International Journal of Oral Biology, Vol. 43, No. 1 March 31 2018, p. 43-51

http://dx.doi.org/10.11620/IJOB.2018.43.1.043
pISSN 1226-7155, eISSN 2287-6618

International Journal of Oral Biology

Effects of Paroxetine on a Human *Ether-a-go-go*-related Gene (hERG) K^+ Channel Expressed in *Xenopus* Oocytes and on Cardiac Action Potential

Hee-Kyung Hong, Soobeen Hwang and Su-Hyun Jo*

Department of Physiology, Kangwon National University Institute of Bioscience & Biotechnology, BK21 plus Graduate Program, Kangwon National University College of Medicine, Chuncheon 200-701, Korea

(received March 13 2018; revised March 15, 2018; accepted March 19, 2018)

K^+ channels are key components of the primary and secondary basolateral Cl^- pump systems, which are important for secretion from the salivary glands. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) for psychiatric disorders that can induce QT prolongation, which may lead to *torsades de pointes*. We studied the effects of paroxetine on a human K^+ channel, human *ether-a-go-go*-related gene (hERG), expressed in *Xenopus* oocytes and on action potential in guinea pig ventricular myocytes. The hERG encodes the pore-forming subunits of the rapidly-activating delayed rectifier K^+ channel (I_{Kr}) in the heart. Mutations in hERG reduce I_{Kr} and cause type 2 long QT syndrome (LQT2), a disorder that predisposes individuals to life-threatening arrhythmias. Paroxetine induced concentration-dependent decreases in the current amplitude at the end of the voltage steps and hERG tail currents. The inhibition was concentration-dependent and time-dependent, but voltage-independent during each voltage pulse. In guinea pig ventricular myocytes held at 36℃, treatment with 0.4 μM paroxetine for 5 min decreased the action potential duration at 90% of repolarization (APD_{90}) by 4.3%. Our results suggest that paroxetine is a blocker of the hERG channels, providing a molecular mechanism for the arrhythmogenic side effects of clinical administration of paroxetine.

Key words: hERG channel; LQT; Paroxetine; Rapidly-activating delayed rectifier K^+ current; *Torsades de pointes*

*Correspondence to: Su-Hyun Jo, Ph.D. Department of Physiology, Kangwon National University College of Medicine, Hyoja-Dong, Chuncheon 200-701, Korea
Tel: 82-33-250-8824, Fax: 82-33-255-8809
E-mail: suhyunjo@kangwon.ac.kr
ORCID : 0000-0002-4090-9680

Introduction

Many antidepressant medications have adverse cardiovascular effects that restrict use, particularly among older patients and patients with preexisting cardiac disease [1]. Selective serotonin reuptake inhibitors (SSRIs) are increasingly becoming the agents of choice in the treatment of depression, replacing the well established tricyclic antidepressants (TCAs) probably because of their better side-effect profile and safety [2]. Although SSRIs are not without problematic side effects (e.g., anorgasmia), they do not have anticholinergic effects nor do they induce weight gain [3]. Also, SSRIs are considered to be safer than TCAs for patients with ischemic heart disease [4]. Paroxetine has been widely used as an SSRI for the treatment of depression and other psychiatric disorders such as panic and obsessive-compulsive disorders, social phobia, and premenstrual dysphoric disorder [5]. Paroxetine has been shown to be absent of any cardiac adverse effects in comparison with a tricyclic antidepressant; it has also been shown to have decreased platelet activity and increased heart rate variability [6].

K^+ channels are key components of the primary and secondary basolateral Cl^- pump systems, which are important for secretion from the salivary gland [7]. In 1994, hERG (human *ether-a-go-go*-related gene) was identified from a human hippocampal cDNA library as a human relative of *Drosophila ether-a-go-go* and found to map to chromosome 7 [8]. The following year, mutations in hERG were implicated in chromosome 7-linked long QT syndrome [9]. The hERG encodes the pore-forming α-subunits of channels that conduct rapid delayed rectifier K^+ current (I_{Kr}) [10], which is one of the most important membrane currents responsible for ventricular action potential repolarization. The QT interval on the surface electrocardiogram (ECG) reflects time for repolarization of the ventricular myocardium. Prolongation of the QT interval is associated with ventricular arrhythmias, and abnormal repolarization has been implicated in the genesis of life-threatening arrhythmias [11]. Acquired long QT syndrome is far more common than inherited long QT syndrome and is most often caused by blockage of hERG channels as a side effect of treatment with commonly used medications including antiarrhythmic, antihistamine, antibiotic, and psychoactive agents [12]. 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, and arsenic trioxide) [13]. Some authors reported that antidepressant drugs, including SSRI (fluvoxamine, paroxetine, and sertraline), TCA (amytriptiline, clomipramine, imipramine), and lithium can also prolong the QTc interval [14]. It has been reported that SSRIs slightly decrease heart rate, do not routinely slow intracardiac conduction, do not affect supine or standing systolic or diastolic blood pressure, and do not induce orthostatic hypotension [15].

