Wenxin Keli attenuates ischemia-induced ventricular arrhythmias in rats: Involvement of L-type calcium and transient outward potassium currents

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Abstract. Wenxin Keli is the first state-sanctioned traditional Chinese medicine (TCM)-based antiarrhythmic drug. The present study aimed to examine whether long-term treatment with Wenxin Keli reduces ischemia-induced ventricular arrhythmias in rats *in vivo*, and if so, which mechanisms are involved. Male rats were treated with either saline (control group) or Wenxin Keli for 3 weeks and were subjected to myocardial ischemia for 30 min with assessment of the resulting ventricular arrhythmias. The L-type calcium current ($I_{Ca,L}$) and transient outward potassium current (I_{to}) were measured by the patch clamp technique in normal rat cardiac ventricular myocytes. During the 30-min ischemia, Wenxin Keli significantly reduced the incidence of ventricular fibrillation (VF) ($P<0.05$). The number of ventricular tachycardia (VT)+VF episodes and the severity of arrhythmias were significantly reduced by Wenxin Keli administration compared to the control group ($P<0.05$). In addition, Wenxin Keli inhibited $I_{Ca,L}$ and I_{to} in a concentration-dependent manner. These results suggest that long-term treatment with Wenxin Keli may attenuate ischemia-induced ventricular arrhythmias in rats and that $I_{Ca,L}$ and I_{to} may be involved in this attenuation.

Introduction

Ventricular fibrillation (VF) induced by acute myocardial infarction (AMI) frequently occurs without warning, often leading to death within minutes in patients who do not receive prompt medical attention. As is widely known, the cardiac arrhythmia suppression trial (CAST) confirmed that traditional antiarrhythmic drug therapy following myocardial infarction (MI) effectively reduced ventricular premature beats and non-sustained tachycardia, but these drugs were found to increase sudden death and the total mortality rate compared to a placebo (1). Thus, it is critical to develop an effective and safe approach to attenuate ischemia-induced VF in the early phase of AMI in order to reduce sudden cardiac death (SCD). Traditional Chinese medicine (TCM) has documented the use of natural products, primarily plants (the source for over 80% of the natural products), for over 2,000 years. The substances used medicinally by different ethnic or cultural groups are viewed by researchers as increasingly relevant and important sources of new medicinal products.

Wenxin Keli is the first state-sanctioned TCM-based antiarrhythmic drug and was developed by the Chinese Academy of TCM. Baicalin, the major component of Wenxin Keli, is a flavone, a type of flavonoid, and is found in several species in the genus *Scutellaria*. This compound has protective effects against heart injury in rats (2,3). Clinical studies have documented the effects of Wenxin Keli in the clinical treatment of arrhythmias, and no significant adverse reactions were observed. Recently, Burashnikov *et al* (4) found that Wenxin Keli possesses potent anti-atrial fibrillation (AF) properties due to its ability to depress sodium channel-dependent parameters in the atria. However, the effects of Wenxin Keli on ischemia-induced ventricular arrhythmias *in vivo* remain to be elucidated. In the present study, we demonstrated that long-term oral treatment with Wenxin Keli is capable of attenuating ischemia-induced ventricular arrhythmias in rats, and $I_{Ca,L}$ and I_{to} may be involved.

Materials and methods

Animal preparation and experimental design. All experiments were performed in accordance with the local Institutional Committee on Animal Research of Renmin Hospital of Wuhan University (Wuhan, China) (permit no. 00015816). Rats (250-300 g) were purchased from the Experiment Animal Center of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). The investigation complied with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes

