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Block of the human *ether-a-go-go*-related gene (hERG) K^+ channel by the antidepressant desipramine

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ABSTRACT

Desipramine is a tricyclic antidepressant for psychiatric disorders that can induce QT prolongation, which may lead to *torsades de pointes*. Since blockade of cardiac human *ether-a-go-go*-related gene (hERG) channels is an important cause of acquired long QT syndrome, we investigated the acute effects of desipramine on hERG channels to determine the electrophysiological basis for its pro-arrhythmic potential. We examined the effects of desipramine on the hERG channels expressed in *Xenopus* oocytes using two-microelectrode voltage-clamp techniques. Desipramine-induced concentration-dependent decreases in the current amplitude at the end of the voltage steps and hERG tail currents. The IC_{50} for desipramine needed to block the hERG current in *Xenopus* oocytes decreased progressively relative to the degree of depolarization. Desipramine affected the channels in the activated and inactivated states but not in the closed states. The S6 domain mutations, Tyr-652 located in the S6 domain of the hERG channel reduced the potency of the channel block by desipramine more than a mutation of Phe-656 in the same region. These results suggest that desipramine is a blocker of the hERG channels, providing a molecular mechanism for the arrhythmogenic side effects during the clinical administration of desipramine.

1. Introduction

It has long been recognized that some psychotropic drugs, including neuroleptics, antipsychotics, antidepressants, stimulants, and antianxiety agents, can be associated with risks of cardiac arrhythmia and sudden death [1]. Desipramine was the first successful antidepressant and has been widely used for the treatment of depression and other psychiatric disorders, such as panic and obsessive–compulsive disorders, bulimia nervosa, and chronic pain disorder [2]. Inhibition of norepinephrine and/or serotonin (5-hydroxytryptamine (5-HT)) transporters by antidepressants in the brain is generally thought to have important implications in their therapeutic effects [2]. Desipramine belongs to a group of psychotropic compounds called tricyclic antidepressants that have similar chemical structures and share a variety of pharmacologic actions [3]. Tricyclic antidepressants are known to inhibit calcium currents in heart myocytes and in neurons [4]. Neuronal sodium channels are ubiquitous and are crucial in dendritic integration, action potential initiation, and conduction. The potency of tricyclic antidepressants as sodium channel inhibitors was shown by the low micromolar IC_{50} values in vitro, and by their in vivo efficiency against neuropathic pain [5]. The cardiovascular effects and toxicity of tricyclic antidepressants have been well documented in depressed patients without pre-existing cardiac disease [6]. The most common manifestation of such effect are the slowing of intraventricular conduction, manifested by prolonged PR, QRS, and QT intervals on the standard ECG, and orthostatic hypotension [6].

During the last years, hERG channel blockade has become a major topic in pharmacological research [7]. The human *ether-a-go-go*-related gene (hERG) encodes the pore-forming subunits of the rapidly-activating delayed rectifier K^+ channel (I_{kr}) in the heart [8]. The function of hERG was unknown, but it was strongly expressed in the heart and was hypothesized to play an important role in repolarization of cardiac action potentials [9]. Mutations in hERG reduce I_{kr} and cause type 2 long QT syndrome (LQT2), a disorder that predisposes individuals to life-threatening arrhythmias [10]. Acquired and inherited LQTs are both associated with a distinct arrhythmia known as *torsades de pointes* are polymorphic ventricular tachycardia associated with abnormal cardiac repolarizations, as detected by QT prolongation on the electrocardiogram, and characterized by sinusoidal twisting of the QRS axis around the isoelectric line [11]. Because of their potential pro-arrhythmic effects, a number of non-cardiac drugs have been withdrawn from the market (e.g. terfenadine, cisapride, and thioridazine) and many have been labeled for restricted use (e.g. mesoridazine, droperidol,

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and arsenic trioxide) [12]. Therefore, the drug-induced QTc interval prolongation is strongly associated with the blockade of hERG channels, suggesting that drug-screening against recombinant hERG channels is now an important component of cardiac safety pharmacology during drug development.

