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Wide Spectrum of Inhibitory Effects of Sertraline on Cardiac Ion Channels

Hyang-Ae Lee[1,2], Ki-Suk Kim[1], Sung-Ae Hyun[1], Sung-Gurl Park[1], and Sung Joon Kim[2]

[1]Next-Generation Pharmaceutical Research Center, Korea Institute of Toxicology, Korea Research Institute of Chemical Technology, Daejeon 305-600, [2]Department of Physiology and Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul 110-799, Korea

Sertraline is a commonly used antidepressant of the selective serotonin reuptake inhibitors (SSRIs) class. In these experiments, we have used the whole cell patch clamp technique to examine the effects of sertraline on the major cardiac ion channels expressed in HEK293 cells and the native voltage-gated Ca^{2+} channels in rat ventricular myocytes. According to the results, sertraline is a potent blocker of cardiac K^+ channels, such as *hERG*, I_{Ks} and I_{K1}. The rank order of inhibitory potency was *hERG* $> I_{K1} > I_{Ks}$ with IC_{50} values of 0.7, 10.5, and 15.2 μM, respectively. In addition to K^+ channels, sertraline also inhibited I_{Na} and I_{Ca}, and the IC_{50} values are 6.1 and 2.6 μM, respectively. Modification of these ion channels by sertraline could induce changes of the cardiac action potential duration and QT interval, and might result in cardiac arrhythmia.

Key Words: Antidepressant, Cardiac, Ion channel, Selective serotonin reuptake inhibitor, Sertraline

INTRODUCTION

The most considerable concern about the new drugs is cardiovascular toxicity including tachycardia, QT prolongation, and hypertension. Specially, QT prolongation is associated with potentially fatal, cardiac arrhythmia termed Torsade de Pointes (TdP) [1,2].

It is well known that some psychotropic drugs, including neuroleptics, antipsychotics, antidepressants, stimulants, and antianxiety agents, can be associated with risks of cardiac arrhythmia and sudden death [3]. The common tricyclic antidepressants (TCAs) such as imipramine and amitriptyline exert a significant increase in QT variability that is associated with ventricular arrhythmia [4-6]. Newer compounds, such as selective serotonin reuptake inhibitors (SSRIs) have been reported to have a more benign cardiovascular profile, otherwise fluvoxamine have been reported to prolong QT, even at therapeutic doses [7]. In the perfused rat hearts, SSRIs presented undesired effects on the contractility [8] that may be induced by the inhibition of L-type Ca^{2+} and transient outward K^+ currents of ventricular myocytes [9].

Sertraline is a commonly used antidepressant of the SSRI class (Fig. 1). It was investigated that sertraline had no significant effect on cardiac function like as RR, PR, QRS, and QT intervals in an adult outpatient population (n= 1,048) [10]. Whereas previous studies did not reveal any QT prolongation as a side-effect of sertraline, some reports released recently suggests it may have this potential [11]. The sudden cardiac death is also reported in patient taking clozapine and sertraline together [12].

Many antidepressants, especially TCAs can modulate the cardiac action potential (AP) by blocking different cardiac ion channels present in ventricular myocytes. There are various ion channels involved in both the depolarization and repolarization of AP: the inward sodium channel current (I_{Na}), the inward Ca^{2+} channel current (I_{Ca}), and several types of outward potassium channels, such as the rapid and slow components of outward delayed rectifier potassium channel currents (I_{Kr} and I_{Ks}, respectively), the inward rectifying potassium channel current (I_{K1}). Among these potassium channels, the human ether-a-go-go-related gene (hERG) channels conducting I_{Kr} is mainly responsible for cardiac repolarization [13,14].

To our knowledge, there is no report investigating the effect of sertraline on various cardiac ion channels. In the present study, we investigated the effect of sertraline on the major cardiac ion channels, such as hERG, I_{Ks}, I_{K1}, I_{Na} and I_{Ca} to evaluate the potential effects of the drug on cardiac repolarization.