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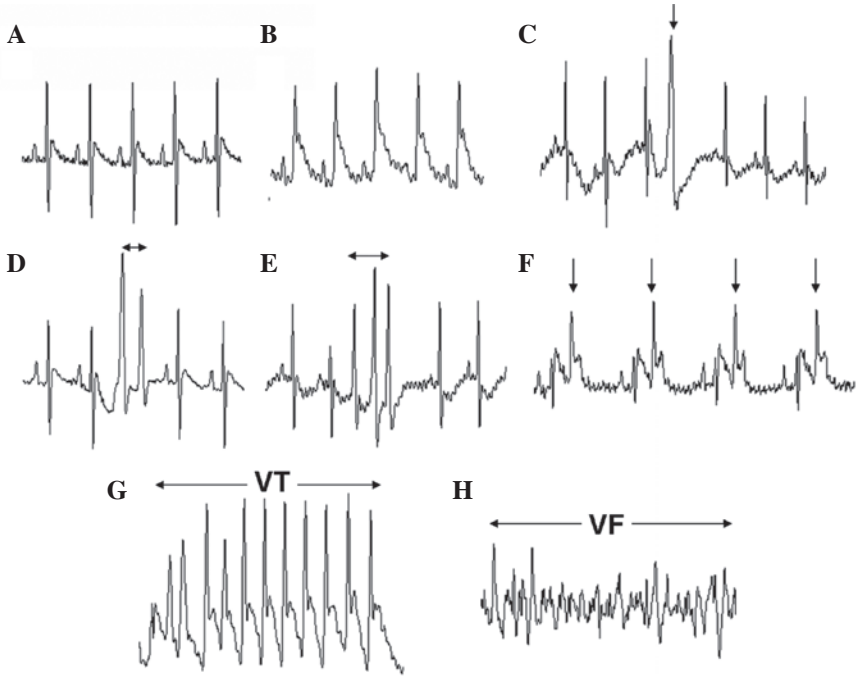

Figure 1. Electrocardiogram recording. (A) At baseline; (B) during coronary artery occlusion; (C) ventricular ectopic beat (VEB); (D) couplet; (E) triplet; (F) bigeminy; (G) ventricular tachycardia (VT); (H) ventricular fibrillation (VF).

of Health (NIH publication no. 85-23, revised 1996). Room temperature was maintained at 23˚C with constant humidity (55%), and the lights were maintained on a 12-h light/dark cycle (8:00 am-8:00 pm light/8:00 pm-8:00 am dark). A total of 34 rats were randomly divided into three groups: Group 1, sham-operated group (n=8), rats underwent surgical procedures without coronary artery ligation; Group 2, control group (n=13), saline was administered for 3 weeks by gavage prior to coronary artery occlusion; Group 3, Wenxin Keli group (n=13), Wenxin Keli (8 g/kg, qd, gavage) was administered for 3 weeks prior to coronary artery occlusion.

After being anesthetized with sodium pentobarbital [40 mg/kg, intraperitoneally (IP)], the rats were ventilated artificially via a tracheal cannula using a constant volume rodent ventilator (tidal volume, 3.0 ml; respiratory rate, 70 strokes/min). The right common carotid artery was cannulated to measure the mean arterial blood pressure (MBP). Lead II of the electrocardiogram was monitored with subcutaneous stainless steel electrodes. A computer-based EP system (LEAD2000B; Jinjiang Ltd., Chengdu, China) was used to record the heart rate and the electrocardiogram. Under sterile conditions, a left thoracotomy was performed in the fourth intercostal space. After pericardiotomy, a 5-0 prolene suture was tied around the left anterior descending coronary artery at 2-3 mm from its origin. A successful myocardial ischemia model was confirmed by ST segment elevation in Lead II and by regional cyanosis of the myocardial surface.

Assessment of ventricular arrhythmias. Ischemia-induced ventricular arrhythmias were identified in accordance with the Lambeth Conventions as in our previous study (5) (Fig. 1). Ventricular ectopic beats (VEBs) were defined as identifiable premature QRS complexes. Ventricular tachycardia (VT) was defined as the occurrence of ≥4 consecutive VEBs at a rate faster than the resting sinus rate. VF was defined as unidentifiable and low voltage QRS complexes. Other multipart forms of VEBs, such as bigeminy, couplets (two consecutive VEBs) and triplets (three consecutive VEBs), were evaluated as separate episodes (Fig. 1). VF may be sustained or may spontaneously revert to a normal sinus rhythm. VF lasting for >5 min was considered irreversible.

