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Inhibitory effects of berberine on I_{K1}, I_K, and HERG channels of cardiac myocytes[1]

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KEY WORDS berberine; potassium channels; myocardium; patch-clamp techniques; recombinant proteins; oocytes; *Xenopus*

ABSTRACT

AIM: To study the effects of berberine on inward rectifier potassium current (I_{K1}) and outward delayed rectifier potassium current (I_K) of guinea pig ventricular myocytes, and on human ether-a-go-go related gene (HERG) channel expressed in *Xenopus* oocytes. **METHODS**: Whole cell patch-clamp and geneclamp techniques were used to record ionic currents. **RESULTS**: Berberine prolonged action potential duration (APD) and inhibited I_{K1} and I_K in a concentration-dependent manner. Berberine 100 μmol/L increased APD_{90} from (450 ± 48) ms to (888 ± 90) ms ($n = 6$, $P < 0.01$), and inhibited I_{K1} by 65 % ± 7 % ($n = 6$, $P < 0.01$). Berberine 50 μmol/L inhibited I_K by 57 % ± 6 %, I_{Ktail} by 53 % ± 6 % ($n = 6$, $P < 0.01$). Berberine produced a voltage-dependent block on I_K that increased with stronger depolarization, and once all channels were activated, there was no further block at positive potentials. Berberine blocked the HERG channels potently with an IC_{50} value of approximately 75 μmol/L. This block was voltage-dependent, suggesting that it probably bind to either open or inactivated HERG channels. **CONCLUSION**: Berberine prolonged APD and possessed blocking effect on I_{K1}, I_K, and HERG channel expressed in *Xenopus* oocytes. The antiarrhythmic mechanism of berberine is related to its inhibitory effects on I_{K1}, I_K, and HERG channel.

INTRODUCTION

Berberine is a benzodioxoloquinolozine alkaloid isolated from the plants of genera Berberis and Coptis. It has been shown that berberine has a protective effect on cardiac arrhythmias in animal and clinical trials[1,2]. Berberine has the protective effects on severe congestive heart failure[3]. Several experiments have shown that many pharmacological and physiological effects of berberine exerting were related to blockade or activation of K^+ channels, such as the cytotoxic effect of berberine in cancer cells may be explained by its direct blockade of the voltage- and calcium-activated potassium channels in human myeloma cells[4]; another example is that berberine exerts an anti-secretory action directly upon epithelial cells, and the mechanism of this action may be at the level of blockade of K^+ channels[5]. However, the ionic mechanism of its antiarrhythmic action is still unclear. I_{K1} and I_K are major components in the process repolarization and may therefore be important targets for antiarrhythmic drug action[6,7]. The effect of berberine on I_{K1} and I_K have been reported[8,9], but their results were different. So in this study, we intended to study the effects of berberine on action potential and the underlying ionic currents, I_{K1}, I_K, with whole cell patch-clamp recording technique in guinea pig ventricular myocytes, and explore its antiarrhythmic mechanisms.

HERG is a member of the ether-a-go-go (EAG) family of genes, which encodes a voltage-gated potassium channel with properties nearly identical to the rapid component of I_{Kr}[10]. The electrophysiological characteristics of both I_{Kr} and HERG currents are dominated by slow current activation at negative membrane potential, large long-lasting tail currents on repolarization, modulation of current amplitudes by external K^+ ions, and a limited amount of outward current. Its strong inward rectification is unusual for voltage-activation K^+ currents and has been attributed to a fast C-type inactivation mechanism. In humans, I_{Kr} plays a central role in repolarization of the myocardium and termination of individual heartbeats. Heterogeneously expressed HERG currents share these pharmacological properties with I_{Kr}, and undergo rapid

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C-type inactivation and are also blocked by dofetilide and MK-499[11].

Actually I_{Kr}/HERG represents an important target for pharmacological management of arrhythmias[12]. So in this study, we used HERG channel expressed in *Xenopus* oocyte as a target to observe the effects of compounds extracted from Chinese medicinal herbs and further confirm the inhibitory effect of berberine on HERG channel.

The goal of our studying is to develop an effective antiarrhythmic agent against malignant ventricular arrhythmias while maintaining a low side-effect profile.

MATERIALS AND METHODS

Agents Berberine hydrochloride was obtained from The Drug and Biological Product Inspection Institute of China, and was dissolved in distilled water to make a stock solution at 4 mmol/L. Collagenase (type Ⅱ), bovine serum albumin (BSA), egtazic acid, *L*-Glutamic acid, Na_2ATP, $BaCl_2$, $CdCl_2$ were purchased from Sigma Co. All chemicals and solvents were of analytical reagent grade.

