Research Article

The Electrophysiological Effects of Qiliqiangxin on Cardiac Ventricular Myocytes of Rats

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Qiliqiangxin, a Chinese herb, represents the affection in Ca channel function of cardiac myocytes. It is unknown whether Qiliqiangxin has an effect on Na current and K current because the pharmacological actions of this herb's compound are very complex. We investigated the rational usage of Qiliqiangxin on cardiac ventricular myocytes of rats. Ventricular myocytes were exposed acutely to 1, 10, and 50 mg/L Qiliqiangxin, and whole cell patch-clamp technique was used to study the acute effects of Qiliqiangxin on Sodium current ($I_{Na}$), outward currents delayed rectifier outward K+ current ($I_{K}$), slowly activating delayed rectifier outward K+ current ($I_{Ks}$), transient outward K+ current ($I_{to}$), and inward rectifier K+ current ($I_{K1}$). Qiliqiangxin can decrease $I_{Na}$ by 28.53% ± 5.98%, and its IC50 was 9.2 mg/L. 10 and 50 mg/L Qiliqiangxin decreased by 37.2% ± 6.4% and 55.9% ± 5.5% summit current density of $I_{to}$. 10 and 50 mg/L Qiliqiangxin decreased $I_{Ks}$ by 15.51% ± 4.03% and 21.6% ± 5.6%. Qiliqiangxin represented a multifaceted pharmacological profile. The effects of Qiliqiangxin on Na and K currents of ventricular myocytes were more profitable in antiarrhythmic therapy in the clinic. We concluded that the relative efficacy of Qiliqiangxin was another choice for the existing antiarrhythmic therapy.

1. Introduction

The traditional Chinese herbs have been proven safe and efficient in the management of some diseases including arrhythmia since ancient times. Presently, there are four main classes of antiarrhythmic agents in clinical therapy. Three classes of them act on ion channels. As for the Chinese herb—Qiliqiangxin—few know the mechanism of antiarrhythmia. How does it impact on ion channels? Qiliqiangxin capsule is the developed Chinese herbs, which includes over 11 ingredients such as Ginseng, Radix Astragali, Aconite Root, Salvia miltiorrhiza, and Semen Lepidii Apetalii. It was proved to be effective and safe by phase 3 clinic trial for the treatment of patients with chronic heart failure [1, 2]. Qiliqiangxin capsule also can improve heart function and decrease serum level of TNF-α and relieve inflammatory cell infiltration of myocardium in rats with adriamycin induced cardiomyopathy [3]. In our previous study, Qiliqiangxin affected L-type Ca2+ channel and blocked $I_{Ca-L}$, as well as affected cardiac function finally. Qiliqiangxin has diphasic action that is either class IV antiarrhythmic agent or the agent for treating chronic heart failure [4, 5]. It is unknown whether Qiliqiangxin has an effect on Na current and K current because the pharmacological actions of this herb's compound are very complex. In this research, we compared the acute effects of Qiliqiangxin on the inward currents $I_{Na}$ and outward currents $I_{K}$, $I_{Ks}$, $I_{to}$, and $I_{K1}$ of ventricular myocytes and hoped to demonstrate the rational usage of Qiliqiangxin.
2. Material and Methods

2.1. Vegetal Material. Qiliqiangxin consists of Ginseng, Radix Astragali, Aconite Root, Salvia miltiorrhiza, Semen Lepidii Apetalii, Cortex Periplocae Sepii Radics, Rhizoma Alismatis, Carthamus tinctorius, Polygonatum Odorati, Seasoned Orange Peel, and Ramulus Cinnamomi [3] (Yiling Pharmaceutical Corporation, Shijiazhuang, China). The drug powder dissolved with sterile water at the concentration of 2.67 g/mL. 1 mg/L, 10 mg/L, and 50 mg/L Qiliqiangxin were prepared for the study.

2.2. Study Models. A total of 26 healthy Sprague-Dawley rats (9–11 weeks old, either sex, weight 210 to 300 g) were used in the study. All the rats used in the following experiments were subject to the Guiding Principles for the Care and Use of Laboratory Animals and the Recommendations from the Declaration of Tongji University. Cardiac ventricular myocytes were isolated from the hearts of rats using previous protocols [6]. Briefly, hearts were quickly excised and cross-perfused with low calcium Tyrode’s solution containing 0.08% collagenase, 0.006% protease, and then we get a single ventricular myocyte. The single ventricular myocyte selected for study is rod shaped and had clear striations and smooth and glossy surface.

2.3. Whole Cell Patch Clamp. We recorded that Na current in the external solution contained (mmol/L) Choline-Cl 145, KCl 5, MgCl₂ 1, EGTA 5; pH was adjusted to 7.3 with LiOH. The pipette solution contained (mmol/L) CsCl 140, NaCl 10, HEPES 10, and Glucose 10; pH was adjusted to 7.4 with CsOH. The inward currents density of $I_{K1}$ was elicited from the holding potential of $-56.46 \pm 4.88$ to $-37.2 \pm 6.4 \%$ and its IC$_{50}$ was 9.2 mg/L (Figure 1). Hypoconcentration (1 mg/L) Qiliqiangxin had no effects on $I_{Na}$ inward, while hyperconcentration Qiliqiangxin can decrease $I_{K1}$ inward, and its IC$_{50}$ was 28.53 \% ± 5.98 \% and its IC$_{50}$ was 9.2 mg/L (Figure 1).