The severity of the arrhythmias was quantified by the following scoring system (6,7): a total of 0-50 VEBs with no other arrhythmias during the 30-min ischemia period resulted in a score of 0; a total of 50-500 VEBs in a score of 1; a total of >500 VEBs or one episode of spontaneously reversible VT or VF in a score of 2; a total of 2-30 episodes of spontaneously reversible VT and/or VF in a score of 3; a total of >30 episodes of spontaneously reversible VT and/or VF in a score of 4; and irreversible VF in a score of 5.

Whole-cell patch clamp recording

Isolation of cardiac ventricular myocytes and patch clamp recordings. Ventricular myocytes were isolated by collagenase type 2 (Type II; Sigma, St. Louis, MO, USA) perfusion from normal adult rats as previously described (8). All steps were performed at 37˚C in solutions gassed with 95% O_2 + 5% CO_2. The ventricles were cut off, cut into small pieces and gently stirred in Tyrode's solution plus 1 mg/ml bovine serum albumin to collect ventricular myocytes.

Membrane currents were obtained and analyzed with an EPC-9 patch clamp amplifier (HEKA Electronik, Lambrecht, Germany) in the whole-cell mode by the Pulse/Pulsefit software program (HEKA Elektronik). Single cardiac ventricular myocytes were placed in the experimental chamber (1.5 ml) mounted on the stage of an inverted microscope (IX70; Olympus, Tokyo, Japan) and perfused with external solution including different concentrations of Wenxin Keli (1 and 10 g/l)

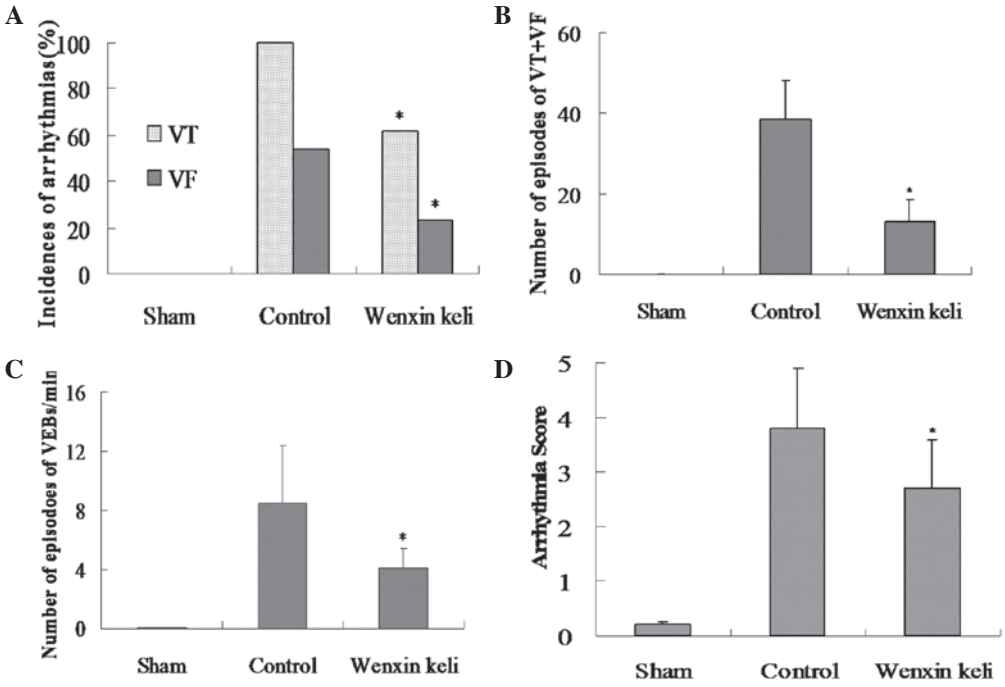

Figure 2. Effects of Wenxin Keli on ischemia-induced ventricular arrhythmias and the distribution of the arrhythmia score during 30-min ischemia in the sham, control and Wenxin Keli groups. (A) Incidence of VT and VF. (B) Number of episodes of VT+VF. (C) Number of episodes of VEBs/min. (D) Distribution of the arrhythmia score. *P<0.05 vs. the control group. VT, ventricular tachycardia; VF, ventricular fibrillation; VEB, ventricular ectopic beats.