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Corresponding to: Sung Joon Kim, Department of Physiology and Department of Biomedical Sciences, Seoul National University College of Medicine, 103, Daehakro, Jongro-gu, Seoul 110-799, Korea. (Tel) 82-2-740-8230, (Fax) 82-2-763-9667, (E-mail) sjoonkim@snu.ac.kr

ABBREVIATIONS: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; hERG, human ether-a-go-go-related gene; AP, action potential.

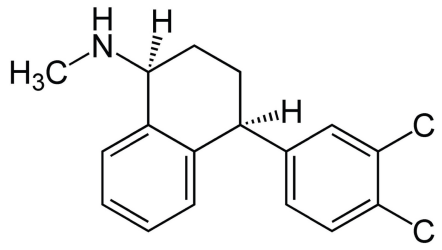

Fig. 1. Structure of sertraline.

METHODS

Reagents

Sertraline and all compounds used to prepare external and internal solutions were purchased from Sigma-Aldrich (MO, USA).

The stock solutions of sertraline were prepared using ethyl alcohol (EtOH), aliquoted and stored frozen. Test concentrations were prepared fresh daily by diluting stock solutions into normal Tyrode (NT) solution. The concentration of EtOH in Tyrode's solution was always kept at 0.1%.

Solutions

The external solution for recording the I_{Kr}, I_{Ks} and I_{Na} channel currents was NT solution as follows (in mM) : 143 NaCl, 5.4 KCl, 1.8 $CaCl_2$, 0.5 $MgCl_2$, 5 HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 0.33 NaH_2PO_4 and 16.6 glucose (pH adjusted to 7.4 with NaOH). The internal solution for I_{Kr} contained the following (in mM) : 130 KCl, 5 ethylene glycol tetraacetic (EGTA), 10 HEPES, 1 $MgCl_2$, 5 Mg-ATP (pH adjusted 7.25 with KOH), and for I_{Ks} in the KCNQ1/KCNE1-cotransfected Human Embryonic Kidney 293 (HEK293) cells, 150 KCl, 5 EGTA, 10 HEPES, 2 $MgCl_2$, 1 $CaCl_2$ and 5 Na_2-ATP (pH adjusted 7.25 with KOH). The internal solution for I_{K1} in KCNJ2-transfected HEK293 cells contained (in mM): 130 K-Asp, 15 KCl, 10 HEPES, 1 $MgCl_2$, 5 Na_2-ATP, 5 EGTA (pH adjusted 7.25 with KOH), and for the I_{Na} in SCN5A-transfected HEK293 cells, 105 CsF, 35 NaCl, 10 EGTA, 10 HEPES (pH adjusted to 7.25 with NaOH). The I_{Ca} was measured in native rat ventricular myocytes, cells were superperfused with an external solution that consisted of (in mM) : 137 cholin-Cl, 5 CsCl, 0.5 $MgCl_2$, 2, 4-Aminopyridine (4-AP), 10 HEPES, 10 glucose and 1.8 $CaCl_2$ (pH adjusted to 7.4 with NaOH), whereas the solution used to fill the pipette had the following ionic solution (in mM) : 20 CsCl, 100 Cs-Asp, 10 EGTA, 10 HEPES, 20 TEA-Cl, 5 Mg-ATP (pH adjusted to 7.25 with KOH). Kraft-Bruhe (KB) solution for storage of the freshly isolated rat ventricular myocytes contained (in mM) : 70 K-glutamate, 55 KCl, 10 HEPES, 3 $MgCl_2$, 20 taurine, 20 KH_2PO_4, 0.5 EGTA (adjusted to pH 7.2 with KOH).

