANG Guo-Xiang
(Department of Pharmacology, Tianjin Medical University, Tianjin 300070, China)

AIM: To study the effects of taurine (Tau) and tetrodotoxin (Tet) on cesium chloride (CsCl)-induced triggered activity and arrhythmia in anesthetized rabbits. **METHODS:** With a cuffed endotracheal tube, the rabbit ventilation was maintained by a respirator. A Franzy's contact electrode catheter was advanced into the right ventricle through the right external jugular vein and positioned against the anteroapical endocardial surface to record the monophasic action potential (MAP). A catheter was placed into femoral vein for systemic drug administration. **RESULTS:** CsCl (1 mmol L^{-1} iv) produced a decrease in the amplitude of MAP from 42.2 ± 2.1 to 37.0 ± 3.8 mV ($P<0.01$), a prolongation of $MAPD_{50}$ (156 ± 22 to 209 ± 26 ms, $P<0.01$) or $MAPD_{90}$ (205 ± 25 to 250 ± 20 ms, $P<0.01$) and an early afterdepolarization (EAD) developed within 30 s after CsCl injection. The ventricular premature (VP) resulted from EAD triggered by CsCl. In the Tau (100 mg kg^{-1})- or Tet (10 μg kg^{-1})-pretreated group, not only was the amplitude of EAD decreased (Tau, 4.2 ± 2.7; or Tet, 5.2 ± 2.6, respectively *vs* 16.1 ± 8.6 mv, $P<0.01$), but also the duration of EAD was shortened (Tau, 695 ± 164; or Tet, 492 ± 172, respectively, *vs* 1068 ± 166 ms, $P<0.01$). The severity of triggered arrhythmia (TA) was alleviated and the incidence of TA was lowered within 30 min after iv CsCl by either Tau or Tet. **CONCLUSION:** The depressant effects of Tau and Tet on EAD and VP induced by CsCl were involved in an increase of outward current or a decrease of an inward current.

KEY WORDS taurine; tetrodotoxin; cesium; arrhythmia; electrophysiology

Triggered activity upon early afterdepolarization (EAD) has been proposed as one of the mechanisms of ventricular arrhythmia. We demonstrated that taurine (Tau), an novel calcium modulator, exerted an antiarrhythmic action in many experimental arrhythmias[1,2]. But the effect of Tau on triggered arrhythmia (TA) remained uncertain. No reports have so far been found about the effect of Tau on cardiac electrophysiology by using monophasic action potential (MAP) recording method to detect the EAD. This study was designed to understand the effects of Tau on TA.

MATERIALS AND METHODS

Protocol Twenty rabbits of either sex, weighing 3.5 ± 0.8 kg, were anesthetized with sodium pentobarbital (30 mg kg^{-1}). A cuffed endotracheal tube was inserted and the ventilation was maintained using a respirator. A catheter was placed in femoral vein for medication. The rabbits were randomly divided into 3 groups: 1) NS 1 mL kg^{-1}; 2) Tau (Shanghai Fifth Pharmaceutical Factory) 100 mg kg^{-1}; 3) Tetrodotoxin (Tet, AR. Hebei Province Aquatic Institute) 10 μg kg^{-1}. CsCl (Sigma) 1 mmol kg^{-1} was given iv over 15 s after 5 min of medication.

MAP measurement MAP was recorded from right ventricular endocardium. A Franzy's contact

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electrode catheter (custom-made by Meditiec, Parma, Italy) consisting of a proximal and a distal compressed Ag-AgCl electrode (1.5 mm in diameter, 6 mm apart) was advanced into the right ventricle through the right external jugular vein and positioned against the anteroapical endocardial surface. The MAP signals were amplified by an amplifier (FL-A). The surface electrocardiographic lead II and amplified MAP signals were simultaneously displayed on an oscilloscope (VC-11) and recorded on a physiological paper recorder (LMS-213). The amplitude of MAP (MAPA) was defined as the potential difference between the phase 2 and phase 4 of MAP. The duration of MAP (MAPD) was determined at 50 % or 90 % repolarization[5]. Either delay in repolarization or true depolarization occurring during the phase 2 or phase 3 of MAP was termed the EAD of MAP. The coupling interval was defined as the interval between the phase 0 of MAP and the peak or shoulder of the EAD that developed.

Data treatment Data were expressed as $\bar{x} \pm s$. Comparison of $\bar{x}$ was performed with paired t test. Correlations between the variables were determined by linear regression.

RESULTS

MAP changes induced by CsCl Baseline MAP recordings showed a rapid upstroke, a plateau, and a smooth continuous repolarization phase. MAPA = 37 ± 4 mV (29 − 44 mV). $MAPD_{50}$ = 156 ± 22 ms (100 − 200 ms). $MAPD_{90}$ = 205 ± 25 ms (168 − 253 ms). No delayed repolarization or afterdepolarizations during either phase 2 or 3 was noted in baseline recordings. A decrease in MAPA and a prolongation of $MAPD_{50}$ and $MAPD_{90}$ were observed and EAD occurred within 30 s after iv CsCl (Fig 1).