There are no reports about the electrophysiological characteristic of interaction of desipramine with the hERG channel. The aim of this study is to examine the effects of desipramine on the cloned hERG potassium channels heterologously expressed in *Xenopus laevis* oocytes, which approach would be helpful to reveal the detailed insights into the biophysical mechanism of hERG block by the drug.

2. Materials and methods

2.1. Expression of hERG in oocytes

hERG (Accession No. U04270) cRNA was synthesized by in vitro transcription from 1 μg of linearized cDNA using T7 message machine kits (Ambion, Austin, TX, USA) and stored in 10 mM Tris–HCl (pH 7.4) at −80 °C. The amino acid mutations where generated by polymerase chain reaction (PCR) with synthetic mutant oligonucleotide primers. The mutations Y652A and F656A were verified by sequencing (ABI3100). Stage V and VI oocytes were surgically removed from female *Xenopus laevis* (Nasco, Modesto, CA, USA) anesthetized with 0.17% tricaine methanesulphonate (Sigma, St. Louis, MO, USA). Using fine forceps, the theca and follicle layers were manually removed from the oocytes, and then each oocyte was injected with 40 nl of cRNA (0.1–0.5 μg/μl). The injected oocytes were maintained in a modified Barth's Solution. The modified Barth's Solution contained (mM): 88 NaCl, 1 KCl, 0.4 $CaCl_2$, 0.33 $Ca(NO_3)_2$, 1 $MgSO_4$, 2.4 $NaHCO_3$, 10 Hepes (pH 7.4), and 50 μg/ml gentamicin sulphonate. Currents were performed according to the Research Guidelines of Kangwon National University IACUC.

2.2. Solution and voltage-clamp recording from oocytes

Normal Ringer's Solution contained 96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM Hepes (pH adjusted to 7.4 with NaOH). Solutions were applied to oocytes by continuous perfusion of the chamber while recording. Solution exchanges were completed within 3 min, and the hERG currents were recorded 5 min after the solution exchange. Currents were measured at room temperature (20–23 °C) with a two-microelectrode voltage-clamp amplifier (Warner Instruments, Hamden, CT, USA). Electrodes were filled with 3 M KCl and had a resistance of 2–4 MΩ for current-passing electrodes. Stimulation and data acquisition were controlled with an AD–DA converter (Digidata 1200, Axon Instruments) and pCLAMP software (v 5.1, Axon Instruments). The antidepressant desipramine and other reagents ware purchased from Sigma (St. Louis, MO, USA). A stock solution of desipramine was prepared in DMSO and added to the external solution at suitable concentrations shortly before each experiment.

The fractional electrical distance (δ), i.e. the fraction of the transmembraneous electrical field sensed by a single positive charge at the binding site, was determined with half-blocking concentrations (K_D) obtained from the fractional current (f_o) as the current with 50 μM desipramine and under control conditions at

