IN VIVO EFFECT OF TAURINE ON CALCIUM FLUX OF HEART DURING EPINEPHRINE-INDUCED ARRHYTHMIAS

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Abstract

The effect of taurine on calcium flux of the heart in vivo during epinenhrine-induced arrhythmia was studied in anesthetized dogs and rabbits. The blood sample was drawn from aorta and coronary sinus before and after administration of a minimal dose of epinephrine which caused ventricular premature contraction (VPC). The same procedure was repeated after taurine infusion. The plasma calcium content was measured by orthocresol-phthalein complexon method. Six min after epinephrine administration, the calcium content of arterial and venous plasma was 5.9 ± 0.25 mEq/l and was 7.5 ± 0.39 mEq/l in dogs respectively. It was 5.6 ± 0.30 mEq/l and 6.6 ± 0.34 mEq/l respectively in rabbits. In response to epinephrine with taurine treatment, venous calcium content was 5.6 ± 0.28 mEq/l in dogs and 5.3 ± 0.37 mEq/l in rabbits ; while arterial calcium cotent was 5.8 ± 0.29 mEq/l in dogs and 5.5 ± 0.34 mEq/l in rabbits respectively. Six min after 2nd dose of epinephrine, venous calcium content was shown significantly lower after taurine than before (5.6 ± 0.28 *vs.* 7.5 ± 0.39 mEq/l ; 5.3 ± 0.37 *vs.* 6.6 ± 0.34 mEq/l), whereas arterial calcium content was shown slightly decrease. The results suggest that epinephrine facilitates calcium release from myocardium both in dogs and rabbits, while taurine tends to bind calcium in heart and thereby abolishes the irregular rhythm induced by epinephrine.

Introduction

It has been well established that taurine content in the myocardium is much higher than any other tissue of the vertebrates(8). Read and Welty (11) have demonstrated that heart tissue can convert taurine to isethionic acid, which has a charged group capable of attracting cation and can prevent the arrhythmias induced by the digitalis and the epinephrine (3,6,12,13). The suggestion that some cardiac effects of taurine could be mediated by an effect on calcium exchange was advanced by many investigators (1,6,14)

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Taurine has also shown to increase the calcium content of sarcoplasmic vesicles of cardiac muscle.(5) However, the relationship between the antiarrhythmic action of taurine and the calcium change has not been reported. Thus, the present study was to analyze the effect of taurine on the calcium flux in heart.

Materials and Methods

A total of 15 dogs (8.5 — 13 kg) and 19 rabbits (2.4 — 3.2 kg) of either sex was used. The dog was anesthetized intravenously with pentobarbital sodium 35 mg/kg, and rabbit intraperitoneal injection of urethane 1 gm/kg. All animals were fasted for 18 hours before use. An incision was made on the right side of the chest. The fourth rib was severed from its attachment to the sternum, and the opening was enlarged with a rid spreader to expose the heart. Artificial respiration was instituted through a tracheal cannula with an respiration pump (Starling) at a rate of 12 — 18/min in dogs and 45 — 62/min in rabbits. Rectal temperature was maintained 37°C by heating lamp. A polyethylene catheter (2 mm, OD) was inserted through the right jugular vein to reach the ostium of coronary sinus. Sampling of the venous blood was accomplished via the catheter, each time 1 ml in dogs and 0.5 ml in rabbits. Arterial blood samples were drawn from an indwelling polyethylene catheter (2 mm, OD) in the right subclavian artery with its tip near the aortic arch. Samples of coronary sinus blood and aortic blood were drawn simultaneously into heparinized syringes and then centrifuged. Control serum calcium was measured by orthocresol-phthalein complexone (OCPC alternated procedure) with electrophotometer at 570 mu as described by Connerty and Briggs (1966).(4) The right femoral vein was catheterized for drug administration. Blood pressure (BP) was recorded from the left femoral artery with a pressure transducer (Hewlett Packard 1280 B) coupled to one channel of recorder (Hewlett Packard 280) and electrocardiogram (Lead II) was also monitored continuously during the experiment.

In order to determine the minimum (threshold) dose of epinephrine required to produce ventricular premature contraction (VPC), epinephrine (epinephrine hydrochloride, Lederle) was i.v. injected initially with a dose of 2 ug/kg and increasing dose by 1 ug/kg. To test the effect of taurine on the epinephrine-induced arrhythmias associated with changes in arterial and venous calcium concentration, taurine (Sigma) was dissolved in distilled water to give a concentration of 0.5 mM/ml, adjusted to pH 7.4 by adding 0.1 N sodium hydroxide. Sampling of the arterial and venous blood was done before, and 1, 3, 6, 10, and 16 minutes after epinephrine injection (Fig. 2). Four minutes after the last sampling, taurine in a total dose of 1.0 — 2.5 mM/kg was infused over a period of 5 — 10 minutes. Approximately 25 minutes after the stop of taurine infusion, a second injection of epinephrine was carried out. Then blood samples from the arterial and venous catheters were taken as before. Any sample showing hemolysis was discarded. The data were expressed by mean ± SE and analyzed by the Student paired *t* test.