Preparation of guinea pig ventricular myocytes Guinea pig ventricular myocytes were isolated by an enzymatic dissociation method similar to that described previously by Li *et al*[13]. Guinea pigs of either sex weighing 250 – 350 g (purchased from The Animal Cencer of Harbin Medical University, grade Ⅱ) were stunned and the heart was mounted in a Langendorff-type apparatus for retrograde coronary perfusion. The heart was initially perfused with modified Tyrode's solution (in mmol/L: KCl 5.4, NaCl 120, $NaHCO_3$ 20, NaH_2PO_4 0.9, $MgCl_2$ 1.0, glucose 10, $CaCl_2$ 1.8. pH was adjusted to 7.4 with NaOH) for 5 min, followed by perfusion with Ca^{2+}-free Tyrode's solution (omitting $CaCl_2$ from the Tyrode's solution) for another 5 min, then it was enzymatically digested for 20 min with a Ca^{2+}-free Tyrode's solution containing 0.02 % collagenase and 1 % bovine serum albumin. All perfusates were bubbled with 100 % O_2 and warmed at 37 ℃. After the collagenase was washed out, the heart was stored in KB (Kraftbruhe) solution (in mmol/L: *L*-Glu 70, taurine 15, KCl 30, KH_2PO_4 10, HEPES 10, $MgCl_2$ 0.5, glucose 10, egtazic acid 0.7, and pH was adjusted to 7.4 with KOH). Only Ca^{2+}-tolerant, clearly striated, rod-shaped cells without any blebs were studied.

Patch clamp recording Isolated single cells were placed in a 500 μL chamber contained regular external solution (in mmol/L: KCl 5.4, NaCl 136, HEPES 5.0, NaH_2PO_4 0.33, $MgCl_2$ 1.0, $CaCl_2$ 1.8, Glucose 10, pH 7.4) on the stage of an inverted microscope (IMT-2, Olympus). macroscopic current recordings were obtained using patch clamp technique with the whole cell method by use of an amplifier (Axopatch 200A, Axon Instrument). A 12-bit D/A converter controlled by pClamp 6.02 software (Axon Instruments) generated command pulses. Glass pipettes had tip resistance of 2 – 4 MΩ when filled with internal solution (in mmol/L: KCl 20, K-aspartate 110, HEPES 5.0, $MgCl_2$ 1.0, egtazic acid 10, Na_2ATP 5.0, and pH was adjusted to 7.2 with KOH). The resistance in series with the cell membrane was compensated to provide the fastest possible capacity transient without current oscillations. Pipette tip potentials (2 – 10 mV) were corrected before the pipette touched the cell. Signals were filtered at 2 kHz and data were acquired by A/D conversion (Digidata 1200, Axon Instruments) and stored in the IBM-compatible computer. After a tight pipette-membrane seal had been obtained (seal resistance > 10 GΩ), the membrane was ruptured with gentle suction to obtain the whole cell voltage-clamp configuration.

Geneclamp recording and data analysis The two-microelectrode voltage-clamp configuration was used to record currents from *Xenopus* oocytes. cRNA of HERG was synthesized *in vitro* using the enzymes. HERG in pSP64 was obtained from Keating MT. In several sets of experiments, oocytes were individually injected with cRNA encoding for the HERG K^+ channels[14].

Recordings were performed at 22 ℃ with a Geneclamp 500 amplifier (Axon Instruments, Foster City, USA) and Digidata 1200 A/D converter (Axon Instruments Inc) and recorded using pClamp software (Axon Instruments). To estimate deactivation kinetics (τ deact) of HERG channels, a single exponential function was fitted to the tail current at – 80 mV after depolarizations to – 10 mV. The control solution contained (in mmol/L: NaCl 114, KCl 2.5, $CaCl_2$ 1.8, $MgCl_2$ 1, HEPES 10, adjusted with NaOH to pH 7.2). Niflumic acid (0.15 mmol/L) was included to block chloride currents. Glass microelectrodes were filled with KCl 3 mol/L solution and had resistances between 0.5 to 3.0 MΩ.

Data are presented as arithmetic $\bar{x} \pm s$ and n represents the number of experiments performed. Relationship between concentration and blocking effect was calculated with the Hill equation and t-test was used to test for sta-

tistical significance.

