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Effect of amiodarone on Kv1.4 channel C-type inactivation: comparison of its effects with those induced by propafenone and verapamil

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As the major component of $I_{to\ (slow)}$, Kv1.4 channel plays an important role in repolarization of cardiac myocytes. C-type inactivation is one of Kv1.4 inactivation and can be affected by open channel blockers. We used the two-electrode voltage clamp technique to observe the effect of amiodarone on Kv1.4 C-type inactivation and compare amiodarone's effects on Kv1.4 with propafenone and verapamil. Our data show that those three antiarrhythmic drugs blocked fKv1.4ΔN (N-terminal deleted Kv1.4 channel from ferret heart) in voltage- and frequent-dependent manners. The amiodarone's IC_{50} was 489.23 $\pm$ 4.72 μM, higher than that of propafenone (98.97 $\pm$ 1.13 μM) and verapamil (263.26 $\pm$ 6.89 μM) for fKv1.4ΔN channel (+50 mV). After application of amiodarone, propafenone and verapamil, fKv1.4ΔN inactivation becomes bi-exponential: the faster portion of inactivation (drug-induced inactivation) and the slower portion of inactivation (C-type inactivation). Amiodarone and verapamil fastened C-type inactivation in fKv1.4ΔN, but propafenone did not. Unlike propafenone that had no effect on fKv1.4ΔN recovery, amiodarone and verapamil slowed recovery in fKv1.4ΔN.

1. Introduction

Transient outward potassium (K^+) current (I_{to}) is important in initiating and modulating repolarization of the cardiac action potential (Campbell et al. 1993; Greenstein et al. 2000). At least two types of I_{to} were found so far. The first one is $I_{to\ (fast)}$ displaying fast recovery kinetics and associating with no obvious accumulated inactivation. The second one is $I_{to\ (slow)}$ that demonstrates slow recovery kinetics and is related to the accumulated inactivation (Wettwer et al. 1994). Recently, molecular biology studies show that Kv4.2 and Kv4.3 encode $I_{to\ (fast)}$ and Kv1.4 encodes $I_{to\ (slow)}$. They are distributed in sub-epicardium and sub-endocardium respectively in mammalian hearts (Brahmajothi et al. 1999; Nerbonne 2000).

Unlike Kv4 channels (Wang et al. 2005), mammalian Kv1.4 channel inactivation is governed by N- and C-type inactivation (Hoshi et al. 1990). In general, N-type inactivation is faster and induced through a mechanism in which a small group of amino acids in the N terminus bind to the activated channel and occlude the intracellular mouth of the channel; while C-type inactivation is slower and generated by a mechanism in which the external mouth of the channel becomes occluded through the conformational changes (Rasmusson et al. 1998). However, C-type inactivation is more rapid in the presence of N-type inactivation (Rasmusson et al. 1998). We and others (Rasmusson et al. 1998; Baukrowitx and Yellen 1995; Li et al. 2003; Wang et al. 1997; Wang et al. 2003) previously reported that alterations of C-type inactivation by increasing $[K^+]_o$ as well as mutation at external or internal mouth of the pore that slowed C-type inactivation also modulated the channel binding affinity for open channel blockers in hERG (human ether-à-go-go related gene) and Kv1.4 channels.

Amiodarone is a potassium channel blocker and widely used in patients suffering from arrhythmias. Even though it was reported that amiodarone inhibits several types of K^+ channels (Kamiya et al. 2001; Sato et al. 2003; Rolf et al. 2000) its effect on Kv1.4 C-type inactivation is still unknown.

In this paper we will (1) study the properties of amiodarone blockage of fKv1.4ΔN channel, an N-terminal deleted Kv1.4 channel; (2) study the effect of amiodarone on Kv1.4 C-type inactivation; (3) compare the electrophysiological effects of amiodarone on fKv1.4ΔN with those of propafenone and verapamil.