Results

(1) Antiarrhythmic effect of taurine on epinephrine-induced arrhythmia

The minimal dose of epinephrine required to produce VPC and the onset and the

TABLE I. The minimal dose, onset and duration of epinephrine to produce ventricular premature contraction (VPC).

Animal	Body wt (kg)	Minimal dose (ug/kg)	Onset (sec)	Duration (sec)
Dogs (n=15)	10.60±1.43*	8.51±1.65	29.13±3.27	33.81±2.76
Rabbits (n=19)	2.73±0.23	5.95±0.29	22.78±2.51	29.26±2.00

*Mean ± SE

TABLE II. Effect of minimal dose of epinephrine (EP) on the blood pressure (BP) and heart rate (HR) without and with taurine (TR) treatment.

		Dogs (n=15)		Rabbits (n=19)	
		BP (mmHg)	HR (beats/min)	BP (mmHg)	HR (beats/min)
Without TR	Before EP	137±10/86±10*	158±8	115±6/63±8	305±7
	1 min after EP	225±11/160±7	217±9	193±8/136±9	334±8
	16 min after EP	142±8/84±7	162±7	114±12/63±7	301±6
With TR	Before EP	128±9/80±7	150±9	106±7/59±8	290±4
	1 min after EP	221±8/155±10	211±10	185±9/128±7	328±6
	16 min after EP	125±12/78±5	152±6	105±10/60±6	296±9

*Mean ± SE ; BP : systolic pressure/diastolic pressure.

TABLE III. Change in calcium content (mEq/l) of arterial (aortic) and venous (coronary sinus) blood before (B) and after (A) taurine infusion responses to epinephrine.

Animal	Before epinephrine		After administration of epinephrine				
			1 min	3 min	6 min	10 min	16 min
Dogs (n=15)	Arterial blood	(B)	5.5±0.22#	5.6±0.28	5.9±0.25	5.4±0.26	5.2±0.36
	5.2±0.24	(A)	5.4±0.21	5.5±0.24	5.8±0.29	5.3±0.28	5.1±0.25
	Venous blood	(B)	6.6±0.26	7.3±0.21	7.5±0.39	6.3±0.33	5.2±0.30
	5.2±0.30	(A)	5.1±0.27**	5.4±0.33**	5.6±0.28**	5.1±0.25**	5.0±0.32
Rabbits (n=19)	Arterial blood	(B)	5.2±0.38	5.4±0.27	5.6±0.30	5.2±0.22	4.9±0.36
	4.9±0.32	(A)	5.1±0.25	5.3±0.29	5.5±0.34	5.1±0.23	4.8±0.32
	Venous blood	(B)	5.8±0.31	6.4±0.23	6.6±0.34	5.7±0.36	4.9±0.35
	4.9±0.21	(A)	4.8±0.30*	5.1±0.26**	5.3±0.37**	5.0±0.26	4.8±0.31

(B) : without taurine infusion ; (A) : 25 min after taurine infusion

: values are mean ± SE.

* : $P < 0.05$; ** : $P < 0.01$ when compared with the value of (B) in the same blood.

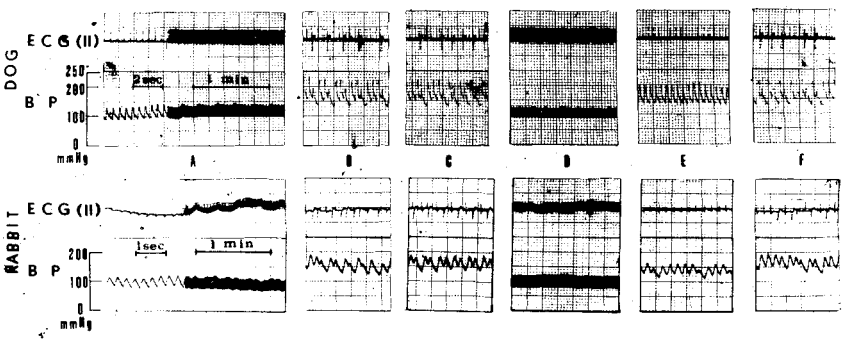

FIG. I. A typical blood pressure (BP, mmHg) and electrocardiogram (ECG, Land II) which shows the effect of taurine in depressing epinephrine-induced ventricular premature contraction (VPC) in an anesthetized dog (♂, 10.5 kg) and an rabbit(♀, 2.8 kg). A: Control record taken at the beginning of the experiment. B: Runs of VPC which was taken at 35 sec after the intravenous administration of epinephrine, 9.5 ug/kg in dog and 7.0 ug/kg in rabbit. C: Present VPC during epinephrine injection at 15 min after taurine infusion, 2.0 mM/kg in dog and 1.0 mM/kg in rabbit. D: Chart was taken at 25 min after taurine infusion. E: Absence of VPC which was taken at 35 sec after epinephrine injection and at 35 min following taurine infusion. F: The VPC reappears during epinephrine injection at 55 min after taurine infusion.