RESULTS

Effect of berberine on action potential In the first series of experiments, the effect of berberine (10, 50, and 100 μmol/L) was studied on action potential duration in guinea pig single ventricular myocytes applying test pulses of 5 ms of duration, at a basic cycle length (BCL) of 1000 ms. The most striking effect of berberine was an increase in the action potential duration. After 8 min of application of berberine, in 6 cells, berberine markedly increased action potential duration measured at 90 % of repolarization (APD_{90}) from (450 ± 48) ms to (545 ± 91) ms at 10 μmol/L ($n = 6$, $P < 0.05$), (681 ± 55) ms at 50 μmol/L ($P < 0.05$), and (888 ± 90) ms at 100 μmol/L ($P < 0.01$). The effect of the drug was poorly reversible after washout for 20 min (Fig 1).

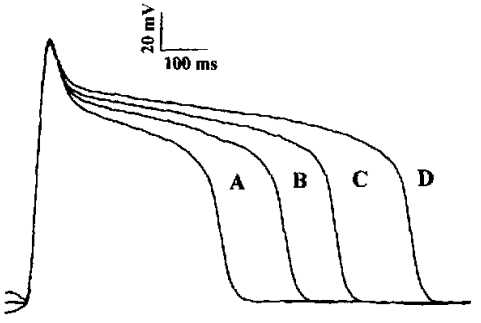

Fig 1. Effect of berberine on action potential of guinea pig ventricular myocytes (BCL = 1000 ms). (A) shorter action potential was obtained under control conditions. (B,C,D) after 8 min of application of berberine 10, 50, and 100 μmol/L to the bath, action potential duration was prolonged without affecting resting potential or amplitude of the action potential.

Effect of berberine on I_{K1} The effect of berberine at concentrations between 10 and 100 μmol/L was studied on the inward rectifier current (I_{K1}). I_{K1} steady-state currents were measured at the end of each test pulse with 300 ms hyperpolarizing and depolarizing voltage steps from a holding potential (HP) of −40 mV to potentials ranging from −120 mV to +60 mV in 10 mV steps. I_{K1} currents were recorded at the presence of $CdCl_2$ 0.2 mmol/L in the external solution to block I_{Ca}. At −110 mV, berberine 10, 50, and 100 μmol/L decreased I_{K1} from (−3.4 ± 0.6) nA to (−2.7 ± 0.4) nA ($n = 6$, $P < 0.05$), (−1.9 ± 0.3) nA ($P < 0.01$) and (−1.2 ± 0.3) nA (decreased by 65 %, $P < 0.01$). The inhibitory effect was concentration-dependent, and poorly reversible after washout (Fig 2).

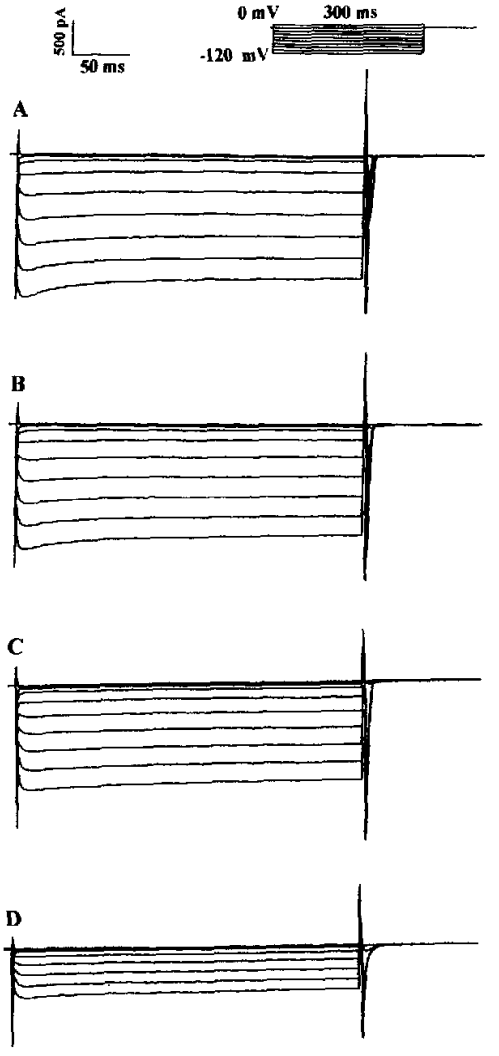

Fig 2. Whole-cell I_{K1} in guinea pig ventricular myocyte. Test Pulses (TP) were applied for 300 ms from a holding potential (HP) of −40 mV to potential ranging from −120 mV to 0 mV in 10 mV steps. (A) I_{K1} current traces in normal Tyrode's solution. (B, C, D) currents traces obtained in the presence of berberine 10, 50, and 100 μmol/L.