Correlation analysis showed that the coupling intervals of EAD (EAD-CI) was nearly identical to those of the corresponding VP (VP-CI). Regressive equation was VP-CI (ms) = 0.9936 EAD-CI − 4.119, r = 0.98.

Effects of Tau and Tet on MAP changes induced by CsCl Tau 100 mg kg^{-1} iv induced: a shortening of $MAPD_{50}$ (149 ± 16 *vs* 127 ± 17 ms, $P < 0.05$), an insignificant effect on $MAPD_{90}$ (178 ± 21 *vs* 180 ± 17 ms, $P > 0.05$), and no change in MAPA (37.3 ± 7.5 *vs* 38.0 ± 4.0 mV, $P > 0.05$). Tet 10 μg kg^{-1} reduced MAPA from 42.1 ± 1.5 to 36.1 ± 3.2 mV ($P < 0.05$), but did not show any notable effect on $MAPD_{90}$ (200 ± 23 *vs* 198 ± 19 ms, $P > 0.05$). Subsequently, both Tau and Tet affected MAP changes induced by CsCl (Tab 1).

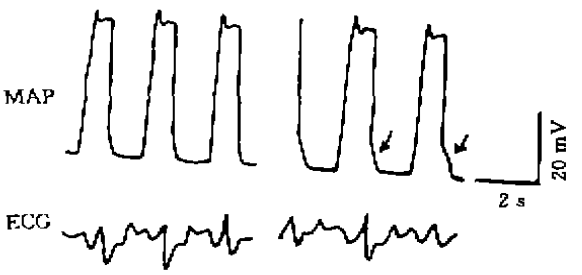

Fig 1. Effects of CsCl 1 mmol kg^{-1} iv on MAP and ECG in anesthetized rabbits. Simultaneous recordings of monophasic action potential and ECG lead II after iv CsCl. The presence of early afterdepolarization was evident.

In the control group, heart rate was decreased by CsCl from 288 ± 30 to 158 ± 14 bpm ($P < 0.01$), EAD developed within 10 s after iv CsCl, ($n = 6$), the duration of EAD was 1068 ± 166 s. Initially EAD appeared as subthreshold depolarization that gradually increased in amplitude and reached threshold to produce the triggered ventricular premature beats (VP). Tet also decreased the heart rate (226 ± 51 to 166 ± 54 bpm, $P < 0.01$), while Tau did not decrease it (244 ± 55 *vs* 224 ± 83 bpm, $P > 0.05$). In the Tau- or Tet-pretreated group, not only was the amplitude of EAD decreased, but the duration of EAD was shortened (Fig 2, Tab 2).

Tab 1. Effects of taurine (100 mg kg^{-1} iv) and tetrodotoxin (10 μg kg^{-1} iv) on CsCl-induced changes of MAPA, $MAPD_{50}$, and $MAPD_{90}$ in rabbits. $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* before CsCl; $^dP>0.05$, $^eP<0.05$, $^fP<0.01$ *vs* control group; $^gP>0.05$, $^hP<0.05$ *vs* Tau group.

	Drug	Rabbit hearts	Before	CsCl administration 30 s	1	5	10 min
MAPA/mV	Control	6	37±4	30.1±2.6^b	30±3^b	29.2±2.1^c	28±3^c
	Taurine	7	38±5^a	35.3±2.1^a	34.4±2.2^{ae}	35±3^{af}	34.3±2.0^{af}
	Tetrodotoxin	7	36±3^{dg}	33±4^{adg}	32.1±2.3^{bdg}	30±4^{bdb}	30.2±2.2^{cdh}
$MAPD_{50}$/ms	Control	6	156±22	209±26^c	233±12^c	248±20^c	253±22^c
	Taurine	7	127±17^e	133±23^{af}	133±35^{af}	164±11^{bf}	168±19^{bf}
	Tetrodotoxin	7	121±34^{dg}	127±23^{afg}	132±18^{afg}	132±20^{afh}	136±21^{afh}
$MAPD_{90}$/ms	Control	6	205±25	250±20^b	276±18^c	312±19^c	328±11^c
	Taurine	7	180±17^d	182±20^{af}	185±22^{af}	199±14^{bf}	215±26^{bf}
	Tetrodotoxin	7	198±19^{dg}	200±16^{afg}	214±22^{adb}	222±29^{adg}	228±30^{adg}

Tab 2. Effects of taurine (100 mg kg^{-1} iv) and tetrodotoxin (10 μg kg^{-1} iv) on EAD and TA induced by CsCl. $\bar{x}\pm s$. n=the number of the preparations. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control; $^dP>0.05$, $^eP<0.05$, $^fP<0.01$ *vs* Tau group.