2. Investigation and results

2.1. Voltage-, concentration- and frequency-dependent blockage of fKv1.4 channel induced by amiodarone

fKv1.4ΔN cDNA (GenBank accession no. U06156) was from Dr. Rasmusson's laboratory, University at Buffalo, State University of New York, USA. The construct and sequence of fKv1.4ΔN cDNA used in this study have been previously described (Li et al. 2003; Comer et al. 1994). Removal of residues 2–146 from the N-terminal domain results in the loss of the fast component of inacti-

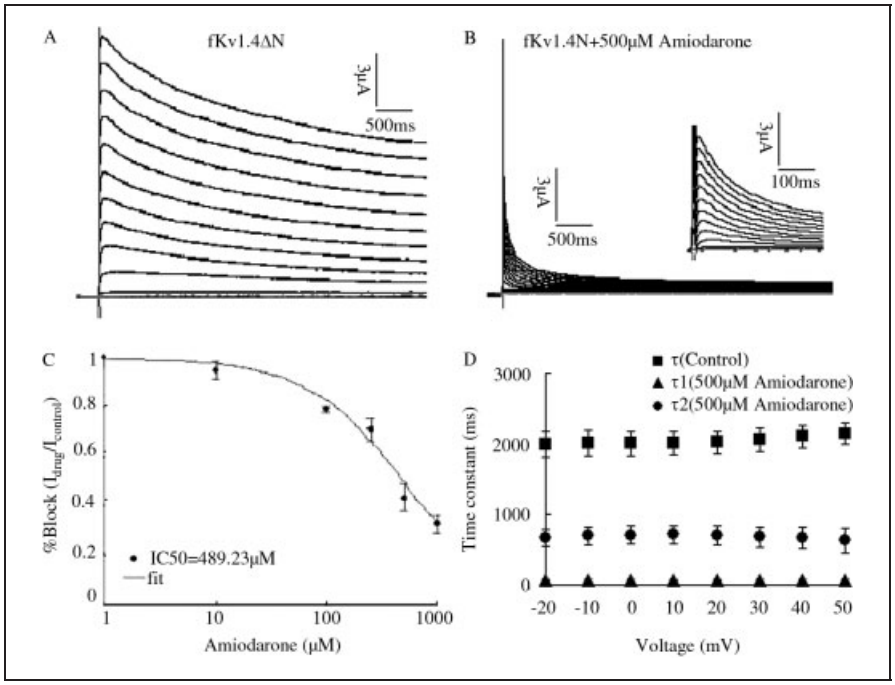

Fig. 1:
Amiodarone induced dose-dependent blockage of fKv1.4ΔN and fastened fKv1.4ΔN inactivation. Panel A and B: fKv1.4ΔN currents were induced by a series of depolarizing pulses from −100 mV to +50 mV (holding potential: −90 mV) for 5 s (10 mV for each increment) in control and after 500 μM amiodarone treatment. The current traces were expended to show the peak of the current for the inset in Panel B. Panel C: the dose-dependent inhibition of fKv1.4ΔN. The peak currents (+50 mV) were normalized to the maximum peak current under control condition and plotted against amiodarone concentrations (0, 10, 100, 250, 500, 1000 μM, $n = 3 \sim 5$). The curves were derived by fitting the mean data to the equation: $f = Kd/(Kd + D)$, where f is fractional current, Kd is the apparent dissociation constant (i.e., IC_{50}) and D is the drug concentration. Panel D: fKv1.4ΔN inactivation time constants are plotted again depolarizing voltages before and after 500 μM amiodarone treatment