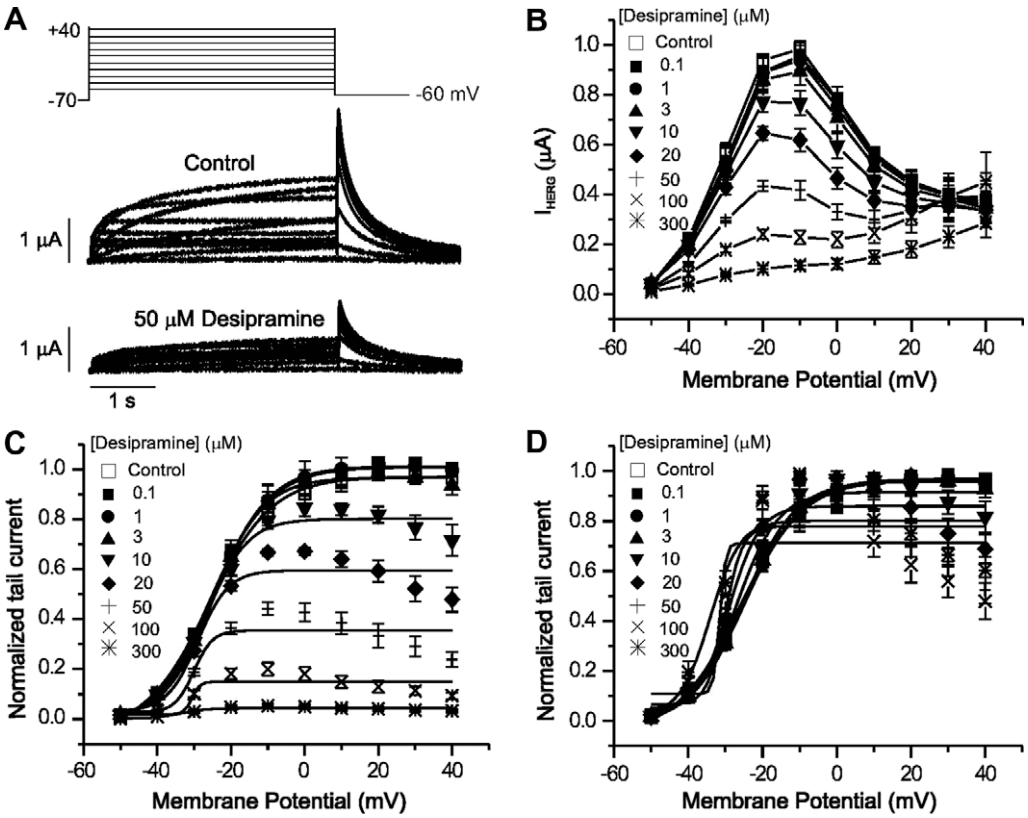

Fig. 1. The effect of desipramine on human *ether-a-go-go*-related gene (hERG) currents (I_{HERG}) elicited by depolarizing voltage pulses. (A) Superimposed current traces elicited by depolarizing voltage pulses (4 s) in 10 mV steps (upper panel) from a holding potential of −70 mV in the absence of desipramine (control, center panel) and in the presence of 50 μM desipramine (lower panel). (B) Plot of the normalized hERG current measured at the end of depolarizing pulses ($I_{HERG,\ nor}$) against the pulse potential in the control and desipramine conditions. The maximal amplitude of the I_{HERG} in the control was given a value of 1. (C) Plot of the normalized tail current measured at its peak just after repolarization. The peak amplitude of the tail current in the absence of the drug was set as 1. Control data were fitted to the Boltzmann equation, $y = 1/\{1 + \exp[(-V + V_{1/2})/dx]\}$, with $V_{1/2}$ of −26.1 mV. (D) Activation curves with values normalized to the respective maximum value at each concentration of desipramine. Symbols with error bars represent mean ± SEM ($n = 5$).

the end of the voltage step with the equation $K_D = (f_o/(1 - f_o)) \times 50$ (in μM). The value of δ was obtained by fitting the K_D values with the equation $K_D = K_{D\,0\,mV} \times \exp(-z\delta FV/RT)$ where $K_{D\,0\,mV}$ represents the half-blocking concentration at the reference potential of 0 mV. V represents the membrane potential and z, R, F, and T have their usual meaning [13].

2.3. Pulse protocols and analysis

To obtain concentration–response curves in the presence of desipramine, dose-dependent inhibition was fitted with the following equation:

$$I_{tail} = I_{tail\cdot max}/[1 + (IC_{50}/D)^n],$$

where I_{tail} indicates peak tail currents, $I_{tail\cdot max}$ is the maximum peak tail current, D is the concentration of the small molecule, n is the Hill coefficient, and IC_{50} is the concentration at which the half-maximal peak tail currents were inhibited.

2.4. Statistical evaluations

All data are expressed as mean ± SEM. Unpaired or paired Student's t tests, or ANOVA were used for statistical comparisons when appropriate, and differences were considered significant at $P < 0.05$.