Cell preparation

For various aspects of cardiac ion channel study, HEK293 (ATCC, Manassas, VA, USA) cells were transiently transfected through the lipofectamine method [15], using lipofectAmin2000 (Gibco BRL, USA) as transfection reagent according to the manufacturer's instructions. The *hERG* (the gene corresponding to I_{Kr}), *KCNQ1/KCNE1* (the gene corresponding to I_{Ks}), *KCNJ2* (the gene corresponding to IK1) or *SCN5A* (the gene corresponding to I_{Na}) cDNA was co-transfected with Green Fluorescence Protein (GFP), the surface marker protein, to allow assessment of the transfection efficiency. L-type calcium currents were recorded form acutely isolated, enzymatically dispersed rat ventricular myocytes.

Recording of ionic currents

The cells were placed in a recording chamber on the stage of a Nikon inverted microscope (Nikon Instruments Inc., Tokyo, Japan), and continuously perfused (5±1 ml/min) with 37±1°C bath solution. Ionic currents were recorded in a whole-cell configuration with a standard patch clamp technique [16] using a HEKA EPC8 amplifier (Electronik, Lambrecht, Germany). Data were recorded during the approximately 5 minutes following initial application of the bath solution to verify currents stability. Test drug solutions were subsequently perfused for approximately 5 minutes to achieve steady-state blocks. To investigate the effect of sertraline on the ion channel currents, various concentrations (0.01～30 μM) were tested. Voltage-clamp protocol generation and data acquisition were controlled by computers equipped with an A/D converter, Digidata (Axon Inc., USA) and Rclamp software developed in Seoul National University (Seoul, Korea). The patch pipettes were made from borosilicate glass capillaries (Clark Electromedical Instruments, UK) using a pipette puller (PP-830, Narishige, Japan). Their resistances were 3～4 MΩ when filled with pipette solution. The current signals were filtered at a sampling rate of 5 kHz, and they were low-pass filtered at 1 kHz and stored on computer. All experimental parameters, such as pulse generation and data acquisition, were controlled using the Rclamp software.

Data analysis and statistical test

Data analysis and curve fitting were carried out using GraphPad InStat (GraphPad Software, San Diego, CA) and SigmaPlot 2000 (Systat Software, Inc. San Jose, CA). All data are expressed as mean±SEM and an n indicated number of replicates. Student's t tests or ANOVA were used for statistical comparisons when appropriate, and differences were considered significant when $p < 0.05$, or $p < 0.01$. Current amplitudes were measured before and after application of sertraline. The relative remaining currents were calculated according to the following equation: Initial current amplitude/Current amplitude in the presence of compound=Relative remaining current. Effects were calculated from the results of 4 experiments per concentration of sertraline. Concentration response relations were calculated by a non-linear least squares fit of equation [Hill equation; $f=x^H/(IC50^H+x^H)$; H=Hill coefficient, IC50=IC_{50}, x=concentration, f=inhibition ratio] using the SigmaPlot 2000 program. The half-maximum inhibiting concentration (IC_{50}) was calculated with this function.