for 5 min at a rate of 2-3 ml/min. The measurements were performed at room temperature (20-25˚C). Glass microelectrodes were made using two-stage pulling with a resistance of 3.0-5.0 MΩ on microelectrodes (PB-7; Narishige, Tokyo, Japan) filled with internal solution. The mean capacitance of the cells was 92.92±35.52 pF, and the series resistances were <25 MΩ. All currents were digitally sampled at 10 kHz, low-pass filtered at 1 kHz, and saved on a hard drive for post hoc analysis.

Measurement of $I_{Ca,L}$ and I_{to}. $I_{Ca,L}$ was recorded using a whole-cell patch clamp configuration. The pipette solution contained 120 mM CsCl, 1.0 mM $CaCl_2$, 5.0 mM $MgCl_2$, 5.0 mM Na_2ATP, 11 mM EGTA, 10 mM HEPES and 11 mM glucose, adjusted to pH 7.2 with CsOH. The external solution was Tyrode's solution (135 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1.0 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 10 mM HEPES and 10 mM glucose, adjusted to pH 7.35 with NaOH), including 1 or 10 g/l Wenxin Keli. In order to estimate the spontaneous decline of $I_{Ca,L}$ with time (run-down) during the first 5 min of recording, we added 5 mmol/l MgATP to the pipette solution and commenced data acquisition after 5-15 min of equilibration between the pipette solution and the intracellular contents.

The external solution used to record I_{to} contained 30 mM NaCl, 110 mM choline chloride, 5.4 mM KCl, 1.0 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 10 mM HEPES, 10 mM glucose and 0.3 mM CdCl, adjusted to pH 7.35 with NaOH. The pipette solution used to record I_{to} contained 45 mM KCl, 85 mM K-aspartate, 5 mM Na-pyruvate, 5.0 mM MgATP, 10 mM EGTA, 10 mM HEPES and 11 mM glucose, adjusted to pH 7.2 with KOH. HEPES, Na_2ATP, CsCl, EGTA and CsOH were purchased from Sigma. All the other chemicals were of analytical grade. Wenxin Keli was provided by the Shandong Buchang Pharmaceutical Company Co., Ltd. (Beijing, China).

Data analysis. All values were presented as the means ± SD. The incidence of VT and VF was compared using the Fisher's exact test, and the arrhythmia scores were analyzed with the Kruskal-Wallis test. Patch clamp data were analyzed using one-way analysis of variance (ANOVA). Statistical significance was defined as P<0.05.

Results

Ventricular arrhythmias during ischemia. The MBP and heart rate (HR) were continuously recorded during the experiments, and the average MBP and heart rate during the 30-min baseline and 30-min ischemia periods were calculated. No significant differences were found in the HR and MBP between the groups (P>0.05) at baseline. The MBP and heart rate after 30-min ligation were lower than those before 30-min ligation, but the differences were not statistically significant (P>0.05). In this model of ischemia, severe ventricular arrhythmias peaked at 0-30 min following coronary artery ligation. Fig. 1 shows the different ventricular arrhythmias during the 30-min ischemia.

Incidence of VT and VF and number of episodes of VT+VF. In the myocardial ischemia group, VT was observed in 100% (13/13) of the rat hearts, and 53.84% (7/13) of the hearts exhibited VF. The administration of Wenxin Keli attenuated the incidence of VT to 61.54% (8/13) and that of VF to 23.08% (3/13) compared with the control group (Fig. 2A). The number of episodes of VT+VF in the Wenxin Keli group (13.2±5.3) was significantly lower compared to that in the control group (38.4±9.8) (P<0.05) (Fig. 2B).