There are no reports about the electrophysiological characteristic of paroxetine interacting with the hERG channel. In the present study, by conducting *Xenopus* oocyte expression assays, we examined whether paroxetine affects the activity of hERG channels and the shape of action potentials in isolated guinea pig ventricular myocytes.

Materials and Methods

Ventricular myocyte isolation

Single ventricular myocytes were isolated from each guinea pig heart using a method described previously [16]. Briefly, guinea pigs (300–500 g) were anesthetized with pentobarbital (~50 mg/kg, i.p.), and the heart was quickly excised. The heart was retrogradely perfused at 37 °C with a 750 μM Ca^{2+} solution and a Ca^{2+}-free solution followed by an enzyme solution. The enzyme solution contained 150 μM Ca^{2+}, collagenase type I, and protease type XIV. The heart was then flushed with a 150 μM Ca^{2+} solution. The ventricles were removed and chopped into small pieces, which were then shaken in a flask containing a 150 μM Ca^{2+} solution. The cell suspension was then left to precipitate. The supernatant was replaced with a 500 μM Ca^{2+} solution. The cells were kept at room temperature. This study was performed according to the Research Guidelines of Kangwon National University IACUC.

Solutions and action potential recordings from myocytes

Myocytes in the experimental chamber were continuously superfused at room temperature (24–26 °C) with Tyrode solution containing 10 mM glucose, 5 mM HEPES, 140 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, titrated to pH 7.4 with 4 M NaOH. The experimental chamber had a volume of 150 μl, and the flow rate of the Tyrode solution was 2 ml/min. Miniature solenoid valves (LFAA1201618H; Lee Products, Bucks, UK) selected the solution entering the chamber, and the superfusate within the chamber could be changed within 5 s. The solution level in the chamber was controlled with a suction system. The chamber and solenoid valves were mounted on the sliding stage of a microscope (Diaphot, Nikon, Japan) that sat on an antivibration table (Newport, USA).

Protease type XIV, dimethyl sulfoxide (DMSO), tetraethylammonium chloride (TEA-Cl) (Sigma, St. Louis, MO, USA), and collagenase type 1 (Worthington Biochemical, Freehold, NJ, USA) were used in the form of stock solutions or test solutions. The antidepressant paroxetine and the other reagents were purchased from Sigma (St. Louis, MO, USA). A stock solution of paroxetine was prepared in distilled water and added to the external solutions at suitable concentrations shortly before each experiment.

Membrane potential was measured with conventional microelectrodes pulled from filamented thin wall glass tubing of 1.5-mm outer diameter and 1.2-mm inner diameter (World Precision Instruments, USA). They were filled with filtered 300 mM KCl and had a resistance between 25 MΩ and 40 M

Ω. Membrane potential was measured with an Axoclamp 900A amplifier (Axon Instruments, USA). Action potentials were elicited at 0.33 Hz by 2-ms depolarizing current pulses passed through the microelectrode. We selected rod shaped myocytes with clear cross striations and rejected the results that showed noisy or drifting baselines. Data acquisition was performed with a digital computer, analogue data acquisition equipment (National Instruments, Austin, TX, USA), and the on-line software WCP (written and supplied by John Dempster of Strathclyde University).

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. Stage V–VI oocytes were surgically removed from female *Xenopus laevis* (Nasco, Modesto, CA, USA) anesthetized with 0.17% tricane methanesulfonate (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 containing (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 sulfonate. The experiments were performed according to the Research Guidelines of Kangwon National University IACUC.

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 three min, and the hERG currents were recorded 5 min after the solution exchange. Currents were measured at room temperature (20~23℃) 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).

Pulse protocols and analysis

To obtain concentration–response curves in the presence of paroxetine, dose–dependent inhibition was fitted with the 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.

Statistical evaluations

All data are expressed as mean S.E.M. Unpaired or paired Student t tests or ANOVA were used for statistical comparisons when appropriate, and differences were considered significant at $P<0.05$.