RESULTS

Effect of sertraline on hERG, I_{Ks}, and I_{K1} currents

Fig. 2 shows the effects of sertraline on hERG K^+ channel

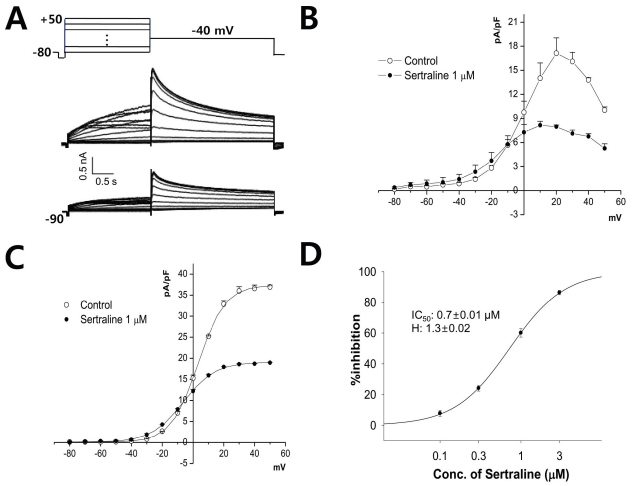

Fig. 2. The effect of sertraline on human ether-a-go-go-related *gene* (*hERG*) currents expressed in HEK293 cells. (A) Current responses to step voltage pulses of −80 to +50 mV in 10 mV steps from a holding potential of −80 mV (upper panel). Center: absence of sertraline, control condition; lower: in the presence of 1 μM sertraline. (B) Voltage-relationship of the hERG current measured at the end of depolarizing pulses against the pulse potential in the control and 1 μM sertraline. (C) Voltage-relationship of the tail current measured at its peak just after repolarization in control and after application of 1 μM sertraline. Data were fitted using Boltzmann equation. (D) Dose-response relationship for inhibition of hERG currents by serial application of 0.1, 0.3, 1, and 3 μM sertraline (n=4). The relationship was fitted to a Hill equation. The IC_{50} and Hill coefficient were 0.7 μM and 1.3, respectively.

currents. Voltage-dependent effects of sertraline on hERG channels were determined using the protocol shown in the inset of Fig. 2A. Representative hERG current traces in the absence and presence of sertraline (1 μM) are, respectively, shown in Fig. 2A. Both activating currents measured at the end of the depolarizing step (Fig. 2B) and peak tail current amplitude (Fig. 2C) measured following the step to −40 mV were dramatically reduced by sertraline. As demonstrated in Fig. 2D, sertraline concentration-dependently inhibited hERG channel currents. Sertraline at concentrations of 1, 3, 10, and 30 μM inhibited the I_{Kr} amplitude by 7.9±1.9%, 24.2±1.9%, 60.1±2.7%, and 86.4±1.4%, respectively (n=4). A non-linear fitting of the experimental values using Hill's equation revealed the 50% inhibitory concentration (IC_{50}) of sertraline. The IC_{50} and Hill coefficient were 0.7±0.01 μM and 1.3±0.02, respectively.

Fig. 3 shows the effects of sertraline on the slowly activating outward K^+ current (I_{Ks}) in *KCNQ1/KCNE1* cDNA-transfected HEK293 cells. Sertraline inhibited I_{Ks} concentration-dependently. Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the I_{Ks} amplitude by 1.5±3.8%, 10.3±2.5%, 36.6±3.5%, and 84.0±5.6%, respectively (n=4). The IC_{50} value calculated from the concentration-response curve was 12.3±1.3 μM, and the Hill coefficient was 2.5±0.1.

And we also investigated the effects of sertraline on I_{K1} in *KCNJ2* cDNA-transfected HEK293 cells (Fig. 4). Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the I_{K1} amplitude by 0.7±2.7%, 9.4±1.1%, 45.7±3.9%, and 92.5±1.2%, respectively (n=4). The IC_{50} value calculated from the concentration-response curve was 10.5±0.5 μM, and the Hill coefficient was 2.1±0.2.

