Inhibitory effects of matrine, E-4031, dofetilide and RP58866 on inward rectifier potassium current in rabbit ventricular myocytes

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Abstract: **AIM** To explore the cause of the weaker antiarrhythmic effects of matrine than that of E-4031, dofetilide and RP58866. **METHODS** Whole-cell patch-clamp technique was used to record ionic currents in rabbit ventricular myocytes. **RESULTS** 1 and 10 $\mu mol \cdot L^{-1}$ matrine did not affect the inward rectifier potassium current (I_{k1}). 50 and 100 $\mu mol \cdot L^{-1}$ matrine reduced I_{k1} by 6% ($n = 8$, $P < 0.05$) and 8% ($n = 8$, $P < 0.05$), respectively at test potential of – 120 mV from holding potential of – 70 mV. At – 50 mV, I_{k1} decreased by 4% ($n = 8$, $P < 0.05$) and 8% ($n = 8$, $P < 0.05$). E-4031, dofetilide and RP58866 significantly inhibited I_{k1}. At test potential of – 120 mV, 1 and 10 $\mu mol \cdot L^{-1}$ E-4031 decreased I_{k1} by 10% ($n = 6$, $P < 0.05$) and 45% ($n = 6$, $P < 0.05$). At – 50 mV, I_{k1} was decreased by 5% ($n = 8$, $P < 0.05$) and 35% ($n = 8$, $P < 0.05$), respectively. 1 and 10 $\mu mol \cdot L^{-1}$ dofetilide decreased I_{k1} by 19% ($n = 6$, $P < 0.05$) and 25% at – 120 mV. At – 50 mV, I_{k1} was decreased by 11% ($n = 6$, $P < 0.05$) and 19% ($n = 6$, $P < 0.05$), respectively. At – 120 mV, 1 $\mu mol \cdot L^{-1}$ and 10 $\mu mol \cdot L^{-1}$ RP58866 decreased I_{k1} by 21% ($n = 8$, $P < 0.05$) and 50% ($n = 8$, $P < 0.05$). At – 50 mV, I_{k1} was decreased by 6% ($n = 8$, $P < 0.05$) and 11% ($n = 8$, $P < 0.05$), respectively. **CONCLUSION** The lower efficacy and potency of matrine in the inhibitory effects on I_{k1} than that of E-4031, dofetilide and RP58866 is one of the reasons for weaker antiarrhythmic effects of the Chinese herb than that of pure compounds.

Key words: matrine; E-4031; dofetilide; RP58866; patch-clamp technique, whole-cell; potassium current, inward rectifier; myocardium

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Matrine is an alkaloid extracted from *Sophore alopecuroides*. It was found to possess a significant antiarrhythmic effect on both animal models and clinical settings[1]. Compared with many other antiarrhythmic agents currently used in clinics, matrine produces much less side effect and toxicity[2]. This property promises matrine as a better choice for antiarrhythmic therapy. Nonetheless, the antiarrhythmic efficacy of matrine was found to be weaker than most of the antiarrhythmic drugs, such as the agents with class Ⅲ antiarrhythmic actions like E-4031, dofetilide and RP58866[1]. To have better understanding of matrine's value for antiarrhythmic therapy, it is of paramount importance to decipher the ionic mechanisms underlying the antiarrhythmic efficacy of matrine.

Besides the major determinant of the cardiac resting membrane potential, inward rectifier K^+ current (I_{k1}) also plays a significant role in regulating the late phase of cardiac repolarization thereby the likelihood of arrhythmias, owing to its inwardly rectifying property. It is known that E-4031, dofetilide and RP58866 are selective blockers of the rapid delayed rectifier K^+ current (I_{kr})[3-5]. However, it is unknown whether these drugs can also block I_{k1} and whether the antiarrhythmic efficacies are related to I_{k1} inhibition. The present study was designed to determine the comparative effects of matrine, E-4031, dofitilide and RP58866 on I_{k1} with whole-cell patch-clamp techniques in enzymatically isolated rabbit ventricular myocytes so as to elucidate the potential ion-

ic mechanisms for the weaker antiarrhythmic effects of matrine.