Group	Rabbit hearts	Early afterdepolarization Amplitude/mV	Duration/s	Triggered arrhythmia Duration/s	Incidence/%
Control	6	16±9	1 068±166	1 452±288	6/6 (100)
Taurine	7	4.2±2.7^c	695±164^c	360±176^c	2/7 (29)^b
Tetrodotoxin	7	5.2±2.6^c	492±172^{cd}	660±251^{cf}	3/7 (42)^{ad}

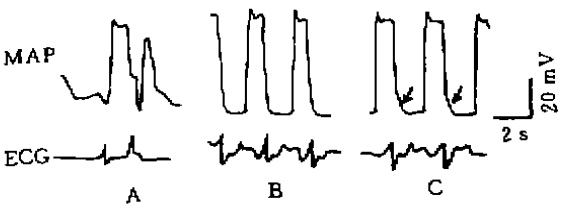

Fig 2. Effects of taurine (100 mg kg^{-1} iv) and Tet (10 μg kg^{-1} iv) on EAD and related VP at 30 s after iv CsCl (1 mmol kg^{-1} iv). A. CsCl-induced EAD and VP in rabbit hearts. B. Tau pretreatment depressed CsCl-induced EAD and VP. C. Tet pretreatment inhibited the CsCl-induced EAD and VP.

DISCUSSION

The present study provided evidences *in vivo* that EAD induced by CsCl was closely related with TA(VP) and that Tau or Tet could reduce the amplitude and duration of EAD, so as to decrease the severity of TA arising from EAD.

Suppressant effects of Tau on EAD and VP both resulting from CsCl administration could involve an increase in outward current or a decrease in inward current. The former prospect appeared unlikely, since Tau had little effect on $MAPD_{90}$. With regard to the effects of Tau on inward current, there are some evidences that Tau reduces the ^{45}Ca influx from ventricular myocardium under the condition of $[Ca^{2+}]_o$ high level[1], and that the inhibiting effect of Tau on calcium influx may be related to the blockage of voltage-dependent calcium channel[4], these evidences suggested that Tau had some feature of calcium antagonists. The calcium blocking effect of Tau was also demonstrated by the shortening of

$MAPD_{50}$, slowing of heart rate and preventing of VP triggered by EAD in the present study. The similar depressant effects of Tau and Tet on the amplitude of EAD suggested that Tau might inhibit the sodium "window" current.

In our study, Tet inhibited the development of EAD and the CsCl-induced TA. The observation that Tet, as well as Tau, suppressed $MAPD_{50}$ supported that Tet could inhibit the EAD by shortening the MAP repolarization and that Tet also reduced calcium entry during the phase 2 of the action potential[5].

The present work demonstrated that the major mechanism for Tau or Tet maybe contributed to the inhibition of the formation and development of EAD. But some VP were still present after pretreatment with Tau or Tet, even though the amplitude of EAD decreased significantly. This suggested that the arrhythmogenesis of CsCl involved some other mechanism.

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REFERENCES

1 Kang Y, Li P, Wang GX. Effect of taurine on modulating calcium of cardiac muscles in rats. Chin Pharmacol Bull 1991; 7: 263—6.

2 Wang GX, Duan JF, Zhou SM, Li P, Kang Y. Antiarrhythmic actions of taurine. Adv Exp Med Biol 1992; 315: 187—92.

3 Franz MR, Flaherty JT, Platia EV, Bulkley BH, Weisfeldt ML. Localization of regional myocardial ischemia by recording of monophasic action potentials. Circulation 1984; 69: 593—604.

4 Kang Y, Li P, Wang GX. The study of mechanism for inhibiting effect of taurine on calcium influx from myocardium in the rats. J Beijing Med Univ 1992; 24 (2 Suppl): 92—3.

5 Brachmann J, Scherlag BJ, Rosenshtraukh LV, Lazzara R. Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. Circulation 1983; 68: 846—56.

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牛磺酸对氯化铯诱发在体家兔心脏触发活动的抑制作用

康 毅，李 萍，王国祥

（天津医科大学药理教研室，天津300070，中国）

目的：研究牛磺酸与河豚毒素对氯化铯诱发的家兔心脏早后去极化(EAD)及室性早搏(VP)的作用. **方法**：气管切开维持人工呼吸，经右颈外静脉向右心室插入 Franzy 导管记录单相动作电位(MAP)，股静脉插管给药. **结果**：注射氯化铯(1 mmol L^{-1})后，MAP 幅度减少，$MAPD_{50}$和 $MAPD_{90}$延长，30秒内发生 EAD，并由此触发 VP. 牛磺酸(100 mg kg^{-1})或河豚毒素(10 μg kg^{-1})能减少 EAD 的幅度，EAD 的持续时间缩短，VP 的程度和发生率减轻. **结论**：牛磺酸和河豚毒素对氯化铯诱发的 EAD 和 VP 的抑制效应涉及增加外向电流或减少内向电流.

关键词 牛磺酸；河豚毒素；铯；心律失常；电生理学