Number of episodes of VEBs/min and severity of arrhythmias. The number of episodes of VEBs/min in the Wenxin Keli

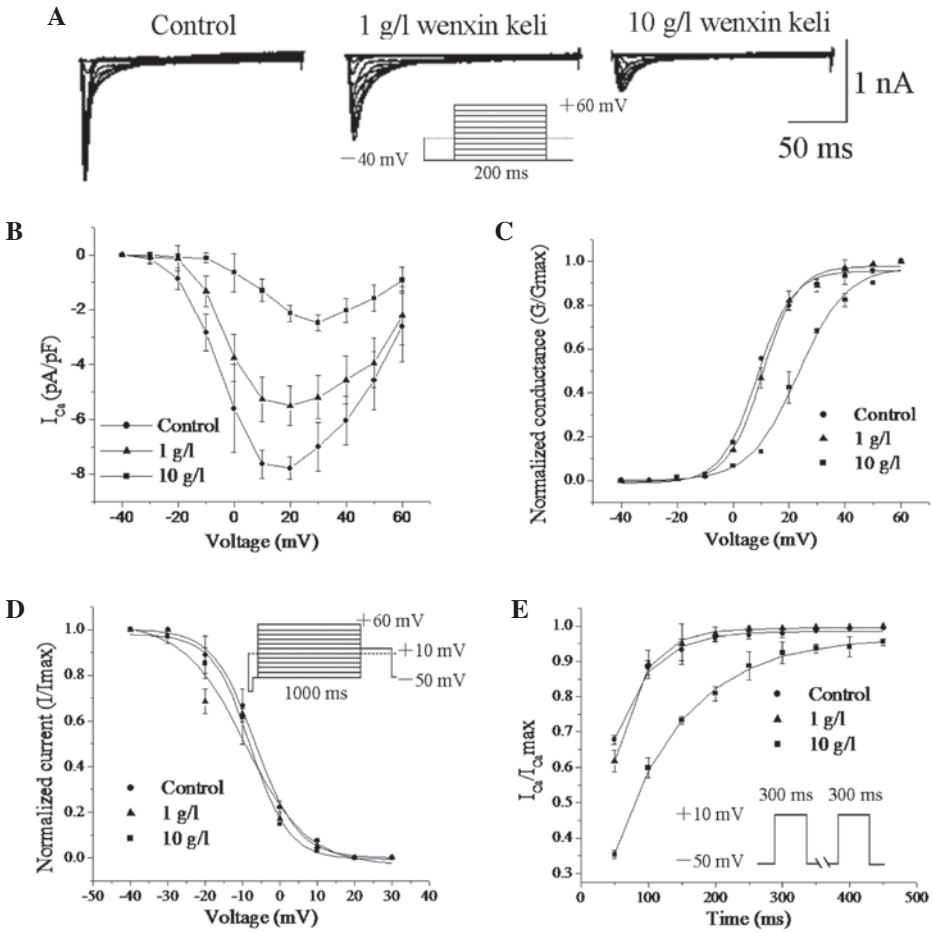

Figure 3. Effect of Wenxin Keli on $I_{Ca,L}$. (A) Original recordings of $I_{Ca,L}$ for the control, 1 and 10 g/l Wenxin Keli groups. (B) Current-voltage (I-V) correlation for $I_{Ca,L}$ in rat ventricular myocytes. (C) Mean values for the voltage dependence of the activation (G/Gmax) of $I_{Ca,L}$. Curves were fitted to the Boltzmann distribution. (D) Mean values for the voltage dependence of the inactivation (I/Imax) of $I_{Ca,L}$. Curves were fitted to the Boltzmann distribution. (E) Mean value curves for the recovery of $I_{Ca,L}$ following inactivation. Recovery curves were fitted to a mono-exponential function.

group (4.1±1.3) was significantly decreased compared to that in the control group (8.5±3.9) (P<0.05) (Fig. 2C). The severity of ventricular arrhythmias was significantly attenuated by Wenxin Keli (2.7±0.9) compared to the severity in the myocardial ischemia group (3.8±1.1) (P<0.05) (Fig. 2D).