1 MATERIALS AND METHODS

1.1 Drugs

Matrine (0805-9703), synthesized by National Institute for the Control of Pharmaceutical and Biological Products. E-4031, dofetilide, and RP58866 were purchased from Sigma Co.

1.2 Myocytes isolation

The myocyte dissociation procedure was very similar to that described in previously[6,7]. Briefly, hearts were removed from rabbits weighing 1.5 – 3.0 kg of either sex (provided by the Experimental Animal Center of Harbin Medical University, Grade Ⅱ) and mounted on a modified Langendorff perfusion system for retrograde perfusion *via* the coronary circulation. The preparation was perfused with Ca^{2+}-containing Tyrode solution (in mmol·L^{-1}: NaCl 126, KCl 5.4, $MgCl_2$ 1, $CaCl_2$ 1.8, NaH_2PO_4 0.33, glucose 10, and HEPES 10, pH 7.4 with NaOH) at 37℃ until the effluent was clear of blood and then switched to Ca^{2+}-free Tyrode solution for 20 min at a constant rate of 12 mL·min^{-1}, followed by perfusion with the same solution containing collagenase (type Ⅱ, 100 – 150 kU·L^{-1}) and 1% bovine serum albumin. The left ventricular tissue was then excised from the softened hearts, minced and placed in a KB medium (in mmol·L^{-1}: glutamic acid 70, taurine 15, KCl 30, KH_2PO_4 10, $MgCl_2$ 0.5, EGTA 0.5, HEPES 10, glucose 10, and 1% albumin, pH 7.4 with KOH) at 4℃ for 1 h before electrophysiological experiments.

1.3 Patch-clamp technique

The cardiomyocytes were transferred to a chamber mounted on an inverted microscope (Nikon Diaphot, Nikon Co., Tokyo, Japan) for electrophysiological recording and were bathed at room temperature (22 – 23℃) in Tyrode solution. First, the currents were recorded free from drugs, then matrine, dofetilide, E-4031 and RP58866 were added to the cell surface, repectively. Five minutes after application of these drugs, we started to record the currents for 30 min while the dosage of these drugs were elevated from 0.1 to 100 μmol·L^{-1} and at last washout.

Whole-cell patch-clamp recording technique used has been described in detail elsewhere[6,8-10]. Ionic currents were recorded in the whole-cell voltage-clamp with an Axo-patch 200 B amplifier (Axon Instruments). Borosilicate glass electrodes had tip resistance of 2 to 4 MΩ when filled with pipette solution (in mmol·L^{-1}: KCl 20, potassium asparate 110, $MgCl_2$ 1, HEPES 5, EGTA 10, and Na_2-ATP 5, pH 7.2 with KOH). Junction potentials were zeroed before formation of the membrane-pipette seal in Tyrode solution. The capacitance and series resistance (Rs) were compensated electrically to minimize the duration of the capacitive surge on the current recording and the voltage drop across the cell membrane during voltage clamp. Experiments were conducted at room temperature (22 – 23℃).

1.4 Data analysis

Data were expressed as $\bar{x} \pm s$ and differences were estimated by paired t-test, and a two-tailed value of $P < 0.05$ was taken to indicate statistical significance.

2 RESULTS

2.1 Effect of dofetilide on inward rectifier K^+ current

I_{k1} was elicited by a family of voltage which steps ranging from – 160 mV to 0 mV from a holding potential of – 70 mV. Extracellular application of dofetilide (10 min) consistently reduced I_{k1} in rabbit ventricular myocytes. One example is shown in Fig 1A. Dofetilide blockade of I_{k1} was seen at all test potentials examined (Fig 1B). The block was completely reversed upon exchange of medium back to dofetilide-free Tyrode solution in the same cell. Appreciable reduction of I_{k1} caused by dofetilide was observed at a concentration of as low as 0.1 μmol·L^{-1}. At a test potential of – 120 mV, dofetilide of 1 and 10 μmol·L^{-1} reduced the currents from (– 4.60 ± 0.72) to (– 3.71 ± 0.58)[Δ(– 0.89 ± 0.11)]and (– 3.48 ± 0.88)