3. Result

3.1. Current Density. The inward currents density of $I_{Na}$ in cardiac ventricular myocytes (pA/pF, n = 10) was $-56.46 \pm 4.88$. The outward current densities of $I_{K1}$, $I_{Ks1}$, $I_{Kt}$, and $I_{Ks}$ (pA/pF, n = 8) were $7.27 \pm 0.95$, $5.68 \pm 0.56$, $5.12 \pm 0.78$, $-22.82 \pm 5.34$ (pK1 inward), and $10.16 \pm 0.20$ (pK1 outward).

3.2. Effects of Qiliqiangxin on $I_{Na}$, $I_{Kt}$, $I_{KD}$, and $I_{K1}$. 1 Mg/L Qiliqiangxin can decrease $I_{Na}$ of ventricular myocytes by 28.53 % ± 5.98 %, and its IC$_{50}$ was 9.2 mg/L (Figure 1). Hypoconcentration (1 mg/L) Qiliqiangxin had no effects on $I_{Na}$ on ventricular myocytes, while hyperconcentration Qiliqiangxin had inhibition action. 10 and 50 mg/L Qiliqiangxin decreased by 37.2 % ± 6.4 % and 55.9 % ± 5.5 % summit current density of $I_{Na}$ (Figure 2). For $I_{K1}$, the difference concentration of Qiliqiangxin had no effects on $I_{K1}$.

Delayed rectifier $K^+$ current ($I_{K1}$) is the major outward current responsible for ventricular repolarization. 1, 10, and
From our previous study, Qiliqiangxin has diphasic action that is either class IV antiarrhythmic agent or the agent for treating chronic heart failure [5]. Qiliqiangxin includes over 11 ingredients. The mechanism of the antiarrhythmic action is complex and not completely understood. It should be contacted with Radix Astragal, Aconite Root, and Shensongyaxin. Radix Astragali effectively protected against cardiac dysfunctional [7]. Aconite Root was proved to have positive inotropic and chronotropic action c [8]. Shensongyaxin capsule was reported to effectively block $I_{Ca-L}$ [9]. There were four main classes of antiarrhythmic agents in Vaughan Williams’ classification. Qiliqiangxin affected L-type $Ca^{2+}$ channel and blocked $I_{Ca-L}$. It should be a class IV agent. Does Qiliqiangxin have an effect on other currents, such as Na current and K currents, because of its antiarrhythmic action? We had introduced Qiliqiangxin to test Na current and K currents. Interestingly, 1mg/L Qiliqiangxin can decrease $I_{Na}$ of ventricular myocytes by 28.53% ± 5.98%, and its IC50 was 9.2 mg/L. K currents are outward currents that repolarize the ventricular myocyte are numerous and complex and there is substantial interspecies variation in the profile of repolarizing currents. Prominent Ito currents have been recorded in ventricular myocytes isolated from the hearts of many species, including mice, rats, rabbits, cows, cats, dogs, ferrets and humans. In ventricular myocytes of rat, 10 and 50 mg/L Qiliqiangxin decreased by 37.2% ± 6.4% and 55.9% ± 5.5% summit current density of $I_{K1}$, 1, 10, and 50 mg/L Qiliqiangxin decreased current density of $I_{K}$ by 20.98% ± 3.97%, 31.18% ± 5.1% and 61.52% ± 5.97%. 10 and 50 mg/L Qiliqiangxin decreased by 15.51% ± 4.03% and 21.6% ± 5.6% current density of $I_{K}$, Acute Qiliqiangxin application can inhibit $I_{Na}$ and $I_{K}$, 10 and 50 mg/L Qiliqiangxin had little effects on $I_{K}$, and the resting membrane potential was not affected by it. Qiliqiangxin represented class I and IV antiarrhythmic agents. It can prolong QT interval, but it does not have a similar deleterious effect as pure class III compounds. Therefore, Qiliqiangxin represented a multifaceted pharmacological profile.

During the last decade, antiarrhythmic strategies have changed dramatically. In general, class I agents have the potential to increase mortality in patients with significant structural heart disease even though they may suppress cardiac arrhythmias. Class III and IV agents did not decrease the outcomes in clinic obviously. Qiliqiangxin is as one developed Chinese herbs, which expressed the inhibition of $I_{Na}$, $I_{Ca-L}$, and multi $K^{+}$ channels. The effects of Qiliqiangxin on ventricular myocytes were more profit in clinic therapy. It is the most promising drug because of the relative efficacy and safety. Even though the mechanism of the antiarrhythmic action of Qiliqiangxin is complex and not completely understood, Qiliqiangxin is another choice for antiarrhythmic therapy at least. As for the further action in clinic of this antiarrhythmic agent, we need more research in the future.

**Authors’ Contribution**

Yidong Wei and Xiaoyu Liu are co-first authors.
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