3. Results

3.1. Concentration-dependence of WT hERG channel block by desipramine in Xenopus oocytes

This study examined the effect of desipramine on the hERG currents using a *Xenopus* oocyte expression system. Throughout these experiments, the holding potential was maintained at −70 mV, and tail currents (I_{tail}) were recorded at −60 mV after depolarizing pulses from −50 to +40 mV. Fig. 1A gives an example of a voltage-clamp recording from a *Xenopus* oocyte and the representative current traces both under the control conditions and after exposure to 50 μM desipramine. The amplitude of the outward currents measured at the end of the pulse (I_{HERG}) increased with increasing positive voltage steps, reaching a maximum at −10 mV. The amplitude of I_{HERG} was normalized to the maximum amplitude of the I_{HERG} obtained under the control conditions, and was plotted against the potential of the step depolarization ($I_{HERG,\,nor}$, Fig. 1B). The amplitude of $I_{HERG,\,nor}$ showed a concentration-dependent decrease with increasing desipramine concentration.

After the depolarizing steps, repolarization to −60 mV induced an outward I_{tail}, which had an amplitude even greater than that of I_{HERG} during depolarization, which is due to rapid recovery from inactivation and a slow deactivation mechanism [14,15]. When 50 μM desipramine was added to the perfusate, both the I_{HERG} and I_{tail} were reduced (Fig. 1A, bottom panel). The amplitude of I_{tail} was normalized to the peak amplitude obtained under the control conditions at the maximum depolarization, and was plotted against the potential of the step depolarization (Fig. 1C). The data obtained under the control conditions were well-fitted by the Boltzmann equation, with a half-maximal activation ($V_{1/2}$) at −26.1 mV. The peak I_{tail} amplitude decreased with increasing desipramine concentration, which indicates that the maximum conductance of the hERG channels is decreased by desipramine. In addition, in the presence of desipramine, I_{tail} does not reach the steady-state level but decreases at more positive potentials, indicating that the blockade is more pronounced at the positive potentials.

The values shown in Fig. 1C were normalized to the respective maximum values at each concentration to determine if desipramine shifts the activation curve (Fig. 1D). The activation curves in the con-

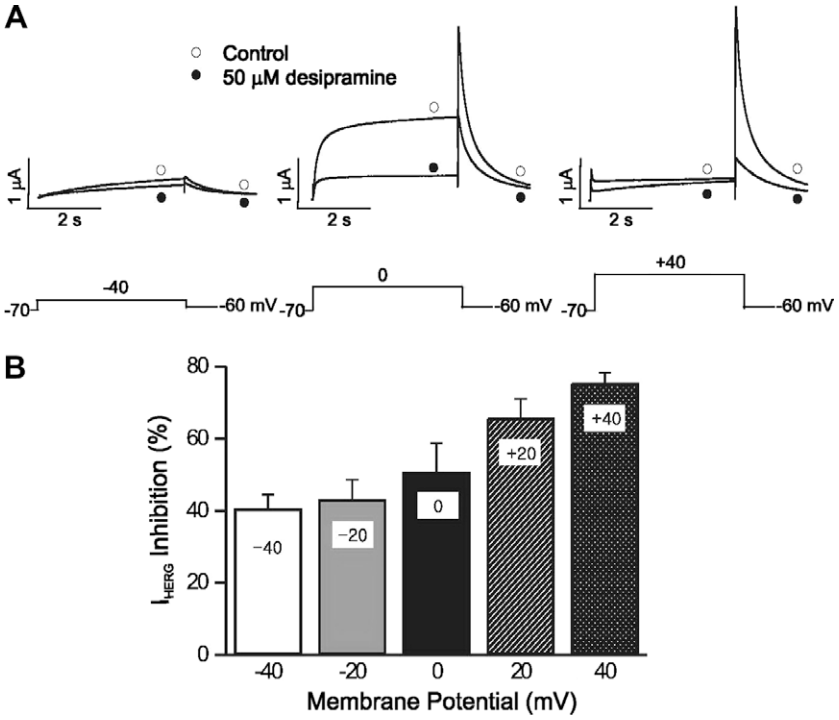

Fig. 2. Voltage dependence of desipramine-induced hERG-current blockade. (A) Current traces from a cell depolarized to −40 mV (left panel), 0 mV (middle panel), and +40 mV (right panel), before and after exposure to 50 μM desipramine, showing increased blockade of hERG current at the more positive potential. The protocol consisted of 4 s depolarizing steps to −40 mV, 0 mV or +40 mV from a holding potential of −70 mV, followed by repolarization to −60 mV. (B) Concentration-dependent block of I_{HERG} by desipramine at different membrane potentials. At each depolarizing voltage step (−40 mV, 0 mV or +40 mV), the tail currents in the presence of various concentrations of desipramine were normalized to the tail current obtained in the absence of drug, and then plotted against desipramine concentrations. Symbols with error bars represent mean ± SEM ($n = 5$).