Wenxin Keli inhibits $I_{Ca,L}$. Fig. 3A shows the voltage-dependent $I_{Ca,L}$ traces recorded in the absence and presence of Wenxin Keli (protocol, HP=-40, 200 ms pulses of voltages between -40 and +60 mV in 10 mV steps preceded by a 50 ms prepulse of -40 mV). Wenxin Keli markedly reduced the amplitude of $I_{Ca,L}$. The current-voltage (I-V) correlations for the $I_{Ca,L}$ density shown in Fig. 3B indicate that Wenxin Keli significantly inhibited $I_{Ca,L}$ at -10 to +60 mV in a concentration-dependent manner.

The activation conductance variable (G/Gmax) of $I_{Ca,L}$ was determined from the I-V relationship for each cell (Fig. 3B) and was fitted to the Boltzmann distribution to obtain the half activation (V0.5) and slope values. The V0.5 of $I_{Ca,L}$ activation positively shifted by 9.6 mV in the cells treated with 10 g/l of Wenxin Keli (12.78±8.7 mV in the control group to 22.38±5.1 mV in the Wenxin Keli group; n=5; P<0.05) (Fig. 3C), whereas no change was observed when using 1 g/l of Wenxin Keli. The values of the variables (I/Imax) for the voltage-dependent inactivation of $I_{Ca,L}$ were determined with the double-pulse protocol (a 1,000 ms prepulse of potentials between -50 and +60 mV in 10 mV steps, followed by a fixed 400 ms test pulse of 10 mV) (Fig. 3D), and these data were also fitted to the Boltzmann distribution. The V0.5 of $I_{Ca,L}$ inactivation was not significantly changed by the administration of Wenxin Keli.

The time-dependent recovery of $I_{Ca,L}$ following inactivation was studied with the double-pulse protocol consisting of two identical pulses (holding potential from -50 to +10 mV for 300 ms) in variable intervals from 50 to 500 ms in 50 ms increments (Fig. 3E). The recovery curves were fitted to a mono-exponential function. The recovery time constant of $I_{Ca,L}$ was slowed by 10 g/l Wenxin Keli (55.76±5.98 ms in control, 104.13±4.71 ms in 10 g/l; n=6; P<0.05), whereas no change was observed for 1 g/l Wenxin Keli (59.82±7.24 ms). These results demonstrate that Wenxin Keli inhibits $I_{Ca,L}$ by decelerating the activation process and delaying recovery from inactivation without changing the inactivation process.

Wenxin Keli inhibits I_{to}. Fig. 4A illustrates the voltage-dependent I_{to} trace in the absence and presence of Wenxin Keli (500 ms depolarization step pulses from -40 to +60 mV with a step size of 10 mV). Wenxin Keli at 10 g/l markedly reduced the amplitude of I_{to}. The I-V relationship for the I_{to} density, shown in Fig. 4B, indicated that Wenxin Keli inhibited I_{to} in a concen-