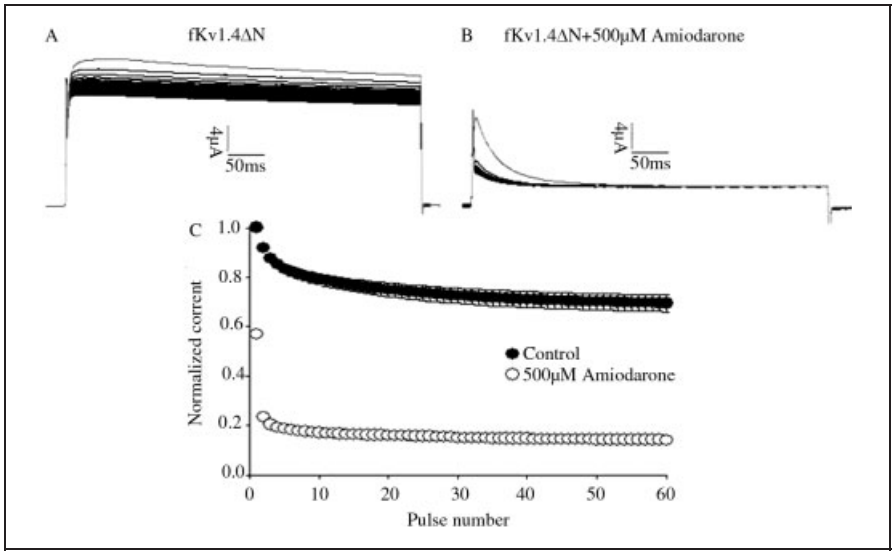

Fig. 2:
Frequency-dependent block of fKv1.4ΔN channel induced by amiodarone. The currents were induced by a series of 500 ms depolarizing pulses from −90 to +50 mV with a frequency of 1 Hz for a period of 1 min. Panel A and B: the currents traces before and after amiodarone perfusion in fKv1.4ΔN. Panel C: the normalized current. The peak currents were normalized to the maximum peak current under control condition and plotted against pulse number

vation but leaves C-type inactivation. C-type inactivation was slower under the influence of the depolarizing potentials (Fig. 1A). Amiodarone 500 μM markedly reduced fKvΔ1.4 channel current (Fig. 1B). The voltage-dependence of amiodarone blockage was found during the experiment (data not shown). Figure 1C shows the concentration-dependent reduction of fKv1.4ΔN current induced by amiodarone. The calculated apparent dissociation constant (i.e., IC_{50}) was 489.23 ± 4.72 μM ($n = 3 \sim 5$).
Frequent-dependent block of fKv1.4ΔN channels induced by amiodarone can be identified in Fig. 2. The currents generated by a train of stimulating pulses are shown in Fig. 2A (control) and Fig. 2B (500 μM amiodarone). The current induced by the first pulse of the pulse train in the presence of 500 μM amiodarone was dramatically decreased comparing with that in the pre-drug control (Fig. 2C) and then quickly reached a steady-state level, when the cell was continuously stimulated at 1 Hz. All these behaviors reflected the process of 500 μM amiodarone blocking fKv1.4ΔN (at +50 mV).

2.2. Effects of amiodarone on channel inactivation and recovery

Because of the deletion of its N-terminal, fKv1.4ΔN inactivation was mono-exponential. Its inactivation was slower with a time constant of $2{,}137.81 \pm 151.63$ ms in control (Fig. 1A, at +50 mV, $n = 4$). It became bi-exponential and both of the inactivation components gradually faster when amiodarone concentration increased (10 μM, 100 μM, 250 μM, 500 μM, 1000 μM respectively, $n = 3 \sim 5$, data not shown). In the presence of 500 μM amiodarone (Fig. 1B), the time constant τ_1 was 71.11 ± 13.01 ms and τ_2 was 630.44 ± 178.16 ms (Fig. 1D, at +50 mV, $n = 4$). The faster inactivation dominated fKv1.4ΔN inactivation. In addition, the inactivation time constants from both groups are not voltage-dependent at positive depolarizing potentials which is consistent with that reported in the literature (Hoshi et al. 1990) (Fig. 1D).
We also examined the effect of amiodarone on fKv1.4ΔN recovery from inactivation with a standard two-pulse pro-