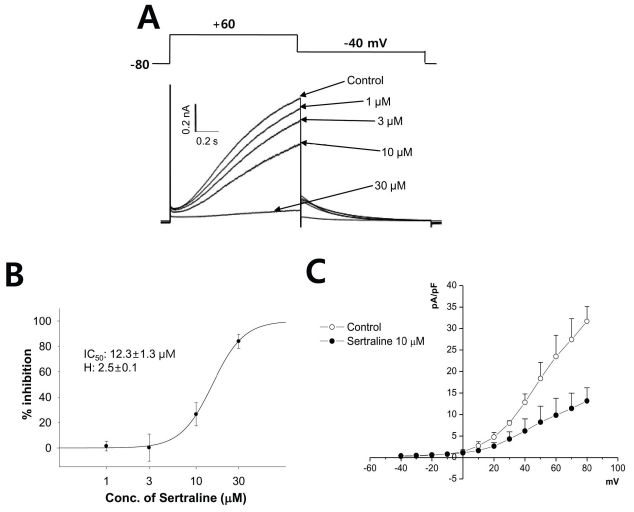

Fig. 3. The effect of sertraline on I_{Ks} expressed in HEK293 cells. (A) The cells were depolarized to +60 mV from a holding potential of −80 mV, followed by a 3-s repolarization back to −40 mV (upper). Representative current traces under control condition and after application of 1, 3, 10, and 30 μM sertraline (lower). (B) Concentration response curve for inhibition of I_{Ks} by serial application of 1, 3, 10, and 30 μM sertraline. The relationship was fitted to a Hill equation. The IC_{50} and Hill coefficient were 12.3 μM and 2.5, respectively (n=4). (C) Voltage-relationship of the peak I_{Ks} measured at the end of depolarizing pulses against the pulse potential in the control and 10 μM sertraline (n=4).

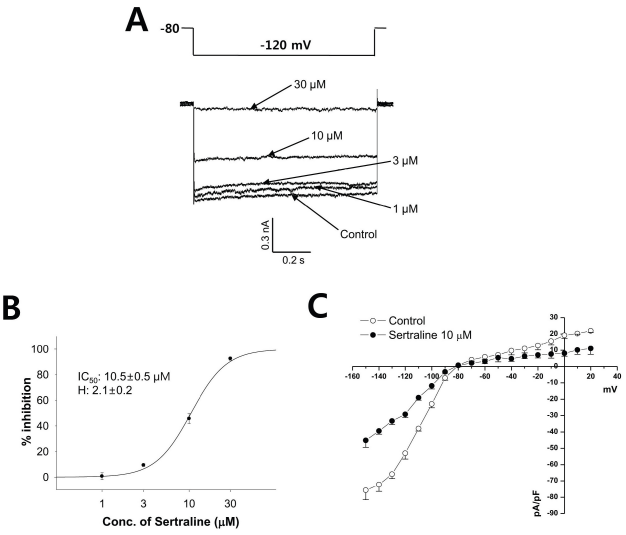

Fig. 4. The effect of sertraline on I_{K1} expressed in HEK293 cells. (A) The I_{K1} was elicited by the voltage of a one-step pulse (lasting 1 s) from −80 mV to −120 mV (upper). Representative current traces under control condition and after application of 1, 3, 10, and 30 μM sertraline (lower). (B) Concentration response curve for inhibition of I_{K1} by serial application of 1, 3, 10, and 30 μM sertraline. The relationship was fitted to a Hill equation. The IC_{50} and Hill coefficient were 10.5 μM and 2.1, respectively (n=4). (C) Voltage-relationship of the I_{K1} measured at the end of hyperpolarizing pulses against the pulse potential in the control and 10 μM sertraline (n=4).