trol oocytes, as well as those treated with 0.1, 1, 3, and 10 μM desipramine basically overlapped, whereas the curves representing the higher concentrations of the drug (20–300 μM) were shifted downward without a significant leftward-shift. The $V_{1/2}$ calculations are consistent with this finding, yielding values of −26.1 ± 0.67, −25.4 ± 0.63, −24.8 ± 0.37, −25.1 ± 0.53, −26.9 ± 1.65, −29.0 ± 2.57, −30.1 ± 2.56, −31.5 ± 2.90, and −34.1 ± 4.34 mV in the control and 0.1, 1, 3, 10, 20, 50, 100, and 300 μM desipramine-treated groups, respectively ($n = 5$, $P > 0.05$). Thus, the $V_{1/2}$ values for experiments run in the presence of 1–10 μM desipramine were not significantly different from each other, whereas that for experiments run in the presence of 20–300 μM were significantly lower than controls. These findings indicate that desipramine does not change activation gating at 1–10 μM.

3.2. Voltage-dependent block of WT hERG channel by desipramine

The desipramine-induced decrease in I_{tail} at different potentials was compared in order to determine if the effect of desipramine was voltage-dependent (Fig. 2A). The percentage inhibition in the hERG current by 50 μM desipramine at −40, −20, 0, +20, and +40 mV was 39.0% ± 6.1%, 43.4% ± 4.0%, 50.7% ± 4.6%, 62.0% ± 5.0%, and 71.0% ± 4.9%, respectively (Fig. 2B). This suggests that the desipramine-induced blockade of the hERG currents progressively increases with increasing depolarization.

3.3. Time-dependence of WT hERG channel block by desipramine

The currents were activated using a protocol containing a single depolarizing step to 0 mV for 8 s to determine if the channel was blocked in the closed or activated (i.e. open and/or inactivated) state (Fig. 3A). After obtaining the control measurement, 50 μM desipramine was applied and the recordings were made. Fig. 3B shows the degree of inhibition (i.e. (1 − desipramine current/control current) × 100 (in %)). Analysis of the test pulse after the application of desipramine revealed a time-dependent increase in blockage in this representative cell to 69% at 4 s (Fig. 3B). At the beginning of the pulse, the fractional sustained current, which was obtained by normalizing the currents with desipramine relative to control currents, was 0.76 ± 0.07 of the control ($n = 5$). This indicates that the hERG channels were only slightly blocked by desipramine while remaining at the holding potential. In this series of experiments, 50 μM desipramine reduced the hERG outward currents at the end of the 0 mV pulse by 71.3% ± 4.2% ($n = 5$).

In order to address the question as to whether the hERG channels are also blocked by desipramine in its inactivated state, a long test pulse to +80 mV (4 s) was applied to inactivate the channels, which was followed by a second voltage step (0 mV, 3.5 s) to open the hERG channels ($n = 5$). Fig. 4C shows typical current traces under the control conditions and after the application of 50 μM desipramine. Fig. 4D shows the normalized relative blockage upon channel opening during the second voltage pulse (0 mV), indicating that the pronounced inhibition of the hERG channels had already been reached during the previous inactivating +80 mV pulse. No additional time-dependent blockage of the open channels was observed during the 0 mV pulse. The currents at the end of the second voltage step (0 mV) were decreased by 39.6% ± 3.8% ($n = 5$). Overall, desipramine inhibits the hERG channels mainly in the open and inactivated state rather than in the closed state.