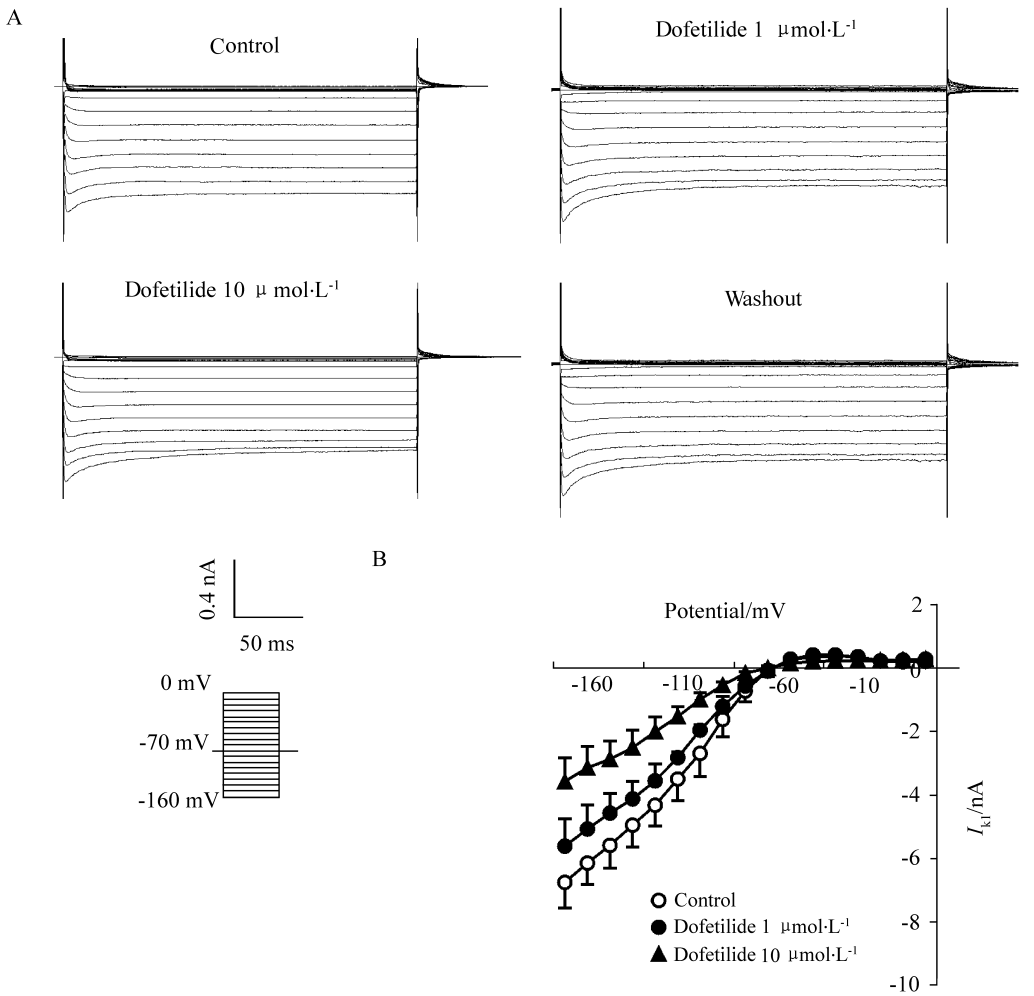

Fig 1. Effects of dofetilide on inward rectifier K^+ current (I_{k1}) in single rabbit ventricular cell. Currents were elicited by 300 ms pulse to potentials ranging from − 160 mV to 0 mV with 10 mV increments from a HP of − 70 mV at an interpulse interval of 10 s. (A) Analog data from a representative cell showing families of current traces recorded before drug perfusion, in the presence of 1 and 10 μmol·L^{-1}, and after washout of the drug, respectively. (B) Current-voltage relation with and without dofetilide. Shown are averaged data from a total of six cells.