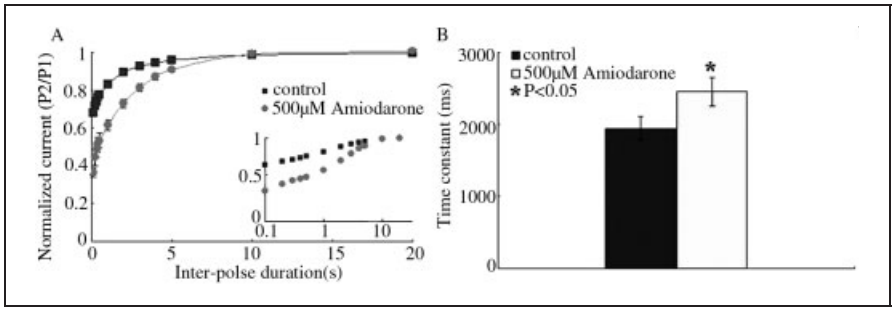

Fig. 3: Effect of amiodarone on fKv1.4ΔN recovery from C-type inactivation. The membrane was depolarized to +50 mV from the holding potential −90 mV for 5 s (P1) followed by a second pulse (P2) to +50 mV for 1 s with variable inter-pulse durations (inter-pulse potential was −120 mV, n = 5). The inter-pulse durations were set as the following: 0.1 s, 0.2 s, 0.3 s, 0.4 s, 0.5 s, 1 s, 2 s, 3 s, 4 s, 5 s, 10 s and 20 s. The peak currents induced by P2 were normalized to peak current induced by P1 and plotted against inter-pulse duration. Panel A: normalized current of recovery from inactivation. The curves were derived by fitting the mean data to the equation: $f = 1 - A^* \exp(-\tau/t)$, where A is current amplitude, τ is time constant and t is duration. Insert: the same data were normalized between 0 and 1 and plotted against inter-pulse duration expressed as a log scale. Panel B: recovery time constants for control and 500 μM amiodarone treated

tocol (Fig. 3). Amiodarone (500 μM) slowed fKv1.4ΔN recovery from inactivation. The 50% recovery time was 1,028.65 ± 154.27 ms for control and it was 1,531.38 ± 114.38 ms for drug-treated group ($n = 5$; $p < 0.05$, Fig. 3A) and also, the recovery time constant was 1,827.16 ± 124.90 ms in control and 2,507.27 ± 192.86 ms after 500 μM amiodarone treated (interpulse potential −120 mV, $n = 5$; $P < 0.05$, Fig. 3B).

2.3. Effects of propafenone and verapamil on fKv1.4ΔN channel inactivation

Voltage- and frequency-dependent blockage of fKv1.4ΔN induced by propafenone and verapamil was observed in this study (data not shown). Like amiodarone, 100 μM propafenone (Figs. 4A and B) and 250 μM verapamil (Figs. 5A and B) also dramatically inhibited fKv1.4ΔN channel currents, which were in a concentration-dependent manner. The apparent dissociation constants were 98.97 ± 1.13 μM for propafenone (Fig. 4C, $n = 3 \sim 5$) and 263.26 ± 6.89 μM for verapamil (Fig. 5C, $n = 3 \sim 5$).

The effects of propafenone and verapamil on fKv1.4ΔN inactivation were monitored in this study. The alteration of fKv1.4ΔN inactivation from mono-exponential to bi-exponential was evidenced. In control, the inactivation time constants (+50 mV) was 2,348.88 ± 66.48 ms and after using 100 μM propafenone the faster inactivation component (τ_1) was 446.43 ± 17.71 ms and the slower inactivation component (τ_2) was 2,246.71 ± 131.09 ms ($n = 3$, $P > 0.05$, compared with control). While the inactivation time constant (+50 mV) was 2,193.77 ± 40.44 ms in control; τ_1 was 22.65 ± 4.15 ms and τ_2 was 334.67 ± 80.76 ms after 250 μM verapamil application ($n = 3$, $P < 0.01$ compared with control).

The effects of propafenone and verapamil on recovery from inactivation were observed (at −120 mV). The 50% recovery time was 997.04 ± 46.60 ms for control and 1,256.38 ± 147.72 ms after 100 μM propafenone treatment ($n = 4$; $p > 0.05$). Application of 250 μM verapamil slowed the rate of recovery from inactivation as the 50% recovery time was 1,015.08 ± 92.99 ms in control and 1,834.57 ± 187.35 ms with verapamil ($n = 4$; $p < 0.05$).