3.4. Desipramine block of WT and mutant hERG channels expressed in oocytes

Previous studies reported that two aromatic residues, Tyr-652 and Phe-656, which are located in S6 domain and face the pore cavity

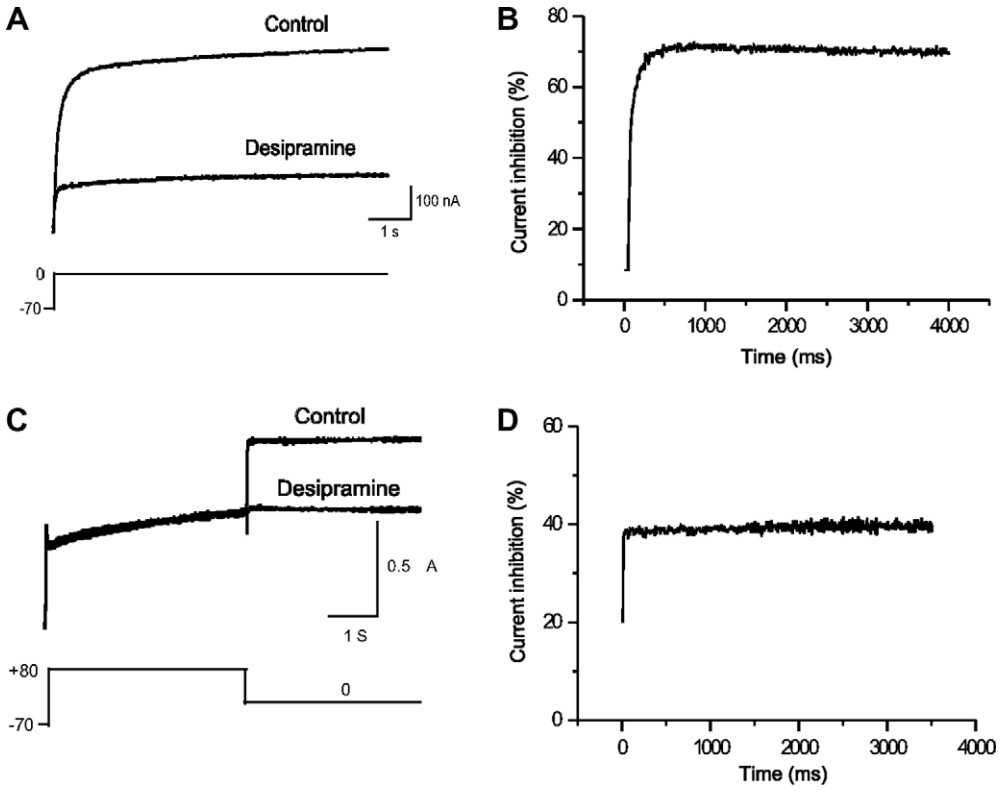

Fig. 3. Blocking of activated hERG channels by desipramine. (A) An original recording of currents under control conditions (control) and after exposure to 50 μM desipramine (for 7 min, without any intermittent test pulse). (B) The degree of hERG-current inhibition in percentages (%). Current inhibition increased time-dependently to 69% at 2 s in this representative cell, indicating that mostly open and/or inactivated channels were blocked. (C) Inhibition of inactivated channels by 50 μM desipramine. hERG channels were inactivated by a first voltage step to +80 mV, followed by channel opening at 0 mV. (D) The corresponding relative block during the 0 mV step is displayed. Maximum inhibition was achieved in the inactivated state during the first step, and no further time-dependent blockage occurred upon channel opening during the second voltage step.