Results

Effects of paroxetine on action potentials in guinea pig ventricular myocytes

To analyze the physiological relevance of paroxetine-induced hERG block, action potentials were recorded in freshly isolated guinea pig ventricular cardiomyocytes. Fig. 1A shows superimposed traces of the action potentials recorded before and during exposure to different concentrations of paroxetine for 10 min. Paroxetine at concentrations of 0.4 μM decreased the APD_{90} and APD_{50} of guinea pig ventricular myocytes (Fig. 1B, C) within 5 min. The APD_{90} and APD_{50} decreased to 95.7 ± 0.84 and 96.3 ± 0.98% of control after 0.4 μM paroxetine treatment for 5 min, respectively (n = 4, $P < 0.05$). However, paroxetine at the same concentrations did not change APD_{20}, APA, or RMP even after exposure of 4 μM paroxetine for 10 min (n = 4, $P < 0.05$; Fig. 2D, E, and F, respectively).

Concentration-dependence of WT hERG channel block by paroxetine in *Xenopus* oocytes

This study examined the effect of paroxetine 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

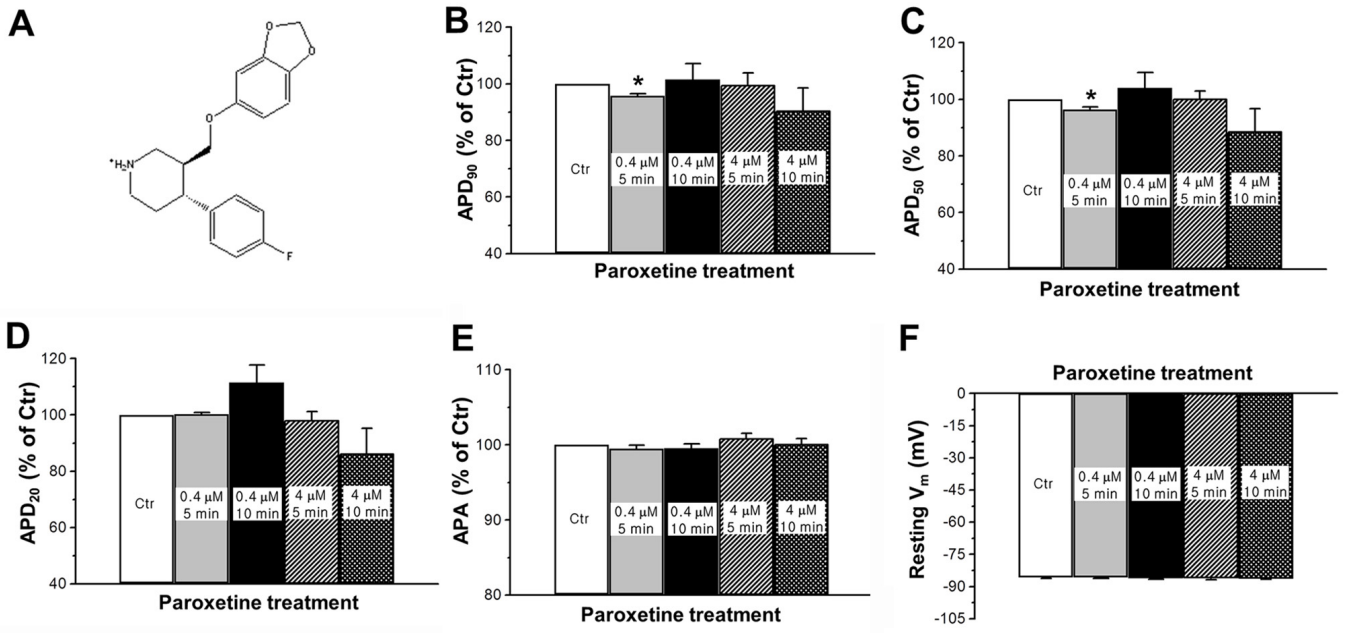

Fig. 1. Effects of paroxetine exposure on action potential of guinea pig ventricular myocytes. (A) Chemical structure of paroxetine. (B)-(F) The effects of 0.4 ~ 4 μM paroxetine on action potential duration at 90% of repolarization (APD_{90}), action potential duration at 50% of repolarization (APD_{50}), action potential duration at 20% of repolarization (APD_{20}), action potential amplitude (APA), and resting membrane potential (RMP). *Bars* with error bars represent mean ± S.E.M. (n = 4). $^{*}P < 0.05$.