[Δ(−1.11 ± 0.18)]nA ($P < 0.05$, $n = 6$ cells from four rabbits). At −50 mV, the current decreased from (0.40 ± 0.08) to (0.36 ± 0.08) [Δ(0.04 ± 0.02)] and (0.33 ± 0.07) [Δ(0.07 ± 0.02)]nA, respectively ($P < 0.05$, $n = 6$ cells from 4 rabbits).

2.2 Effect of E-4031 on inward rectifier K^+ current

E-4031 (10 min) consistently reduced I_{k1} at all test potentials examined (Fig 2). A representative example is shown in Fig 2A. The blockade was completely restored after washout of E-4031 in the same cell. Appreciable reduction of I_{k1} caused by E-4031 was observed at a concentration of as low as 0.1 μmol·L^{-1}. At test potential of −120 mV, E-4031 1 and 10 μmol·L^{-1} reduced the currents from (−4.02 ± 0.65) to (−3.66 ± 0.54) [Δ(−0.36 ± 0.10)] and (−2.21 ± 0.47) [Δ(−1.18 ± 0.26)]nA ($P < 0.05$ *vs* control, $n = 6$ from 5 rabbits), respectively. At −50 mV, the currents were inhibited from (0.35 ± 0.11) to (0.35 ± 0.08) [Δ(0.018 ± 0.004)]