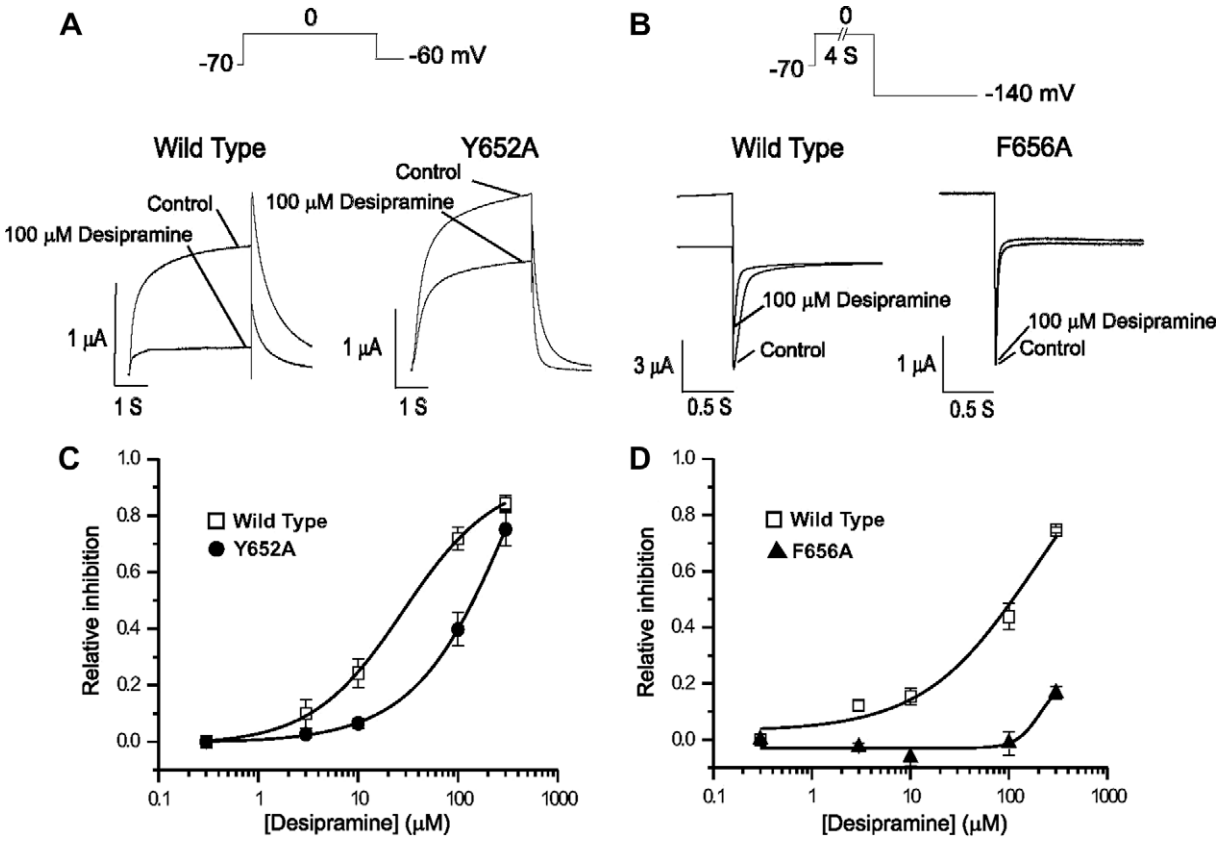

Fig. 4. Concentration-dependent inhibition of WT and mutant hERG channels expressed in oocytes. (A and B) Representative traces for WT and mutant hERG channel currents in the presence and absence of indicated concentrations of desipramine. The effect of the drug on WT and Y652A was quantified during a 4 s activating pulses to 0 mV from a holding potential of −70 mV. To increase the amplitude of poorly expressed F656A mutant channels, tail currents were recorded at −140 mV instead of −60 mV after the 4 s activating pulses. (C and D) The concentration–response curves were fitted with a logistic dose–response equation to obtain the IC_{50} values of 28.5 ± 3.2 μM (n = 5), 402.9 ± 121 μM (n = 8), 177.3 ± 527 μM (n = 10), and 208.8 ± 2.8 μM (n = 6) in WT (obtained using protocol of panel A), Y652A, WT (obtained using protocol of panel B), and F656A hERG channels, respectively. Data were expressed as mean ± SEM.

of the channel, are important components of the binding site for a number of compounds [15,16]. The potency of a channel block for the wild type and two mutant hERG channels (Y652A and F656A) were compared in order to determine if these key residues are also important in the desipramine-induced blocking of the hERG channel. As shown in Fig. 4, the inhibitory effect of desipramine (100 μM) was partially attenuated by a F656A mutation (panel B) or abolished by a Y652A mutation (panel A). The IC_{50} values were consistent with this finding. The IC_{50} values were 28.5 ± 3.2 μM (n = 5) in WT (obtained using protocol of panel A), 402.9 ± 121 μM (n = 8) in Y652A mutant channels, 177.3 ± 527 μM (n = 10) in WT (obtained using protocol of panel B), and 208.8 ± 2.8 μM (n = 6) in F656A mutant hERG channels (panel C and D). This indicates that a mutation of Tyr-652 located in the S6 domain of the hERG channel reduced the potency of the channel block by desipramine more than a mutation of Phe-656 in the same region.