Effect of berberine on I_K and I_{Ktail} I_K was recorded from guinea pig ventricular myocytes. The de-

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layed outward rectifier potassium current I_K and I_{Ktail} were significantly decreased after treatment with berberine. At +50 mV, berberine 10, 50 μmol/L decreased I_K from (490±140) pA to (340±90) pA ($n=6$, $P<0.05$) and (210±40) pA (decrease by 57 %, $P<0.01$); decreased I_{Ktail} from (270±60) pA to (180±40) pA and (130±10) pA (decrease by 52 %, $n=6$, $P<0.01$) (Fig 3). Fig 4 illustrated the current-voltage relation of I_K obtained by 3 s depolarizing pulses from a HP of −60 mV to potentials ranging from −40 mV to +60 mV.

The effect of berberine 50 μmol/L on activation kinetics of I_K was analyzed after step depolarization between −40 mV and +60 mV. Analysis of the activation kinetics indicated that the block of berberine increased with stronger depolarization, suggesting that the block was voltage-dependent. The maximal effects was attained at +30 mV, which was the level of maximal activation of I_K. The blocking effect was similar for voltages between +30 mV and +50 mV, suggesting that there was no further block at positive potentials once all channels were activated.

Inhibitory effect of berberine on HERG potassium channels expressed in *Xenopus* oocytes

Injection of oocytes with cRNA encoding for HERG channels resulted in the induction of a K^+ conductance with previously described activation and rectification properties[11]. Channels were activated by depolarization, but because of their more rapid C-type inactivation compared to their activation, outward currents at 0 mV were relatively small. However, the tail currents, obtained during repolarizing steps to −60 mV were twice larger as a result of a fast relief from inactivation combined with slow deactivation.

Berberine blocked both the relatively small outward currents during 4 s depolarizing pulses to 0 mV and the large tail outward current at −60 mV (holding potential was −80 mV; interval of pulses was 3 s). Analysis of the blockade of the tail currents with the Hill equation resulted in an IC_{50} value of (0.075±0.012) mmol/L and a Hill coefficient of 1.2 (Fig 5, $n=5$).

In order to study the voltage-dependence of block more extensively, the effects of Berberine on HERG current-voltage relationship and deactivation kinetics were analyzed. Three second voltage steps from −40 to 40 mV (increment 10 mV) were performed and the tail currents were measured. The data showed that the voltage

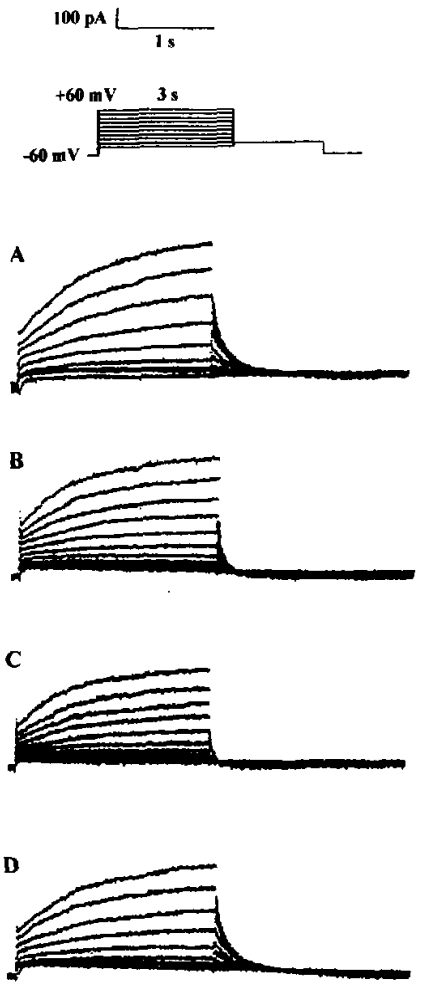

Fig 3. Effect of berberine on I_K in guinea pig ventricular myocytes. I_K was elicited by 3 s depolarizing pulse to potentials ranging from −40 mV to +60 mV at a holding potential of −60 mV. I_{Ca} and I_{K1} were abolished with 0.2 mmol/L $CdCl_2$ and 0.1 mmol/L $BaCl_2$ to the bath solution. (A) control. (B, C) Berberine 10, 50 μmol/L. (D) Washout.

at which half-maximal current were activated.