3. Discussion

We have characterized the effects of amiodarone on fKv1.4ΔN in this study. Amiodarone inhibits fKv1.4ΔN in voltage-, frequency- and concentration-dependent man-

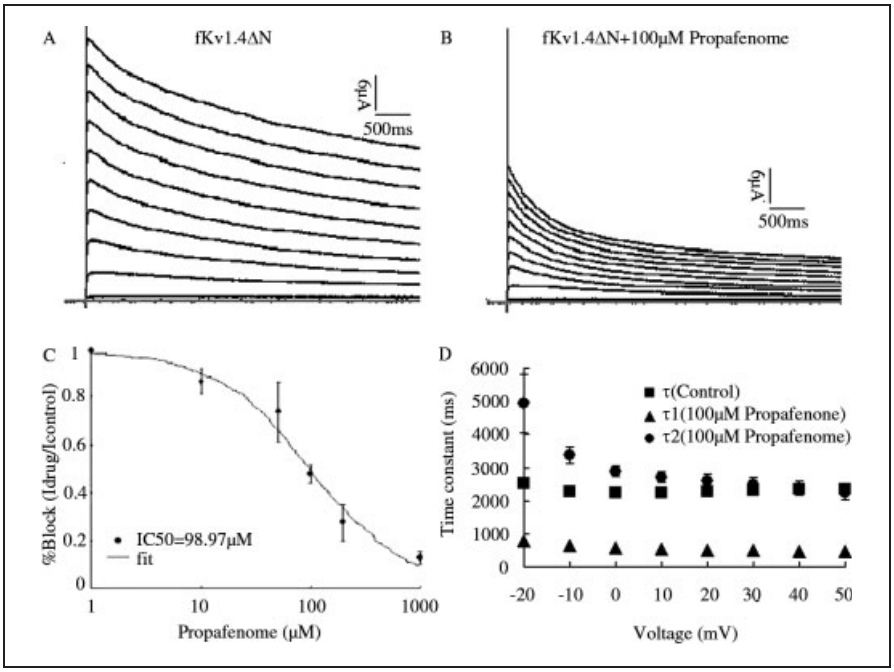

Fig. 4:
Propafenone induced dose-dependent blockage of fKv1.4ΔN and fastened fKv1.4ΔN inactivation. Panel A and B: fKv1.4ΔN current traces were derived by a series of depolarizing pulses from −100 mV to +50 mV (holding potential: −90 mV) for 5 s (10 mV for each increment) in control and after application of 100 μM propafenone. Panel C: the dose-dependent inhibition of fKv1.4ΔN. The peak currents (+50 mV) were normalized to the maximum peak current under control condition and plotted against propafenone concentrations (0, 10, 50, 100, 200, 1000 μM, $n = 3 \sim 5$). The curves were derived by fitting the mean data to the equation: $f = Kd/(Kd + D)$, where f is fractional current, Kd is the apparent dissociation constant (i.e., IC_{50}) and D is the drug concentration. Panel D: fKv1.4ΔN inactivation time constants are plotted again depolarizing voltages before and after 100 μM propafenone