4. Discussion

Our results indicate that desipramine is an inhibitor of hERG channels. The IC_{50} values of desipramine were ~20 μM for hERG channels heterologously expressed in *Xenopus* oocytes. Desipramine is a tricyclic antidepressant that inhibits reuptake of noradrenaline and 5-HT and determines the level of down regulation of the β- and α_2-adrenoceptors and 5-HT_2 receptors. Among tricyclics, nortriptyline may have a relatively low risk of inducing postural blood pressure changes [2]. Tricyclic antidepressants are avoided following an acute myocardial infarction, in the presence of defects in bundle-branch conduction, or when other cardiac depressants are being administered [2]. Besides their use for depressive illness, TCAs, including desipramine, are important for patients with neuropathic pain syndrome.

Other drugs that cause acquired long QT syndrome and *torsades de pointes* have also been shown to block hERG channels in a voltage-dependent manner, suggesting that these drugs bind to the open or inactivated state of hERG channels. For example, two histamine-receptor antagonists, terfenadine, and astemizole [17], have been found to preferentially bind to the inactivated state of hERG, whereas the gastrointestinal prokinetic agent cisapride has been shown to block the channel in its open state [18]. We have shown here that the amplitudes of the maximum outward current and the maximum peak tail current decreased with desipramine (Fig. 1), and the magnitude of the blockade increased with greater positive voltage, which increased the open probability and enhanced inactivation (Fig. 2). In addition, desipramine block may be state-dependent: the hERG channels are blocked mainly in the open and inactivated states but not in the closed state (Fig. 3). Finally, desipramine did not significantly alter the $V_{1/2}$ values of the activation curve, which indicates that the drug blocks the hERG channels without changing the activation properties (Fig. 1).

Potent hERG channel blockers require for binding several residues lining the inner cavity (T623, S624, V625, G648, Y652, F656, and V659) [16]. However, two residues (Y652 and F656) located in the S6 domain that face the central cavity of the channel appear to be essential components of the hERG binding site for high and low potency drugs [19]. Our finding, that the blockade of Y652A

mutant hERG channel by desipramine is significantly enhanced compared with F656A mutant hERG channel (Fig. 4).

The TCAs are associated with an increased heart rate, largely mediated through their anticholinergic effect [20]. The increased heart rate by tricyclic antidepressants is due primarily to the anticholinergic action, whereas the ECG changes and conduction disturbances induced by the drugs are largely the result of direct membrane effects [21].

Drug-induced QT interval prolongation and the appearance of *torsades de pointes* have been recognized as potential risks during treatment with a broad range of drugs, among them antidepressant drugs [19]. It was shown that desipramine inhibits the major component of I_{Kr}, hERG, which suggests that desipramine-induced cardiac arrhythmia may also result from hERG inhibition. Besides the relatively low incidence of arrhythmia during the desipramine treatment can be explained by the inhibition of the L-type Ca^{2+} channels [4], which might counteract the potential arrhythmogenic effects of the hERG blockage. In this respect, it could be interesting to examine the effect of desipramine on APD in cardiomyocytes. Desipramine has other effects which are relevant to the development of arrhythmias. For example, desipramine increases the level of plasma norepinephrine, which may augment vulnerability to arrhythmia [22]. Desipramine significantly reduces heart rate variability which, in theory, might increase the risk of arrhythmias [22].

5. Conclusion

In conclusion, the antidepressant drug, desipramine, blocks the hERG channels in *Xenopus* oocytes are important molecular determinants for blocking the hERG channel by desipramine. We recommend appropriate monitoring of desipramine therapy in patients with risk factors for acquired long QT syndrome.

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