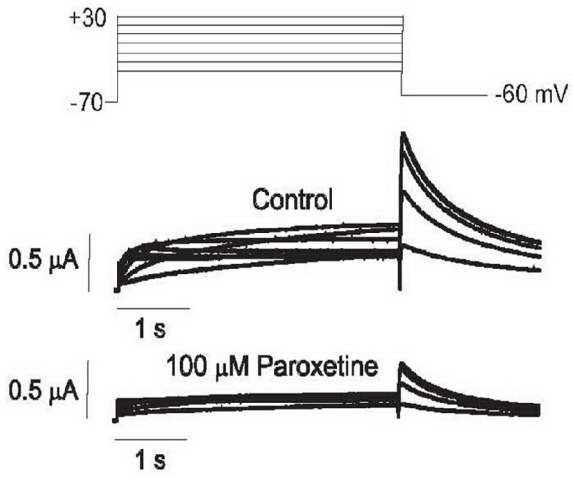

Fig. 2. The effect of paroxetine on *human-ether-a-go-go*-related gene (*hERG*) current (I_{HERG}) elicited by depolarizing voltage pulses in *Xenopus* oocytes. Superimposed current traces elicited by depolarizing voltage pulses (4 s) in 10 mV steps (upper panel) from a holding potential of −70 mV in the absence of paroxetine (control, center panel) and in the presence of 100 μM hydroxyzine (lower panel).

at −60 mV after depolarizing pulses from −30 to +30 mV. Fig. 2 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 100 μM paroxetine. 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 step depolarization ($I_{HERG,\ nor}$, Fig. 3A). The amplitude of $I_{HERG,\ nor}$ showed a concentration-dependent decrease with increasing paroxetine 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 due to rapid recovery from inactivation and a slow deactivation mechanism [12, 17]. When 100 μM paroxetine was added to the perfusate, both I_{HERG} and I_{tail} were reduced (Fig. 2, 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. 3B). The data obtained under the control conditions were well-fitted by the Boltzmann Equation, with half-maximal activation ($V_{1/2}$) at -22.5 mV. The peak I_{tail} amplitude decreased with increasing paroxetine concentration, which indicates that the maximum conductance of the hERG channels is decreased by paroxetine. In addition, in the presence of paroxetine, I_{tail} did not reach the steady-state level but decreased at more positive potentials, indicating that the

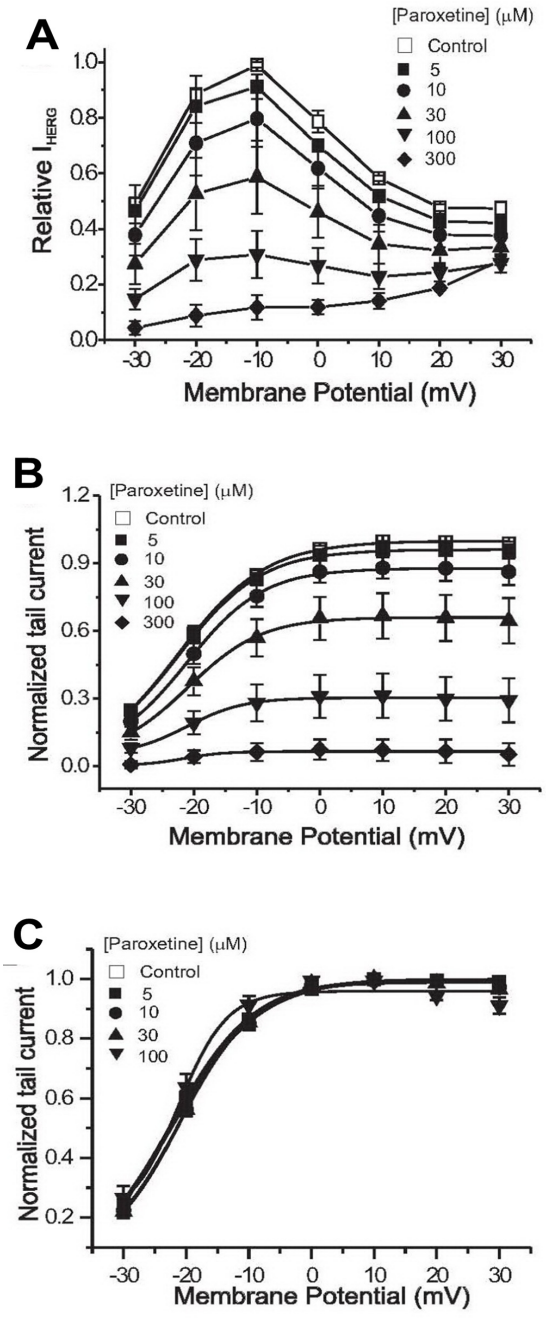

Fig. 3. The effect of paroxetine on *human-ether-a-go-go-* related gene (*hERG*) channels expressed in *Xenopus* oocytes. (A) Plot of the normalized hERG current measured at the end of depolarizing pulses (I_{HERG}) against the pulse potential in the control and paroxetine conditions. The maximal amplitude of the I_{HERG} in the control was given a value of 1. (B) 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 −22.5 mV. (C) Activation curves with values normalized to the respective maximum value at each concentration of paroxetine. *Symbols* with error bars represent mean ± S.E.M. (n = 4). blockade is more pronounced at positive potentials.

