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呋喃二氢吡啶 I 对离体兔心全心缺血再灌注损伤的保护作用

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提要 离体兔心全心缺血 30 min，再灌注 1 h，使心肌损伤逐渐加重。呋喃二氢吡啶 I 20 μmol · L^{-1} 能明显抑制缺血心肌肌酸磷酸激酶、α-羟丁酸脱氢酶、丙二醛的释放量；减少缺血复灌心肌钙、钠含量；降低缺血复灌心肌冠脉阻力的增加，预防再灌注心律失常的发生。提示该药保护心肌与减少缺血心肌钙含量及脂质过氧化程度有关。

关键词 钙通道阻滞剂；二氢吡啶类；心肌再灌注损伤；脂质过氧化；钙；钠；钾

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Effects of isocorydine on action potentials in isolated canie Purkinje fibers and ventricular muscles[1]

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ABSTRACT Standard microelectrode techniques were used to study the effects of isocorydine (Isoc) on potential characteristics of canine cardiac Purkinje fibers (PF) and ventricular myocardium (VM) *in vitro*. In PF, the action potential durations (APD), APD_{50}, and APD_{90}, were prolonged at 3 μmol · L^{-1} but shortened at 30 μmol · L^{-1} by Isoc. The action potential amplitude (APA) and the maximal upstroke velocity (V_{max}) were decreased at 100 μmol · L^{-1}. In VM, the action potential characteristics were changed by Isoc at above 30 μmol · L^{-1}. APD_{50} was shortened but APD_{90} was prolonged. V_{max} were decreased at 30 μmol · L^{-1}. The effective refractory period (ERP) was prolonged by Isoc in PF and VM. The results suggest that Isoc may interfere with K^+, Na^+, and Ca^{2+} currents in myocardiac cell membrane at different concentrations.

KEY WORDS isocorydine; Purkinje fibers; myocardium; action potentials

Isocorydine (Isoc), an alkaloid contained in many plants including *Dactylicapnos scandens* (Hutch) and *Dicranostigma leptopodum* (Maxim) Fedde, possesses a potent anti-arrhythmic effect[1]. Electrophysiological study has shown that Isoc 30 μmol · L^{-1} reduced the APA of rabbit sinoatrial node and the spontaneous electical activity induced by Ba^{2+} ion in guinea pig VM[2]. It was considered that Isoc may inhibit the slow calcium inward current. The purpose of this study was to elucidate the effects of Isoc on action potentials of canine PF and VM to reveal the basic mechanism of its anti-arrhythmic effect.

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MATERIALS AND METHODS

Adult mongrel dogs of either sex weighing 14± SD 4 kg were anesthetized with iv pentobabital (30 mg · kg^{-1}). The heart was put in oxygenated Tyrode's solution. Several Purkinje–ventricular myocardiac preparations dissected from the endocardial surface of both ventriculars were immersed in the Tyrode's solution (pH 7.4, 7℃). The preparation were fixed with fine pins to bath and superfused with the Tyrode's solution, gassed with 100% O_2, pH 7.2–7.4 (37± 0.5℃), in a flow rate of 10 ml · min^{-1}. The preparations were stimulated with square wave pulse of twice the threshold intensity and 3 ms duration in 1 Hz.

The transmembrane potentials were recorded with glass microelectrodes filled with KCl 3 mol · L^{-1} and having a tip resistance of 10–30 MΩ. The potentials were amplified by a microelectrode amplifier (MEZ–7101) and displayed on the upper line of a double beam oscilloscope and photographed. The first deriative (dV / dt) of the action potential upstroke was obtained by a differentiator with a time constant of 20 μs, and displayed on the lower line of the oscilloscope simutaneously. The effective refractory period was studied with the method of coupling stimuli. After all the preparations had been stablized in superfusion with Tyrode's solution for 2 h, APA, maximal rate of rise of phase 0 depolarization of the action potentials (V_{max}), APD (including APD_{50} and APD_{90}), and ERP were recorded during control period. Then, Isoc was added into Tyrode's solution successively 1–300 μmol · L^{-1} for PF and VM. Measurements were made after 15–20 min exposure to each concentration of Isoc.

RESULTS

Effects of Isoc on action potential characteristics in PFs The data from 8 experiments were shown in Tab 1. The records from one experiment were shown in Fig 1. No significant changes occured during 20 min of superfusion with Isoc 1 μmol · L^{-1}. In the presence of Isoc 3 μmol · L^{-1}, the APD_{50} and APD_{90} and ERP were prolonged. Isoc 100 μmol · L^{-1} decreased the APA and V_{max}. In addation, APA was shortened further but ERP remained a slight prolongation. Isoc 300 μmol · L^{-1} caused the preparations to become unresponsive to electrical drive. These effects of Isoc on action potential characteristics in PF were partly reversible after 45–60 min of superfusion with drug–free Tyrode's solusion.

Effects of Isoc on action potentials of VM

Tab 1. *Effects of isocorydine on action potentials of isolated canine Purkinje fibers (n=8 dogs) and ventricular myocardium (n=6 dogs).* $\bar{x}\pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$.