duration of VPC are summerized on Talbe I. The range of dose in dogs is larger than that of rabbits. Both onset and duration of VPC are shorter in rabbits than dogs. Intravenous taurine 1.0 to 2.5 mM/kg can convert the epinephrine-induced arrhythmias to sinus rhythm. The latent period and the duration of antiarrhythmic action of taurine were 27 ± 6 and 50 ± 18 min respectively. Typical antiarrhythmic action of taurine are shown in Fig. 1. Taurine infusion (1.0—2.5 mM/kg) causes a slight elevation of heart rate (HR) in rabbits and a little reduction in dogs, whereas these dose of taurine did not significantly affect the blood pressure (BP) and the ECG in both of dogs and robbits. Neither did the taurine pretreatment prevent the immediate increase in HR and BP responses to epinephrine. Summarized data of HR and BP before and after taurine infusion are given in Table II.

(2) Effect of taurine on calcium flux in heart

Table III. summarizes the change of arterial and venous plasma calcium content after epinephrine injection prior to and following taurine treatment. Epinephrine (5.5—13.2 ug/kg, dogs; 4.5—8.5 ug/kg, rabbits) increased the arterial plasma calcium content with the maximal effect at the sixth minute and varied from resting value of 5.2 ± 0.24 to 5.9 ± 0.25 mEq/l in dogs and from 4.9 ± 0.32 to 5.6 ± 0.30 mEq/l in rabbits. But the venous plasma calcium level rose from 5.2 ± 0.30 to 7.5 ± 0.39 mEq/l in dogs ($P < 0.01$, $n = 15$) and

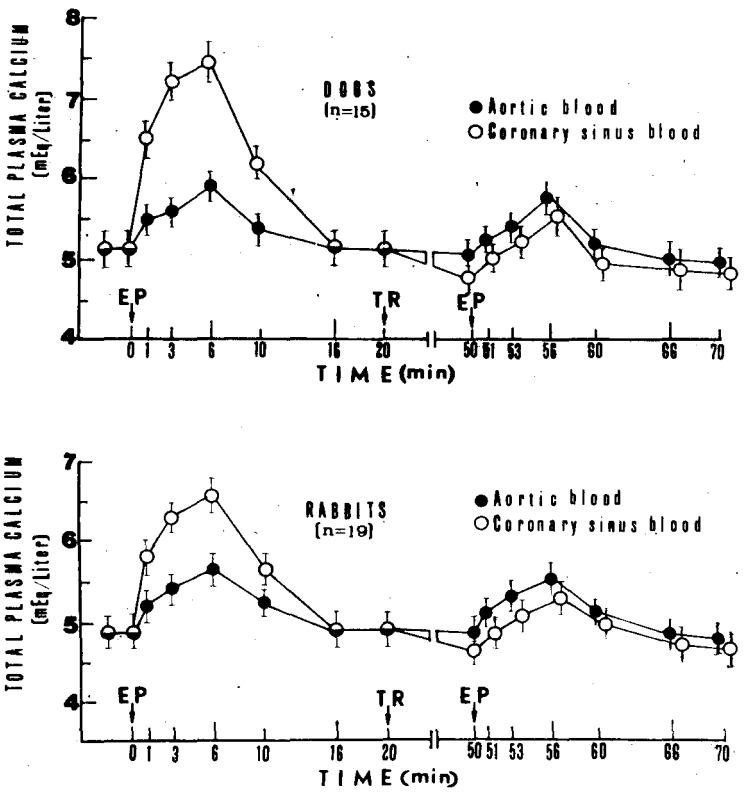

FIG. 2 The change of total plasma calcium concentration upon a minimal dose of epinephrine (EP) injection before and after taurine (TR) infusion. Intravenous injection and infusion are made at the interval indicated by the arrows. Each point of the graph shows the mean ± SE.

from of 4.9 ± 0.21 to 6.6 ± 0.34 mEq/l in rabbits ($P < 0.01$, n=19) indicating an efflux of calcium from heart during epinephrine administration. Taurine did not alter the arterial calcium level, but significantly decreased venous calcium content in both dogs and rabbits. Six minutes after 2nd dose of epinephrine, venous calcium content varied from 4.8 ± 0.35 to 5.6 ± 0.28 mEq/l in dogs and from 4.6 ± 0.34 to 5.3 ± 0.37 mEq/l in rabbits. The venous calcium variation evoked by epinephrine before and after taurine treatment (7.5 ± 0.39 *vs.* 5.6 ± 0.28 mEq/l, dogs ; 6.6 ± 0.34 *vs.* 5.3 ± 0.37 mEq/l, rabbits) was shown a significant difference ($P < 0.01$, n = 15 ; n = 19), but was insignificant in arterial blood of both dogs and rabbits. Summarized data are given in Fig. 2.