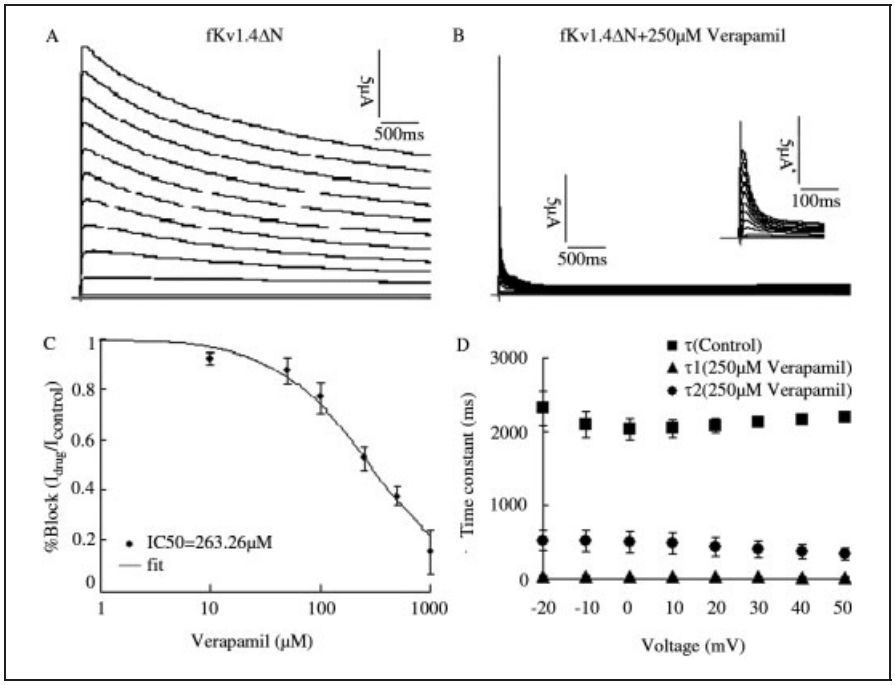

Fig. 5:
Verapamil induced dose-dependent blockage of fKv1.4ΔN and fastened fKv1.4ΔN inactivation. Panel A and B: fKv1.4ΔN currents were induced by a series of depolarizing pulses from −100 mV to +50 mV (holding potential: −90 mV) for 5 s (10 mV for each increment) in control and after 250 μM verapamil. The current traces were expended to show the peak of the current (Panel B inset). Panel C: the dose dependent inhibition of fKv1.4ΔN. The peak currents (+50 mV) were normalized to the maximum peak current under control condition and plotted against verapamil concentrations (0, 10, 50, 100, 250, 500, 1000 μM, $n = 3 \sim 5$). The curves were derived by fitting the mean data to the equation: $f = Kd/(Kd + D)$, where f is fractional current, Kd is the apparent dissociation constant (i.e., IC_{50}) and D is the drug concentration. Panel D: fKv1.4ΔN inactivation time constants are plotted again depolarizing voltages before and after 250 μM verapamil

ners. We found that amiodarone altered fKv1.4ΔN inactivation i.e., the originally single exponential inactivation became bi-exponential: the extremely fast drug-induced inactivation and relatively slower C-type inactivation. However, C-type inactivation is 3.4-fold faster than its control. The explanation is that binding of amiodarone to the intracellular site of the channel triggers the conformational change at external mouth of the pore that facilitates C-type inactivation. This phenomenon was also observed in the same channel induced by quinidine (Wang et al. 2003). Even though it is reported that amiodarone blocks many kinds of native and cloned K^+ channels such as I_{kur}, Kv1.2, Kv1.3, Kv1.4, hERG, KvLQT1+minK and K_{ATP} (Kamiya et al. 2001; Sato et al. 2003; Rolf et al. 2000; Yue et al. 2000; Zhang et al. 1999; Rauer and Grissmer 1999; Yamagishi et al. 1995), this paper is the first to verify the relationship between amiodarone binding and Kv1.4ΔN C-type inactivation.

Amiodarone, propafenone and verapamil are different types of antiarrhythmic drugs (amiodarone belongs to type III and propafenone is type I antiarrhythmic drugs, while verapamil is a type IV antiarrhythmic drug). The electrophysiological effects of those three drugs on fKv1.4ΔN inactivation were determined. All three compounds decrease fKv1.4ΔN current in voltage-, concentration- and frequency-dependent manners. However, differences among those compounds were discovered. First, propafenone has a higher, verapamil has a median and amiodarone has a lower binding affinity to fKv1.4ΔN channel (at +50 mV). Second, after application of amiodarone, propafenone and verapamil, fKv1.4ΔN inactivation becomes bi-exponential: the faster portion of inactivation (drug-induced inactivation) and the slower portion of inactivation (C-type inactivation). It is interesting to find that amiodarone and verapamil facilitate C-type inactivation. However, propafenone has no effect on it, demonstrating that binding of propafenone to the channel does not induce the conformation change at the external mouth of the pore. Third, amiodarone and verapamil slow the recovery from inactivation, but propafenone has no effect on it.