The values shown in Fig. 2C were normalized to the respective maximum values at each concentration to determine if paroxetine shifts the activation curve (Fig. 3C). The activation curves in the control oocytes and those treated with 5, 10, and 100 μM paroxetine basically overlapped. The $V_{1/2}$ calculations are consistent with this finding, yielding values of -22.5 ± 1.01, -22.4 ± 0.94, -20.9 ± 1.10, -20.8 ± 1.45, and -21.2 ± 2.06 mV in the control and 5, 10, 20, 30, and 100 μM paroxetine-treated groups, respectively (n = 4, $P > 0.05$). Therefore, the $V_{1/2}$ values in the presence of 5 - 100 μM paroxetine were similar, indicating that paroxetine does not alter the activation gating at this concentration range.

Voltage−independent block of WT hERG channel by paroxetine

The paroxetine-induced decrease in I_{tail} at different potentials was compared in order to determine if the effect of paroxetine was voltage-dependent in the hERG-expressed oocytes (Fig. 4A). The degree of inhibition was calculated as (1- paroxetine current/control current)×100 (in %). The percentage inhibition in the hERG current by 100 μM paroxetine at -30, -10, +10, and +30 mV was 68.2% ± 7.7%, 67.3% ± 9.2%, 68.7% ± 9.8%, and 70.5% ± 9.8%, respectively (Fig. 4B). For hERG channels, the percentage inhibition showed no significant difference across voltages. These results suggest that inhibition of hERG channels by paroxetine was voltage-independent.

Time−dependence of WT hERG channel block by paroxetine

To determine whether the channel is blocked in the closed, open, or inactivated state, we activated currents using a protocol with a single depolarizing step to 0 mV for 8 s. After having obtained the control measurement, 100 μM paroxetine was applied, and recordings were performed (Fig. 5A). The degree of inhibition was calculated as (1- paroxetine current/control current)×100 (in %). Analysis of the test pulse after the application of paroxetine revealed a time-dependent increase in blockage in this representative cell to 61% at 4 s (Fig. 5B). These results suggest that inhibition of hERG channels by paroxetine was time-dependent.

S6 domain mutation, Y652A, failed to attenuate hERG channel block by paroxetine

Tyr-652 is located in the S6 domain, faces the pore cavity of the channel, and is an important component of the binding

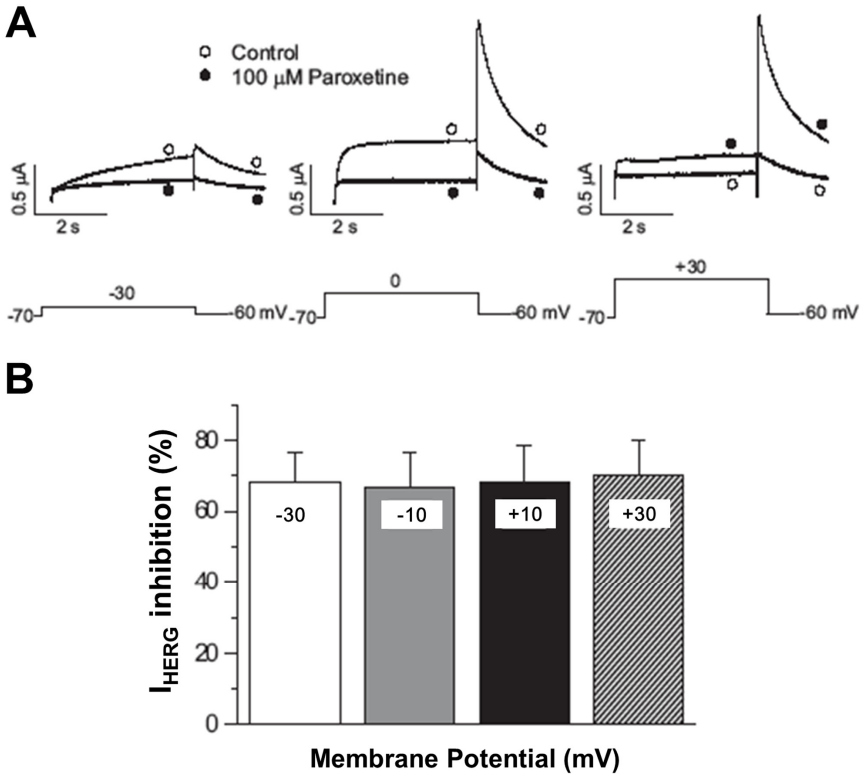

Fig. 4. Voltage independence of paroxetine in the hERG channel. (A) Current traces from a cell depolarized to −30 mV (left panel), 0 mV (middle panel), and +30 mV (right panel) before and after exposure to 100 μM paroxetine, showing increased blockade of hERG current at more positive potential. The protocol consisted of 4 s depolarizing step to −30 mV, 0 mV, or +30 mV from a holding potential of −70 mV, followed by repolarization to −60 mV. (B) Concentration-dependent block of I_{HERG} by paroxetine 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 paroxetine were normalized to the tail current obtained in the absence of drug and then plotted against paroxetine concentration. *Symbols* with error bars represent mean ± S.E.M. (n = 4).