Discussin

Many studies have indicated that taurine counteracts the extrasystole induced by epinephrine as well as the arrhythmia induced by digitalis in various species of animal (3,6,11,13). In addition, taurine has been known to affect the ion movement in heart (12) and to increase the entry of calcium into the cell and the calcium content of myocardium. (1,10). Cardiac glycosides facilitate

the release of calcium from the sarcoplasmic reticulum of myocardium (2,9,10).The present results demonstrate that epinephrine accelerates the release of calcium from heart and consequently causes VPC, whereas the taurine decreases the calcium content of coronary sinus blood, probably by depressing the flux of calcium out of myocardial cell. This effect may partially account for the antiarrhythmic action of taurine on the epinephrine-induced VPC. It is possible that conjugation of aminonic group and sulphonic group of taurine with calcium occurs in myocardial cells to form ammonium and calcium isethionate. In the heart tissue, taurine is deaminated to isethionic acid (13),the latter compound may actively promote cellular accumulation of calcium ions. Epinephrine enhances the conversion of taurine to isethionic acid (14) and the calcium uptake by myocardium in vitro (7). Calcium release from cardiac muscle is accelerated by epinephrine and it reaches to maximal level at six minutes after administration (Fig. 2). As is shown in Fig. 1, it is necessary to take 25 minutes for taurine before inhibiting the arrhythmia induced by epinephrine. This may be the time required for transforming taurine into isethionic acid which combines with calcium to decrease the available calcium for epinephrine and thus causes the decrease of venous calcium content. The antiarrhythmic action of taurine begins at 25 minutes after infusion and lasts about half an hour in most animals. Within this period of time, the calcium content of venous plasma keeps in a lower level and the rise of venous calcium content caused by a minimal dose of epinephrine is always smaller than before. This corresponds with the duration of taurine action. Thus the suggestion exists that there is a connection between the antiarrhythmic effect of taurine and the flux of calcium in heart. According to the hypothesis proposed by Winegrad et al (1,5,15) there are 3 calcium components in myocardium. It seems likely that taurine prevents the exchangeable components (sarcoplasmic reticulum and vascular space) from releasing calcium and increases the formation of calcium-isethionate responses to epinephrine. Taurine pretreatment increases the intracellular calcium accumulation and reduces the efflux of calcium and its content in venous plasma during epinephrine injection, and therefore abolishes the arrhythmia. In conclusion, the present results not only agree with the previous results of investigators (1,7),which indicate that taurine increases the affinity of myocardium for calcium, but also show the relationship of antiarrhythmic effect of taurine to the decrease of calcium efflux in intact heart.

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Taurine對心律不整時的心肌鈣離子變動影響

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摘 要

麻醉下的家犬及白兎用OCPC法分別測定實驗前及因腎上腺素所引起的動物心律不整時，主動脈及冠狀竇血液的鈣離子含量。用足以消除此種心律不整的Taurine劑量

處理後再注入腎上腺素，同樣測定其動脈及靜脈血鈣含量。腎上腺素注入後6分鐘家犬及白兎的動脈及靜脈鈣含量分別為5·9± 0·25 mEq /l 與 7·5 ± 0·39 mEq/l, 及 5·6 ± 0·30 mEq/l 與 6·6 ± 0·34 mEq/l 。經Taurine 處理後再以腎上腺素注入則家犬靜脈血鈣含量為5·6 ± 0·28 mEq/l ，白兎為 5·3 ± 0·37 mEq/l ；但家犬動脈血鈣含量則為5·8 ± 0·29 mEq/l ，白兎則為5·5 ± 0·34 mEq/l 。腎上腺素注入後6分鐘動物靜脈血鈣含量經Taurine 處理者較未經Taurine 處理者呈顯著恨減少（ 5·6 ± 0·28 對 7·5 ± 0·39 mEq/l ； 5·3 ± 0·37 對 6·6 ± 0·34 mEq/l ），而靜脈血鈣含量則僅略為下降。此結果可獲一結論，就是腎上腺素確實可加速家犬及白兎的心肌鈣離子釋放，而Taurine 却顯示具有結合心肌內鈣離子傾向，以致產生抗腎上腺素性心律不整的效果。