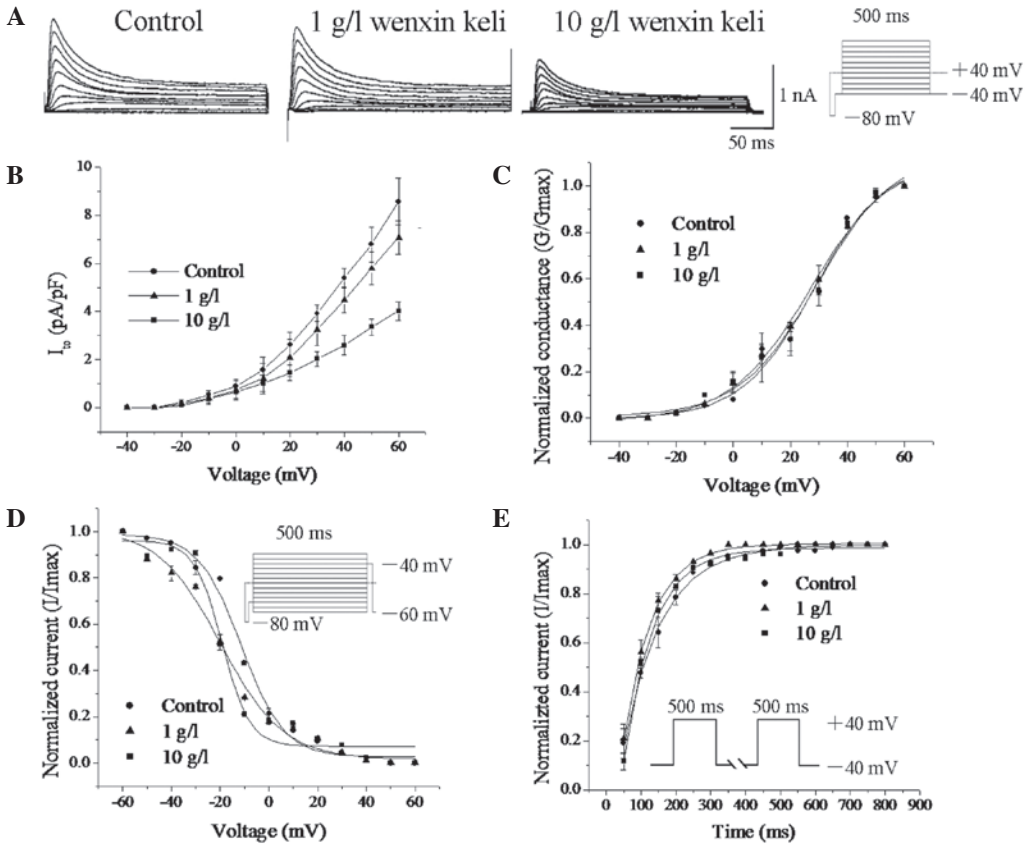

Figure 4. Effect of Wenxin Keli on I_{to}. (A) Original recordings of I_{to} for the control, 1 and 10 g/l Wenxin Keli groups. (B) I-V relationship for I_{to} in rat ventricular myocytes. (C) Mean values for the voltage dependence of the activation (G/Gmax) of I_{to}. Curves were fitted to the Boltzmann distribution. (D) Mean values for the voltage dependence of the inactivation (I/Imax) of I_{to}. Curves were fitted to the Boltzmann distribution. (E) Mean value curves for the recovery of I_{to} following inactivation. Recovery curves were fitted to a mono-exponential function.

tration-dependent manner. The peak amplitude decreased to 15.31±7.21% at 1 g/l and to 53.25±4.74% at 10 g/l (n=6, P<0.05).

By fitting the activation process of I_{to} to the Boltzmann distribution, we found that Wenxin Keli (1 and 10 g/l) had no significant effect on voltage-dependent activation (Fig. 4C). Steady-state inactivation was analyzed using a double-pulse protocol: a 1,000 ms prepulse of potentials between -60 and +60 mV in 10 mV steps, followed by a fixed 400 ms test pulse of +40 mV. The V0.5 of voltage-dependent inactivation was negatively shifted by treatment with Wenxin Keli (-11.30±2.6 mV for control, -19.75±3.02 mV for 1 g/l, and -19.21±4.15 mV for 10 g/l, n=6, P<0.05) (Fig. 4D).

Recovery of I_{to} after inactivation was investigated with a paired-pulse protocol (HP=-80 mV, a 500-ms conditioning pulse of +40 mV was separated from a 50-ms test pulse of -40 mV by a gradually prolonged recovery interval between 50 and 800 ms) (Fig. 4E), and the recovery curves were fitted with a mono-exponential function. No significant changes in the recovery time constants were observed. These results demonstrate that Wenxin Keli inhibits I_{to} by accelerating its inactivation without changing its activation process or recovery from inactivation.