In clinical, amiodarone is widely used as an anti-arrhythmic drug, which is used to treat tachyarrhythmia originated from both atrium and ventricle. It is believed that amiodarone prolongs action potential duration due to (1) the blockage of hERG and KvLQT1+mink channels leading to action potential phase III prolongation as described in the literature and (2) as we demonstrate in this study, the blockage of Kv1.4. Since Kv1.4 encodes I_{to} which is a major contributor to phase 1 and early part of phase 2 of the action potential, the magnitude of I_{to} determines the magnitude of repolarization during phase 1 and as a result, the subsequent contribution of other voltage-gated current during the remainder of the action potential (Strauss et al. 2001). Therefore, a reduction of Kv1.4 induced by amiodarone prolongs action potential duration as well.

Kv1.4 channel inactivation is involved in N- and C-types. Since the basic biophysical mechanisms underlying C-type inactivation in voltage-gated K^+ channel are reportedly applicable to other channel types such as Na^+ and Ca^{++} channels (Wang and Wang, 1997; Balser et al. 1996; Zhang et al. 1994), it is of great significance to study the effects of the antiarrhythmic drugs on C-type inactivation.

Amiodarone is a potassium channel blocker, propafenone is a sodium channel blocker and verapamil is a calcium channel blocker. We found in this study that all those three compounds depress Kv1.4ΔN channel. Since amiodarone, propafenone and verapamil have different antiarrhythmic effects, especially as a calcium antagonist, verapamil is also widely used as an anti-hypertension drug, their blockage actions on Kv1.4ΔN channel need to be addressed when amiodarone is applied in combination with propafenone to a patient suffering from complicated arrhythmia or when amiodarone is applied in combination with verapamil to patients suffering from arrhythmia accompanied by hypertension.

4. Experimental

Mature female *Xenopus laevis* were used in this study. Frogs were anesthetized by immersion in tricaine solution (1 g/l, Sigma). Oocytes were removed from the frog's abdomen as described previously in detail (Wang et al. 1997). All procedures were approved by the Institutional Animal Care and Use Committee of Wuhan University. Oocytes were digested by

placing them in a collagenase-containing, Ca^{++}-free OR2 solution (mM: 82.5 NaCl, 2 KCl, 1 $MgCl_2$ and 5 HEPES, adjusted to pH 7.4 with NaOH; 1 mg/ml collagenase, type I; Sigma). The oocytes were gently shaken for 1.5–2 h, with the enzyme solution refreshed at 1 h. Defolliculated oocytes (stage V–VI) were injected with up to 50 ng cRNA using a microinjection system (Nanoliter 2000, WPI Co., FL USA) and incubated at 18 °C for 24–72 h in a Barth's solution (mM: 88 NaCl, 1 KCl, 2.4 $NaHCO_3$, 0.82 $MgSO_4$, 0.33 $Ca(NO_3)_2$, 0.41 $CaCl_2$ and 10 HEPES, adjusted to pH 7.4 with NaOH) with 2% (v/v of 100 X stock) antibiotic-antimycotic (Sigma).

Oocytes were clamped using a two-microelectrode bath clamp amplifier (CA-1B, DAGAN Corp., MN USA). Microelectrodes were fabricated from 1.5 mm o.d. borosilicate glass tubing (TW150F-4, WPI) using a two stage puller (PUL100, WPI Co., FL USA) to produce electrodes with resistances of 0.6–1.5 MΩ when filled with 3M KCl. During recording, oocytes were continuously perfused with control solution (mM: 96 NaCl, 2 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$ and 10 HEPES, adjusted to pH 7.4 with NaOH). Whenever amiodarone, propafenone and verapamil were used, 10 min of perfusion was used to allow equilibration of drugs with the oocyte. After this wash-on period, a series of 500 ms depolarizing pulses (from −90 to +50 mV at a frequency of 1 Hz for 1 min) was employed to ensure steady-state block before beginning experimental protocols. Currents were recorded at room temperature (21–23 °C) and were filtered at 2.5 kHz.

Data were recorded on a computer installed with pClamp 9 software and were analyzed with Clampfit 9 (Axon instruments, CA USA) and Microsoft Excel (Microsoft, WA USA). Unless otherwise stated, raw data traces from two-electrode voltage-clamp recordings were not leakage or capacitance subtracted. The pulse protocols and equations used to fit the data are given in each figure legend. Data are shown as means ± SEM. Confidence levels were calculated using Student's paired t test, and significance was accepted at the level of $P < 0.05$.

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