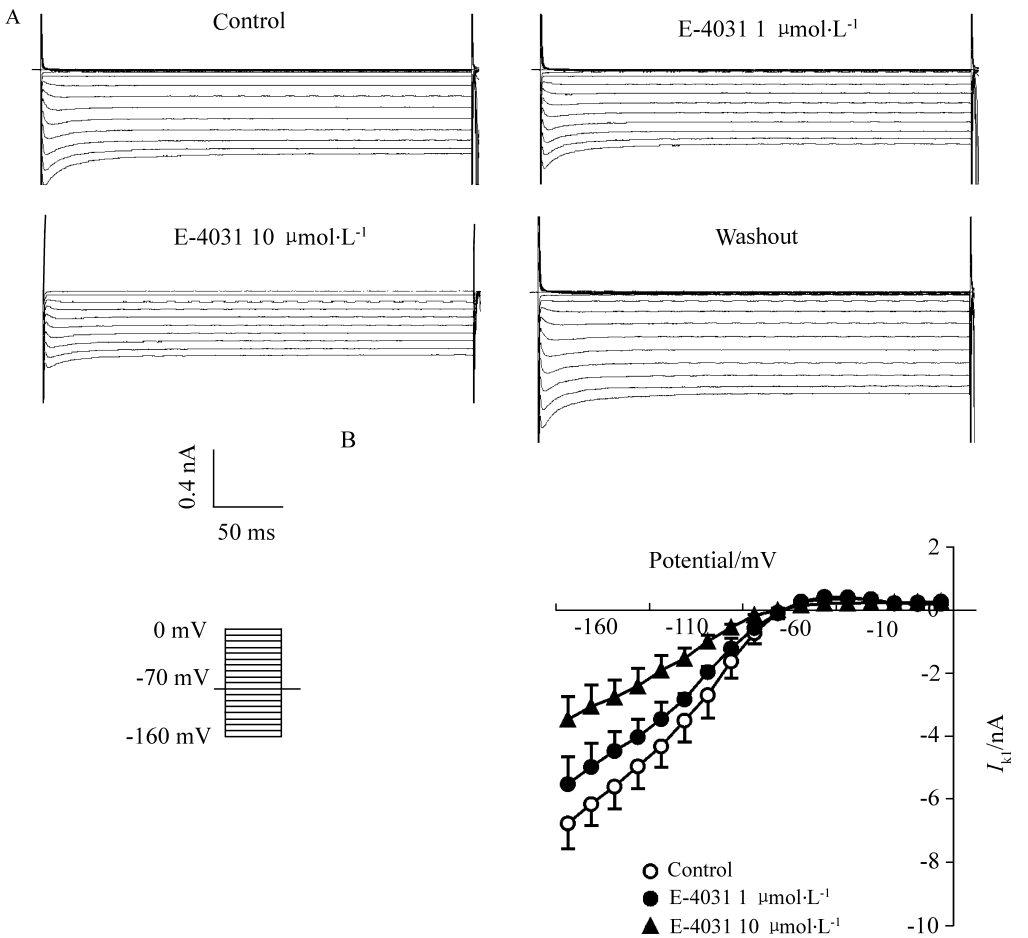

Fig 2. Effect of E-4031 on I_{k1} in single rabbit ventricular cell. Currents were elicited by 300 ms pulse to potentials ranging from − 160 mV to 0 mV with 10 mV increments from a HP of − 70 mV at an interpulse interval of 10 s. (A) Analog data from a representative cell showing families of current at test potential of − 120 mV recorded before drug perfusion, in the presence of 1 and 10 μmol·L^{-1}, and after washout of the drug, respectively. (B) Current-voltage relation with and without E-4031. Shown are averaged data from a total of six cells.

and (0.233 ± 0.029)[Δ(0.120 ± 0.015)]nA, respectively($P < 0.05$, $n = 6$ cells from 5 rabbits).

2.3 Effect of RP58866 on inward rectifier K^+ current

Superfusion with RP58866 for 10 min consistently reduced I_{k1} at various test potential studied (Fig 3). A typical example is displayed in Fig 3A. The blockade was completely restored upon exchange of medium back to RP58866-free Tyrode solution in the same cell. Appreciable reduction of I_{k1} caused by RP58866 was observed at a concentration of as low as 0.1 μmol·L^{-1}. At test potential of − 120 mV, RP58866 of 1 and 10 μmol·L^{-1} reduced the currents from (− 5.27 ± 0.76) to (− 4.15 ± 0.67) [Δ(− 1.12 ± 0.26)] and (− 2.62 ± 0.51) [Δ(− 2.65 ± 0.46)] nA ($P < 0.05$, $n = 8$ cells from seven rabbits), respectively. At − 50 mV, the current decreased from (0.39 ± 0.05) to (0.37 ± 0.04) [Δ(0.02 ± 0.00)] and (0.35 ± 0.05) [Δ(0.04 ± 0.01)] nA, respectively($P < 0.05$, $n = 8$ cells from seven rabbits).

2.4 Effect of matrine on inward rectifier K^+ current

Matrine of 1 and 10 μmol·L^{-1} did not effect I_{k1}. Only when matrine concentration was elevated