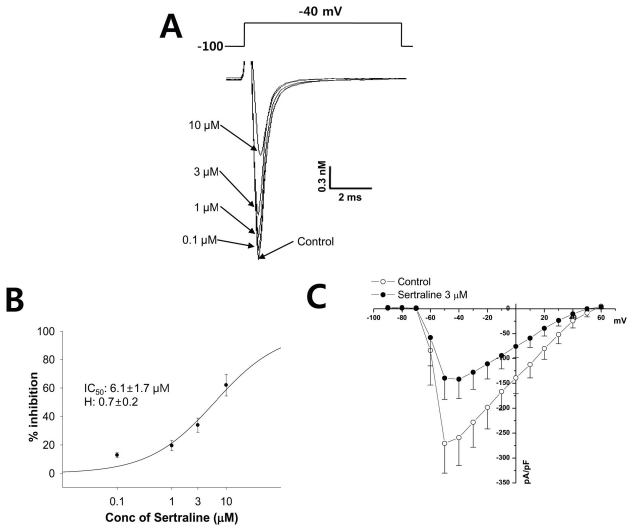

Fig. 5. The effect of sertraline on I_{Na} expressed in HEK293 cells. (A) The peak inward I_{Na} was generated by pulses of 20 ms duration to −40 mV from a holding potential of −100 mV delivered at a frequency of 10 Hz (upper). Representative current traces under control condition and after application of 0.1, 1, 3, and 10 μM sertraline (lower). (B) Concentration response curve for inhibition of I_{Na} by serial application of 0.1, 1, 3, and 10 μM sertraline. The relationship was fitted to a Hill equation. The IC_{50} and Hill coefficient were 6.1 μM and 0.7, respectively (n=4). (C) Voltage-relationship of the I_{Na} measured at its peak just after depolarization pulse against the pulse potential in the control and 3 μM sertraline.

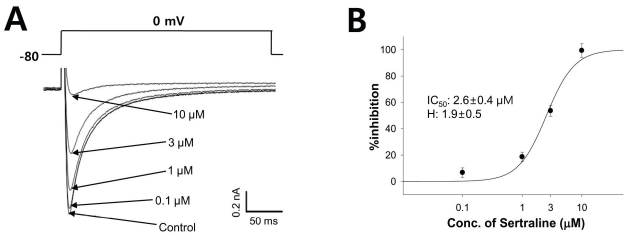

Fig. 6. The effect of sertraline on I_{Ca} in rat ventricular myocytes. (A) The peak of the I_{Ca} was induced by a single 500 ms voltage pulse to 0 mV from the holding potential of −80 mV (upper). Representative current traces under control condition and after application of 0.1, 1, 3, and 10 μM sertraline (lower). (B) Concentration response curve for inhibition of I_{Ca} by serial application of 0.1, 1, 3, and 10 μM sertraline. The relationship was fitted to a Hill equation. The IC_{50} and Hill coefficient were 2.6 μM and 1.9, respectively (n=4).

Effect of sertraline on I_{Na}

Fig. 5 shows the inhibitory effect of sertraline on I_{Na} in SCN5A-transfected HEK293 cells. Sertraline at concentrations of 0.1, 1, 3, and 10 μM reduced the I_{Na} amplitude by 12.8±1.8%, 19.5±3.6%, 33.9±5.0%, and 62.0±7.6%, respectively (n=4). The IC_{50} value calculated from the concentration-response curve was 6.1±1.7 μM, and the Hill coefficient was 0.7±0.2 (Fig. 5B). Fig. 5C demonstrated the current-voltage relationship (I-V curve) of I_{Na} in the contro1 and presence of 3 μM sertraline. Sertraline exerted a concentration-dependent inhibition of I_{Na}. The peak amplitidude was observed similary observed at around −50 mV.

Effect of sertraline on I_{Ca}

Fig. 6 shows the effects of sertraline on the I_{Ca} in freshly isolated rat ventricular myocytes. Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the I_{Ca} amplitude by 6.7±3.5%, 18.6±3.6%, 53.5±4.1%, and 99.4±5.2%, respectively (n=4). The IC_{50} value calculated from the concentration-response curve was 2.6±0.4 μM, and the Hill coefficient was 1.9±0.5 (Fig. 6B).

DISCUSSION

The use of SSRIs has increased dramatically [17], because of their superior safety profile compared to TCAs [18]. Several studies have shown that the SSRIs affected various ion channels including volume-regulated anion channels (VRAC) in endothelial cells [19], rat Nav1.4 (encoded by SCN4A both in GH3 cells and heterologously expressed in HEK293) [20], and G protein-activated inwardly rectifying K^+ (GIRK) channels expressed in Xenopus oocyte [21].

In the present study, we investigated the effect of sertraline on *hERG* (for I_{Kr}), *KCNQ1/KCNE1* (for I_{Ks}), *KCNJ2* (for I_{K1}), and *SCN5A* cDNA-transfected HEK293 cells and native rat ventricular myocyte for L-type calcium currents (I_{Ca}). All potassium channel currents tested in this study were inhibited by sertraline in concentration-dependent manner. Sertraline is a potent blocker of hERG current with an IC_{50} of 0.7 μM (Fig. 2), and of I_{Ks} (Fig. 3) and I_{K1} (Fig. 4) as well. The rank order of potency was $hERG > I_{K1} > I_{Ks}$ with IC_{50} values of 0.7, 10.5, and 15.2 μM, respectively.