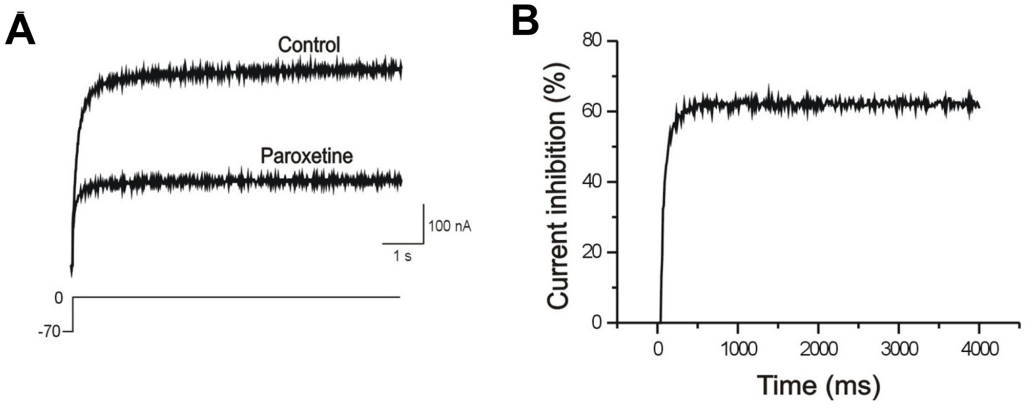

Fig. 5. Blocking of activated hERG channels by paroxetine. (A) An original recording of currents under control conditions (control) and after exposure to 100 μM paroxetine (for 7 min, without any intermittent test pulse). (B) The degree of hERG-current inhibition in percentage (%). Current inhibition increased time-dependently to 61% at 2 s in this representative cell, indicating that mostly open and/or inactivated channels were blocked.

site for a number of compounds [12, 18]. The potency values of a channel block for the wild type and mutant hERG channel (Y652A) were compared in order to determine if the key residue is also important in the paroxetine-induced blocking of the hERG channel. For WT hERG channels, the IC_{50} values were 71.7 ± 10.4 μM in WT and 50.4 ± 8.7 μM

in Y652A mutant channels (n = 4, $P > 0.05$). This indicates that a mutant of Tyr-652 located in the S6 domain of the hERG channel failed to act as a block compared with that of wild-type hERG.

Discussion

Drug-induced QT interval prolongation and the appearance of *torsade de pointes* have been recognized as potential risks during treatment with a broad range of drugs, among them antidepressant drugs [19]. Recently, SSRIs are increasingly becoming the agents of choice in the treatment of depression, replacing the well established TCAs probably because of their better side-effect profile and safety [2]. Paroxetine has been widely used as an SSRI for the treatment of depression and other psychiatric disorders such as panic and obsessive-compulsive disorders, social phobia, and premenstrual dysphoric disorder [5]. The therapeutic effects of paroxetine are generally thought to be primarily due to inhibition of the reuptake of serotonin in the brain [20]. Inhibition of serotonin (5-hydroxytryptamine, 5-HT) transporters by paroxetine in the brain is generally thought to have important implications in its therapeutic effects [20]. Recently, paroxetine was shown to block cardiac-type GIRK1/4 channels, which are abundantly present in the atrium [21]. A number of psychotropic drugs are associated with QTc prolongation, which may lead to a fatal paroxysmal ventricular arrhythmia [22].

The hERG encodes the pore-forming α-subunits of channels that conduct the rapid delayed rectifier K^+ current (I_{Kr}) [10]. Decreased I_{kr} due to pharmacological inhibition can result in QT prolongation and facilitate the development of cardiac arrhythmia, especially *torsade de Pointes* [23].

In the present study, we examined the effects of paroxetine on hERG potassium channels. The inhibition of hERG channels by paroxetine was concentration-dependent and time-dependent, but voltage-independent during each voltage pulse. In guinea pig ventricular myocytes held at 36℃, treatment with 0.4 μM paroxetine for 5 min decreased the APD_{90} by 4.3 %. The effects of myocytes to decrease APD_{90} are of potential interest because these effects have been associated with LQT syndrome and increased risk of the polymorphic ventricular tachycardia *torsade de pointes*. The blood levels in postmortem cases involving toxicity from paroxetine overdoses are approximately 4 to 40 times higher than the upper limit of the therapeutic level [5].