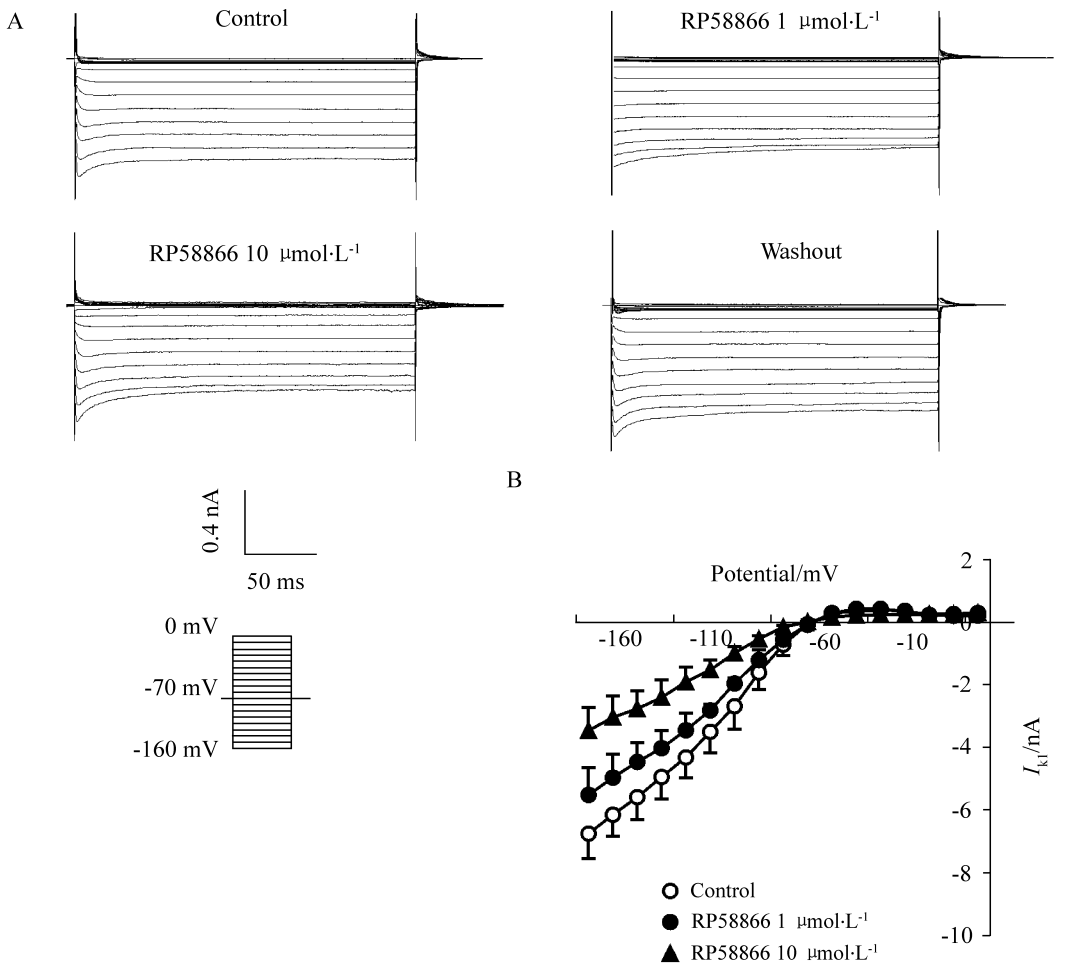

Fig 3.　Effect of RP58866 on I_{k1} in single rabbit ventricular cell. Currents were elicited by 300 ms pulse to potentials ranging from －160 mV to 0 mV with 10 mV increments from a HP of －70 mV at an interpulse interval of 10 s. (A) Analog data from a representative cell showing families of current traces recorded before drug perfusion, in the presence of 1 and 10 μmol·L^{-1}, and after washout of the drug, respectively. (B) Current-voltage relation with and without RP58866. Shown are averaged data from a total of eight cells.

to 50 μmol·L^{-1}, statistically significant suppression of I_{k1} was achieved (Fig 4). Matrine of 50 and 100 μmol·L^{-1} reduced I_{k1} from (－4.61 ± 0.42) to (－4.31 ± 0.43)[Δ(－0.30 ± 0.02)] and (－4.21 ± 0.41)[Δ(0.40 ± 0.03)]nA, respectively, at test potential of －120 mV (P < 0.05 *vs* control, n = 8 cells from seven rabbits). At －50 mV, the current decreased from (0.39 ± 0.09) to (0.38 ± 0.08) [Δ(0.01 ± 0.00)] and (0.36 ± 0.07) [Δ(0.03 ± 0.00)]nA, respectively(P < 0.05, n = 8 from seven rabbits). The block was completely restored after washout. Matrine caused considerably smaller I_{k1} inhibition than E-4031, dofetilide and RP58866; 100 μmol·L^{-1} matrine inhibited I_{k1} by only about 8% and the same concentration of E-4031, dofetilide or RP58866 nearly abolished I_{k1}.

3　DISCUSSION

Our data clearly demonstrated that E-4031, dofetilide, RP58866 and matrine all blocked I_{k1}, but the concentration required for I_{k1} inhibition by matrine was about 50-folds higher.