	Isocorydine (μmol · L^{-1})	APA (mV)	V_{max} (V · s^{-1})	APD_{50} (ms)	APD_{90} (ms)	ERP (ms)
Purkije fiber	0	118±9	535±77	250±31	325±39	301±34
	3	117±7*	523±81*	268±33**	352±43**	332±37**
	30	114±11*	499±73*	227±28**	324±41*	323±41**
	100	101±10**	402±88***	209±34***	296±38**	305±44*
Ventricular myocardium	0	110±6	259±43	174±27	213±23	204±29
	30	111±6*	254±51*	166±28*	225±27**	224±26**
	100	109±5*	238±80*	157±29**	226±25***	226±30**
	300	107±7*	213±66**	148±31**	218±24*	235±29**

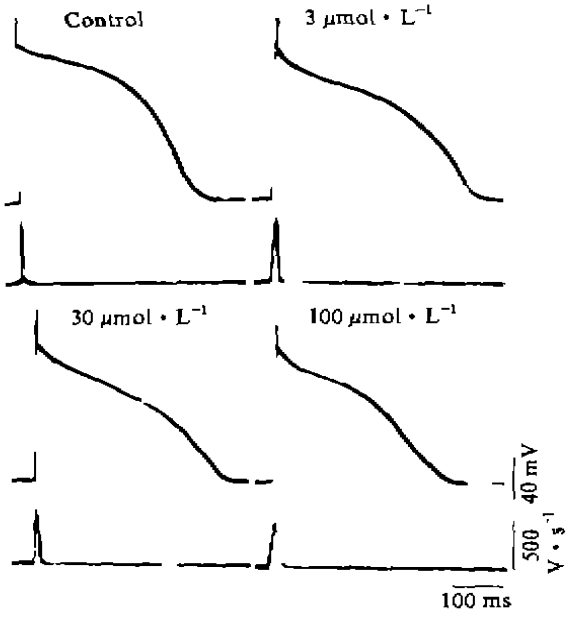

Fig 1. Effects of isocorydine on isolated canine Purkinje fiber action potentials. The experiment was performed in the same cell throughout the successive increases in isocorydine concentration. Upper tracing = transmembrane potentials; lower tracing = first derivative of the action potential upstroke (V_{max}).

The experiments were performed in 6 preparations. The results are summarized in Tab 1. Isoc 10 μmol · L^{-1} had no consistent effects to all parameters. At 30 μmol · L^{-1}, Isoc prolonged the duration of ERP and APD_{50}. In individual preparations, however, there were a decrease in APD_{50} coupled with alterations in the action potential plateau. At 100 μmol · L^{-1} there were a reduction of APD_{50} (shortened period of plateau), while ERP and APD_{90} were further prolonged. Following 300 μmol · L^{-1} perfusion the reduction of APA and V_{max} occured, but the former was insignificant. A further shortening of APD_{50} and a prolongation continuously of ERP were seen. In addation, the effects of Isoc described above were reversed as the preparations was exposed to Isoc-free perfusive solution; reversibility was, however, not rapid nor complete.

DISCUSSION

The experiments described in this paper confirm that Isoc elicits a prolongations of APD in PF as well as in VM. It was also shown that higher concentration of Isoc produced a secondary shortening of APDs accompainied by a decreased in V_{max}. The prolongation of APDs is simular to our previous results in guinea pig papillary muscles[2] and rabbit VM[1], but there were a less sensitivity than rabbit were.

Inhibition of outward K^+-currents can lead to a prolongation of APDs[4]. It would be cosidered that Isoc may inhibit the I_K. Furthermore, I_{KI} may be specifically decreased by Isoc, because I_{KI} accounts for the prolongation especially of late phase of the action potentials[5], which may be the major effects of Isoc.

The depressive effect of Isoc on V_{max} were only observed at highest concentration (ie, 300 μmol · L^{-1}). It was established that V_{max} can indirectly represents the inward sodium current, I_{Na}[6]. Therefore, we think that Isoc at large doses may inhibit I_{Na} in heart, especially in PF, which is a benificial effect to preventing arrhythmias produced by the reentry.

The duration of action potentials and plateau phase in PF are governed principally by slow inward Ca^{2+} current, I_{si}[7]. In the presence of Isoc 30 μmol · L^{-1}, a shortening of duration of action potentials, especially APD_{50}, occured. It suggested that Isoc interfered with the I_{si}. The results were consistent with our previously studies[2,8] have demonstrated that Isoc can obviously depress the Ca^{2+}-mediated action potentials in many kinds of slow response cells.

Isoc, no matter at lower (3 μmol · L^{-1}) or higher (30 μmol · L^{-1}) concetration, prolonged the effective refractiriness in both PF

and VM. Then the ratio of ERP and APD_{90} (ERP/APD_{90}) increased significantly. The increase of the ERP/APD_{90} ratio is an impotant evidence to judge a drug having anti-arrhythmic effect or not. So, it is reasonably to think that anti-arrhythmic effect of Isoc is due, mainly, to the prolongation of ERP. Our results suggest that Isoc may not only inhibit Ca^{2+} current but also, to some degree, inhibit K^+ and Na^+ currents at different concentrations.

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异紫堇定对犬浦肯野纤维和心室肌动作电位的影响

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提要 本文应用细胞内微电极技术研究了异紫堇定对 PF 和 VM 动作电位的影响. 异紫堇定 3 μmol·L^{-1} 使 PF 的 APD_{50} 和 APD_{90} 延长，30 μmol·L^{-1} 使之缩短；在 >30 μmol·L^{-1} 时，异紫堇定使 VM 的 APD_{50} 缩短、APD_{90} 延长，V_{max} 的降低仅出现在 300 μmol·L^{-1} 时. 各种浓度的异紫堇定均可使 PF 和 VM 的 ERP 延长. 说明异紫堇定对心肌细胞膜的 Na^+, K^+和 Ca^{2+}离子流均有影响.

关键词 异紫堇定；浦肯野纤维；心肌；动作电位