HERG channels was a little shifted from (−18.2±2.3) mV under control conditions ($n=5$) to (−20.6±2.3) mV after perfusion of berberine 0.1 mmol/L. The conductance of HERG channels decreased at depolarized potentials (>0 mV) in the presence of berberine as a result of the increased blocking effect.

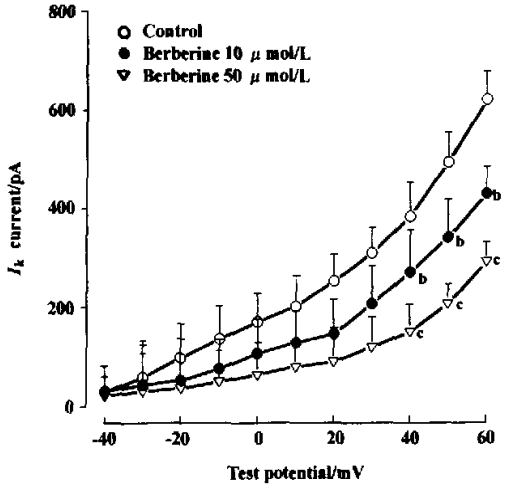

Fig 4. Effect of berberine on current-voltage relation of I_K in guinea pig ventricular myocytes. (○) Control. (●, ▽) Berberine 10, 50 μmol/L.

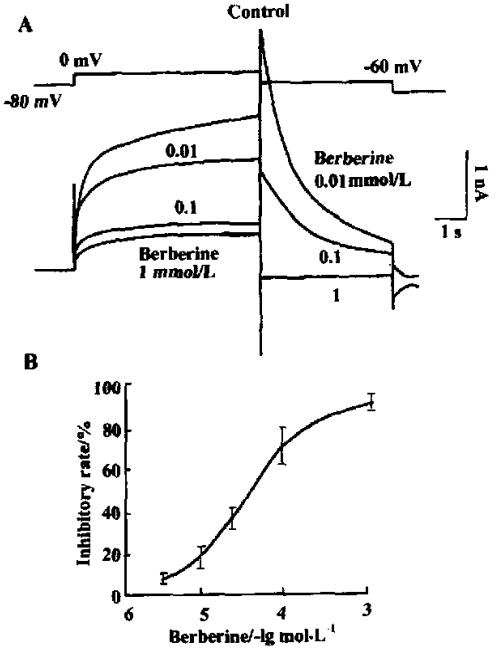

Fig 5. (A) Concentration-dependent blockade of HERG channel by berberine (mmol/L). HERG currents were activated with 4 s depolarizating pulses to 0 mV from a holding potential of −80 mV every 3 s. Taill currents were recorded at −60 mV and filtered at 0.5 kHz. (B) Relationship between concentration and blockade of HERG channel by berberine. The HERG channel tail currents after depolarizations to 40 mV were calculated. The Hill equation was fitted to the data with 100 % blockade as a fixed maximal effect. $n = 5$. $\bar{x} \pm s_{\bar{x}}$.

DISCUSSION

In the present study, we have found that in guinea pig isolated ventricular myocytes, berberine prolongs action potential duration without affecting resting membrane potential or action potential amplitude. Similar results have been reported for multicellular preparation[15,16]. In dog Purkinje and ventricular muscle fibres, berberine at concentrations of 3 – 30 μmol/L did not affect maximum upstroke velocity (V_{max})[16]. These findings and ours show that berberine selectively increases action potential duration.

The results of the present study show that berberine exerts an inhibitory effect on I_{K1}, I_K, and I_{Ktail} in a concentration-dependent manner. I_{K1} and I_K play a critical role in the repolarization process of cardiac action potential. The effect of berberine on I_K shows a voltage-dependent block, however this block was similar at voltages between +30 and +50 mV, suggesting that there is no further block at positive potentials once all channels are activated suggesting that berberine blocks open channels. Blockade of I_{K1} and I_K may be capable of preventing ischaemia-induced ventricular tachycardia (VT) and reperfusion-induced ventricular fibrillation (VF) from occurring, the reason is by reducing diastolic injury potential (by causing partial depolarization of nonischaemic tissue) or by reducing systolic injury potential (by altering the shape of the terminal phase of the action potential). Moreover our results show that the inhibitory effect of berberine on action potential duration and potassium channel was poorly reversible after washout, this effect may be explained by its probable binding to the intracellular site of the channel transmembrane segment. This characteristics is similar to verapamil.