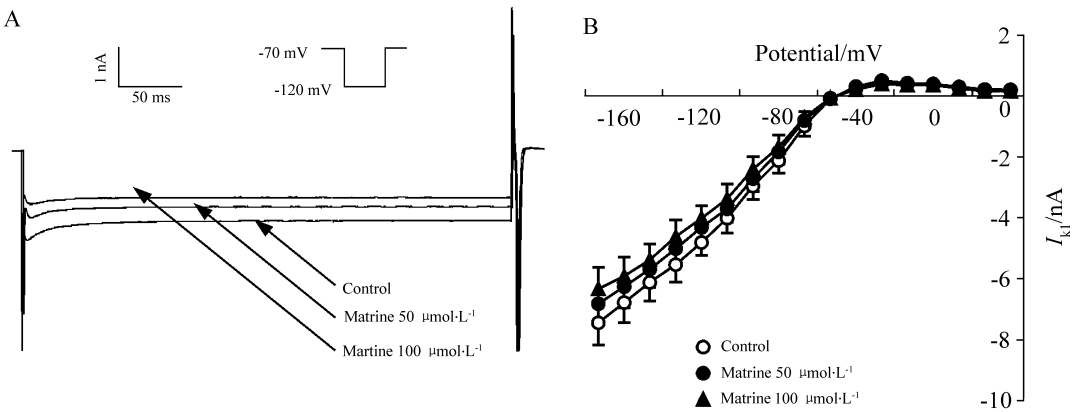

Fig 4. Effect of matrine on I_{k1} in single rabbit ventricular cell. Currents were elicited by 300 ms pulse to potentials ranging from − 160 mV to 0 mV with 10 mV increments from a HP of − 70 mV at an interpulse interval of 10 s. Recording was conducted in the presence of martine. (A) Analog data from a representative cell showing families of current at test potential of − 120 mV recorded before drug prefusion, in the presence of 50 and 100 μmol·L^{-1}, and after washout of the drug, respectively. (B) Current-voltage relation with and without matrine. Shown are averaged data from a total of eight cells.

I_{k1} plays an important role in final phase of repolarization of mammalian ventricular myocytes and in stabilizing the resting membrane potential[11]. Thus, blockade of I_{k1} would be expected to lengthen total action potential duration. Decrease in I_{k1} has been implicated in a variety of disease states of the heart, including myocardial infarction, ischemia, cardiac hypertrophy and heart failure[12-15]. The decrease is often accompanied by cell membrane depolarization and generation of arrhythmias, such as ectopic beats, early afterdepolarization (EAD), and triggered activity[15-17]. Therefore, I_{k1} is believed to be the major targets of antiarrhythmic drugs[18]. I_{k1} inhibition by E-4031, dofetilide and RP58866 revealed in this study may contribute to their antiarrhythmic efficacies, but does not seem to be the major mechanism by which matrine produces antiarrhythmic effects.

Previous studies have established that E-4031, dofetilide and RP58866 are selective blockers I_{kr}[3-5]. The potent effects of these agents on I_{kr} confer strong reverse use-dependent actions on cardiac repolarization[4,8]. However, excessive blockade of I_{kr} may increase the risk of proarrhythmic reactions, due to an excessive delay of repolarization at slow heart rates[16]. Class Ⅲ antiarrhythmic agents without selectivity for I_{kr} may be a more beneficial profile of rate-dependent actions. The present study revealed that in addition to inhibition of I_{kr}, the class Ⅲ antiarrhythmic agents also markedly block I_{k1}; in other words, class Ⅲ antiarrhythmic drugs do not selectively block I_{kr}. Blockade of I_{k1} may be an advantageous property for class Ⅲ agents.

Recent studies demonstrated that E-4031, dofetilide and RP58866 did not inhibit I_{kr} specifically. But oppositional to our results, Kiehn, *et al*[19] has reported that dofetilide (0.1 mmol·L^{-1}) have not significant effect on I_{k1} with a clamp program progressing from a holding potential of − 80 mV to variable test potentials (− 160 to + 40 mV in 10 mV steps) in guinea pig cardiomyocytes, test potential duration was 1000 ms. Gwilt, *et al*[20] has reported the similar results. But our results indicated dofetilide at 1 and 10 μmol·L^{-1} inhibited I_{k1} by 19% in rabbit ventricular myocytes. The difference between two experiments, one is the holding potential in the protocol (one is − 70 mV, the other − 80 mV). The other is the kind of animal. The membrane potential of rabbit and guinea pig has not significant distinction, so the different consequence did not result from the holding potential.