We have shown here that the amplitudes of the maximum outward current and the maximum peak tail current decreased with paroxetine, and paroxetine 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. 3). Potent hERG channel blockers require for binding several residues lining the inner cavity (T623, S624, V625, G648, Y652, F656, and V659) [18]. 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 shows that a mutant of Tyr-652 located in the S6 domain of the hERG channel

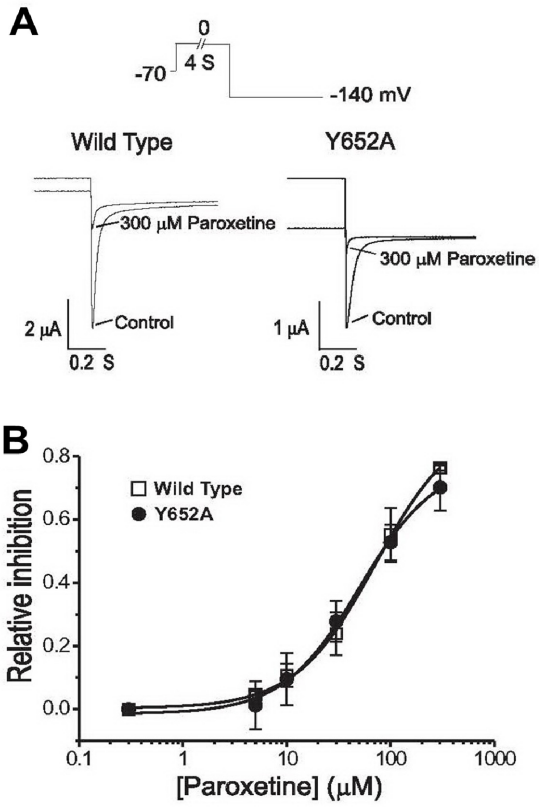

Fig. 6. Concentration-independent inhibition of WT and mutant hERG channels expressed in oocytes. (A) Representative traces for WT and mutant hERG channel currents in the presence and absence of indicated concentrations of paroxetine. The effect of the drug on WT and Y652A tail currents were recorded at -140 mV instead of -60 mV after the 4 s activating pulses. (B) The concentration-response curves were fitted with a logistic dose-response equation to obtain the IC_{50} values of 71.7 ± 10.4 μM (n = 4) and 50.4 ± 8.7 μM (n = 4) in WT (obtained using protocol of panel A) and Y652A hERG channels, respectively. Data are expressed as mean ± S.E.M.

failed to act as a block compared with that of wild-type hERG (Fig. 6), indicating that Tyr-652 is not involved in the paroxetine-induced block of hERG channel.

Cardiac myocytes produce important information associated with activities of all participating ion channels making up the cardiac AP. Compounds that potently block the hERG current, but normally do not prolong APD include Ca^{2+} blockers and some Na^{+} channel blockers. Recently, using an electrooptical assay, the SSRIs sertraline and paroxetine were shown to inhibit Na^{+} currents [24].

In conclusion, paroxetine blocked the hERG channel but failed to increase the APD_{90} in guinea pig ventricular myocytes. These results suggest a potential mechanism by which paroxetine may increase the possibility of cardiac arrhythmia in drug-treated patients.

Acknowledgements

This research was supported by a grant (08172KFDA465) from Korea Food & Drug Administration in 2008, by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2015R1D1A1A01057549) and by 2016 Research Grant from Kangwon National University (No. 520160392).