The new class Ⅲ antiarrhythmic agent (selectively block I_{Kr})[17] for a reentrant arrhythmia provides use-dependent prolongation of the action potential duration with slow onset and rapid offset kinetics, these drugs prolong the effective refractory period of cardiac tissue during ventricular tachycardia or fibrillation with a delayed onset of action. The pharmacological potential of class Ⅲ antiarrhythmic drugs, however, is limited by their tendency to produce an excessive prolongation of action potentials, which can cause acquired long QT syndrome and sudden cardiac death. Berberine can inhibit multiple ionic channels, such as I_{K1}, I_K and $I_{Ca\text{-}L}$[18], so berberine may be

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a more beneficial antiarrhythmic agent.

The HERG voltage-dependent K^+ channel plays a role in cardiac electrical excitability. HERG as a selected target for detecting the effect of antiarrhythmic compounds in this experiment has two reasons. First, HERG is clearly present in human ventricle, and could be effectively blocked by class Ⅲ antiarrhythic agents. Second, HERG mutations result in Q-T prolongation, *torsade de pointes* and sudden cardiac death[19]. As well known, these arrhythmias typically occur in the setting of a prolonged QT interval, reflecting delayed myocardial repolarization and prolonged action potential duration. Prolongation of the QT interval may be congenital or may result from electrolyte abnormalities, dietary deficiencies, toxins or exposure to a number of medications such as class I_A and class Ⅲ antiarrhythmic drugs[17,20].

The cardiac ion channel gene products that are targets for berberine are unknown. However, previous studies showed that the delayed rectifier tail current and I_{Kr} in cat ventricle were strongly reduced by berberine[9], resulting in a prolongation of the action potential plateau. We therefore tested them for a possible block of HERG expressed in *Xenopus* oocytes. We found that berberine can block both HERG and its mutants (berberine at 0.1 mmol/L could inhibit the channel of S631A, H560T, Y652F, A547C, and M651T. All of these channels are *N*-terminal mutation in wtHERG which cause the change of deactivation). These blocking effects by berberine are reversible. Fortunately the available concentration for blocking the HERG channel which we used in these experiments, is around 0.1 to 0.01 mmol/L. This concentration is higher than the effective concentration in clinical application. So berberine probably has less hazardous for inducing long QT syndrome than other known compounds such as class IA and Ⅲ antiarrhythnic drugs, but further clinical application was needed.

The increase in action potential duration induced by berberine is mainly due to its blocking effect on I_{K1} and I_K. The inhibitory effects of berberine on I_{K1}, I_K, and HERG channels are its major ionic mechanisms of antiarrhythmic action.

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小檗碱对心肌细胞 I_{K1}、I_K 及 HERG 通道的抑制作用[1]

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关键词 小檗碱；钾通道；心肌；膜片箝技术；重组蛋白质类；卵母细胞；爪蟾属

目的：研究小檗碱(Ber)对豚鼠心室肌细胞钾通道和动作电位作用，以及在蛙卵中表达的人的 HERG 通道的作用. **方法**：酶解方法分离单个心肌细胞，采用全细胞膜片箝方法记录钾离子电流及动作电位，基因箝技术研究 HERG 通道电流. **结果**：Ber 可显著延长动作电位时程，并呈剂量依赖性. Ber 100 μmol/L 使 APD_{90} 由对照的(450 ± 48) ms 延长至(888 ± 90) ms ($n=6$, $P<0.01$). Ber 对 I_{K1} 及 I_K 呈剂量依赖性抑制作用. Ber 100 μmol/L 对 I_{K1} 的抑制率达 65 % ± 7 % ($n=6$, $P<0.01$). Ber 50 μmol/L 对 I_K 的抑制率达 57 % ± 6 %；对 I_{Ktail} 的抑制率达 53 % ± 6 %. Ber 对 I_K 作用呈现电压依赖性. Ber 对在蛙卵中表达的 HERG 通道具有很强的阻断作用，IC_{50} 为 75 μmol/L，此阻断作用也呈电压依赖性. **结论**：Ber 可使动作电位时程明显延长，对 I_{K1} 及 I_K 具有阻断作用. Ber 可显著抑制 HERG 通道. Ber 抗心律失常的机制与其抑制 I_{K1}、I_K 及 HERG 通道密切相关.

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