Martin, *et al*[21] observed that E-4031 specifically blocked the fast component of the delayed I_{k1} as its concentration low to 5 $\mu mol \cdot L^{-1}$; however, at high concentrations (100 $\mu mol \cdot L^{-1}$), E-4031 caused a reduction in inward (34%) and outward (64%) I_{k1} in guinea pig cardiomyocytes. But our results demonstrated that E-4031 10 $\mu mol \cdot L^{-1}$ inhibited inward (45%) and outward (35%) I_{k1} in rabbit cardiomyocytes.

Compared to the results reported, in the present experiment we achieved the similar consequences of E-4031 and dofetilide by the less dosage. Perhaps the rabbit and guinea pig cardiomyocytes have different sensitivity to dofetilide and E-4031.

Matrine at 1 and 10 $\mu mol \cdot L^{-1}$ had no effect on I_{k1}, but at 50 and 100 $\mu mol \cdot L^{-1}$ it inhibited I_{k1}. Recently, in our experiment, the significant inhibitory effect of matrine on I_{kr}, I_{ks}, $I_{Ca\text{-}L}$ were observed only when matrine concentration was elevated to 50 $\mu mol \cdot L^{-1}$. The weak effect of matrine on I_{k1}, compared to those of E-4031, dofetilide and RP58866, suggests that I_{k1} inhibition do not fully account for matrine's antiarrhythmic efficacy, and also provides an explanation for the weaker antiarrhythmic efficacy of matrine relative to those of E-4031, dofetilide and RP58866.

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苦参碱与 E-4031，多非利特和 RP58866 对家兔心肌 I_{k1}的作用比较

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摘要：目的　比较苦参碱与 E-4031，多非利特和 RP58866 对家兔单个心室肌细胞的内向整流钾电流（I_{k1}）的效价和效能的不同，揭示苦参碱抗心律失常作用弱于西药的原因。**方法**　应用全细胞膜片钳技术记录苦参碱与 E-4031，多非利特和 RP58866 对家兔 I_{k1}的影响。**结果**　苦参碱 1 和 10 μmol·L^{-1}对家兔 I_{k1}无明显影响。在实验电压为 – 120 mV 和保持电压为 – 70 mV，苦参碱 50 和 100 μmol·L^{-1}对 I_{k1}分别抑制达 6%（n = 8，P < 0.05）和 8%（n = 8，P < 0.05）；在实验电压为 – 50 mV，抑制 I_{k1}达 4%（n = 8，P < 0.05）和 8%（n = 8，P < 0.05）。在实验电压为 – 120 mV，E-4031 1 和 10 μmol·L^{-1}使 I_{k1}分别降低 10%（n = 6，P < 0.05）和 45%（n = 6，P < 0.05）。在 – 50 mV，I_{k1}分别降低 5%（n = 6，P < 0.05）和 35%（n = 6，P < 0.05）。在实验电压为 – 120 mV，多非利特 1 和 10 μmol·L^{-1}使 I_{k1}降低 19%（n = 8，P < 0.05）及 25%（n = 8，P < 0.05）。在 – 50 mV，I_{k1}分别降低 11%和 19%（n = 8，P < 0.05）。在实验电压为 – 120 mV，RP58866 1 和 10 μmol·L^{-1}使 I_{k1}分别降低 21%（n = 8，P < 0.05）和 50%（n = 8，P < 0.05）。在 – 50 mV，I_{k1}分别降低 6%（n = 8，P < 0.05）和 11%（n = 8，P < 0.05）。**结论**　苦参碱对 I_{k1}效价和效能弱于 E-4031，多非利特和 RP588666 是其抗心律失常作用弱于西药的原因。

关键词： 苦参碱；E-4031；多非利特；RP58866；膜片钳技术，全细胞；钾电流，内向整流；心肌

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