Discussion

Ventricular arrhythmias, particularly spontaneous or induced ventricular tachyarrhythmias and fibrillation, are frequently observed post-infarction in various animal models of MI (9,10). The majority of sudden cardiac deaths are thought to be due to ventricular arrhythmias. Thus, the treatment of ventricular arrhythmias, particularly VF, is important in order to reduce the risk of sudden cardiac death post-infarction. In the present study, Wenxin Keli was shown to prevent ventricular arrhythmias *in vivo* following long-term administration in a rat model of MI. Our data also demonstrated that the antiarrhythmic effect of Wenxin Keli is associated with the inhibition of $I_{Ca,L}$ and I_{to}.

Traditional antiarrhythmic drugs may paradoxically precipitate lethal arrhythmias; these drugs occasionally intensify rather than inhibit arrhythmias (11,12). Basic research into the clinical application of traditional Chinese medicine has been conducted. It has been recognized worldwide that traditional Chinese medicine has broad clinical prospects due to its advantages with respect to multiple targets, significant efficacy and safety. Wenxin Keli is useful for treating functional arrhythmia and arrhythmia as a complication of infective cardiomyopathy in the elderly and children. It has been shown that the combined use of Wenxin Keli and amiodarone has a better effect on the conversion rate of AF, shortening the conversion time and decreasing the required dosage of amiodarone in treating AF, compared with treatment with amiodarone alone. The use of Wenxin Keli also protects against the adverse effects of the long-term use of amiodarone (13,14). In addition, Wenxin Keli is capable of greatly improving isoproterenol-induced cardiac dysfunc-

tion and protecting against aconitine-induced arrhythmia in rats (15). Moreover, Wenxin Keli produces atrial-selective depression of I_{Na}-dependent parameters in isolated canine coronary perfused preparations and effectively suppresses AF and prevents its induction (4,16). Therefore, it is implied that Wenxin Keli has good clinical prospects.

It is generally accepted that cardiac repolarization and refractoriness are determined by the balance of inward Ca^{2+} currents and outward K^+ currents. The L-type Ca^{2+} channel is considered to be the primary route for calcium influx into cardiac myocytes and an important determinant of calcium homeostasis. The increased $I_{Ca,L}$ may contribute to the prolongation of the action potential duration and increase the frequency of early afterdepolarizations (EADs), as demonstrated for L-type Ca^{2+} channel agonists (17-21). Pathological remodeling of the myocardium depends on the persistent activation of L-type calcium channels, which alters calcium homeostasis and is responsible for the induction of hypertrophic growth (22,23). In addition, more calcium entered the cell through the L-type Ca^{2+} channel during depolarization, leading to calcium overload and triggering cell death signals (24). I_{to} is a key regulator of phase one action potential repolarization and is the primary cause of spike-and-dome morphology (25). In addition, I_{to} is important in human ventricle repolarization. Its voltage-dependent activation and inactivation kinetics are much faster than those of other cardiac K currents. Increased I_{to} density may eliminate the plateau, which is the primary mechanism responsible for the occurrence and maintenance of VF. The data from our study demonstrate that Wenxin Keli significantly inhibits $I_{Ca,L}$ and I_{to} in adult rat ventricular myocytes. This substance reduced the amplitude of $I_{Ca,L}$, decelerated the activation process and slowed down its recovery from inactivation, whereas the inactivation process remained unaffected. In addition, Wenxin Keli inhibited I_{to} and accelerated its inactivation without changing the activation process or the recovery of its inactivation. These effects of Wenxin Keli on $I_{Ca,L}$ and I_{to} may be protective against cardiac fibrillation.

In conclusion, the present study demonstrates that Wenxin Keli attenuated ischemia-induced ventricular arrhythmias and inhibited $I_{Ca,L}$ and I_{to}. The regulation of $I_{Ca,L}$ and I_{to} contributed, at least in part, to the antiarrhythmic action of Wenxin Keli.

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