References

1. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C and Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. J Clin Psychopharmacol. 2005;25:132-140. doi: 10.1097/01.jcp.0000155815.44338.95.
2. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 2000;58:19-36. doi:10.1016/S0165-0327(99)00092-0.
3. Barbey JT and Roose SP. SSRI safety in overdose. J Clin Psychiatry. 1998;59:42-48.
4. Jiang W and Davidson JR. Antidepressant therapy in patients with ischemic heart disease. Am Heart J. 2005;150:871-881. doi: 10.1016/j.ahj.2005.01.041.
5. Kobayashi T, Washiyama K and Ikeda K. Inhibition of G protein-activated inwardly rectifying K+ channels by the antidepressant paroxetine. J Pharmacol Sci. 2006;10:278-287. doi: 10.1254/jphs.FP0060708.
6. Goryachkina K, Burbello A, Boldueva S, Babak S, Bergman U and Bertilsson L. Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). Eur J Clin Pharmacol. 2008;64:275-282. Doi:10.1007/s00228-007-0404-3.
7. Catalán MA, Peña-Munzenmayer G and Melvin JE. Ca^{2+}-dependent K^{+} channels in exocrine salivary glands. Cell Calcium. 2014;55:362-368. doi:10.1016/j.ceca.2014.01.005.
8. Warmke JW and Ganetzky B. A family of potassium channel genes related to eag in Drosophila and mammals. Proc Natl Acad Sci U S A. 1994;91:3438-3442. doi:10.1073/pnas.91.8.3438.
9. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED and Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell. 1995;80:795-803. doi:10.1016/0092-8674(95)90358-5.
10. Sanguinetti MC, Jiang C, Curran ME and Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. Cell. 1995;81:299-307. dio:10.1016/0092-8674(95)90340-2.
11. Yeragani VK, Pohl R, Jampala VC, Balon R, Ramesh C and Srinivasan K. Effects of nortriptyline and paroxetine on QT variability in patients with panic disorder. Depress Anxiety. 2000;11:126-130.
12. Sánchez-Chapula JA, Navarro-Polanco RA, Culberson C, Chen J and Sanguinetti MC. Molecular determinants of voltage-dependent human ether-a-go-go related gene (HERG) K+ channel block. J Biol Chem. 2002;277:23587-23595. doi: 10.1074/jbc.M200448200.
13. Tu DN, Zou AR, Liao YH, Du YM, Wang XP and Li L. Blockade of the human ether-a-go-go-related gene potassium channel by ketanserin. Sheng Li Xue Bao. 2008;60:525-534.
14. Sala M, Vicentini A, Brambilla P, Montomoli C, Jogia JR, Caverzasi E, Bonzano A, Piccinelli M, Barale F and De Ferrari GM. QT interval prolongation related to psychoactive drug treatment: a comparison of monotherapy versus polytherapy. Ann Gen Psychiatry. 2005;4:1. doi:10.1186/1744-859X-4-1.
15. Roose SP, Laghrissi-Thode F, Kennedy JS, Nelson JC, Bigger JT Jr, Pollock BG, Gaffney A, Narayan M, Finkel MS, McCafferty J and Gergel I. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA. 1998;279:287-291. doi:10.1001/jama.279.4.287.
16. Choi SY, Koh YS and Jo SH. Inhibition of Human ether-a-go-go-Related Gene K+ Channel and I_{Kr} of Guinea Pig Cardiomyocytes by Antipsychotic Drug Trifluoperazine. J Pharmacol Exp Ther. 2005;313:888-895. doi:10.1124/jpet.104.080853.
17. Zhou Z, Gong Q, Ye B, Fan Z, Makielski JC, Robertson GA and January CT. Properties of HERG channels stably expressed in HEK 293 cells studied at physiological temperature. Biophys J. 1998;74:230-241. doi:10.1016/S0006-3495(98)77782-77783.
18. Mitcheson JS, Chen J, Lin M, Culberson C and Sanguinetti MC. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci U S A. 2000;97:12329-12333. doi:

10.1073/pnas.210244497.
19. Ferrer-Villada T, Navarro-Polanco RA, Rodríguez-Menchaca AA, Benavides-Haro DE and Sánchez-Chapula JA. Inhibition of cardiac HERG potassium channels by antidepressant maprotiline. Eur J Pharmacol. 2006;531:1-8. doi:10.1016/j.ejphar.2005.10.036.
20. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: depression and anxiety disorders. In: Harman JG, Limbird LE, Gilman AG (eds). Goodman Gilman's The Pharmacological Basis of Therapeutics, 10th edn. McGraw-Hill, New York. 2001;447-483.
21. Krapivinsky G, Krapivinsky L, Velimirovic B, Wickman K, Navarro B and Clapham DE. The Cardiac Inward Rectifier K+ Channel Subunit, CIR, Does Not Comprise the ATP-sensitive K+ Channel, I_{KATP}. J Biol Chem. 1995;270: 28777-28779. doi: 10.1074/jbc.270.48.28777.
22. Welch R and Chue P. Antipsychotic agents and QT changes. J Psychiatry Neurosci. 2000;25:154-160.
23. Scherer D, Hassel D, Bloehs R, Zitron E, von Löwenstern K, Seyler C, Thomas D, Konrad F, Bürgers HF, Seemann G, Rottbauer W, Katus HA, Karle CA and Scholz EP. Selective noradrenaline reuptake inhibitor atomoxetine directly blocks hERG currents. Br J Pharmacol. 2009;156:226-236. doi:10.1111/j.1476-5381.2008.00018.x.
24. Huang CJ, Harootunian A, Maher MP, Quan C, Raj CD, McCormack K, Numann R, Negulescu PA and González JE. Characterization of voltage-gated sodium-channel blockers by electrical stimulation and fluorescence detection of membrane potential. Nature Biotechnology. 2006;24:439–446. doi:10.1038/nbt1194.