It is well known that K^+ channels play an important role in the repolarization of mammalian cardiac action potential in different species, including human. Specially, *hERG* channel current, mediating the rapidly activating delayed rectifier K^+ current (I_{Kr}) in the heart [22], has a key role in repolarization of the cardiac action potential and in controlling action potential duration. Following multiple oral once-daily doses of 200 mg, the mean peak plasma concentration (Cmax) of sertraline is 0.19 μg/ml, approximately 0.6 μM [23]. This value is similar with the IC_{50} value of the hERG on our study. A 30-fold margin between the effective therapeutic plasma concentration and the IC_{50} value for I_{Kr} block has been suggested as margin of safety relative to the risk of TdP for all drugs with I_{Kr}-blocking properties [24]. In this respect, potentially harmful effect of sertraline on cardiac action potential should be considered afterwards.

It is well known that the congenital dysfunction of I_{Ks} caused by genetic mutations in the KCNQ1 or KCNE1 gene is linked to congenital long QT syndrome subtype LQT1 or LQT5 [25]. Electrical remodeling in the diseased hearts, like as myocardial infarction [26], chronic heart failure [27], and cardiac hypertrophy [28], is often linked with a reduction of I_{Ks}. In case of I_{K1}, the I_{K1}-related heart rhythm disturbances also known [29] but it's less prevalent than those associated with I_{Kr} or I_{Ks}.

In addition to K^+ channels, sertraline also inhibited I_{Na} and I_{Ca}, and the IC_{50} value is 6.1 and 2.6 μM, respectively. Because the voltage-gated sodium channel is important to the upstroke phase of the action potential in most excitable

cells, the malfunction of the I_{Na} cause inherited arrhythmogenic syndromes including long QT syndrome subtype 3 (LQT3), Brugada syndrome, and several cardiac conduction defects (CCD) [30]. Cardiac L-type calcium channel mutations can also induce severe arrhythmic disorder [31].

Although SSRIs (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and venlafaxin) are considered to be free from the cardiotoxicity, there are increasing number of case reports on various arrhythmias and syncope associated with the use of SSRIs including sertraline [32-35]. The study with spontaneously beating isolated guinea-pig atria, the sertraline caused a dose-dependent decrease in the rate contractions and in the contractile force, which decreased ouabain-induced arrhythmia [36]. According to our present result, this effect probably owes to the inhibition of cardiac Na^+ and Ca^{2+} channels.

When ECG effects of sertraline were investigated in an adult outpatient population, sertraline had no significant effect on the parameters such as RR, PR, QRS, and QT intervals [10]. However, several reports have shown clinically significant QT prolongation during sertraline therapy [37,38]. Recently, the case report for QT interval prolongation after an overdose of sertraline was released [31]. In addition, cardiac arrest [39] and tachycardia [40] during sertaline therapy was also reported on several case.

According to this investigation, the QT prolongation and sudden cardiac death can be induced by the effect of sertraline on several major ion channel of involving cardiac repolarization. Cardiac action potential was made by net of the various ion channels like as K^+ channel terminating action potential duration and Na^+ or Ca^{2+} channels prolonging the action potential duration. Some drugs modified these ion channels could induce change of the cardiac action potential duration and QT interval, resulted in cardiac arrhythmia. However, interactions with multiple cardiac ion channels can either enhance or compromise the prolongation of action potential duration and QT. Therefore, in general, an integrated assessment of in vitro and in vivo data is required in order to predict the ventricular arrhythmogenic risk of a new drug candidate in humans.

Taken together with previous *in vivo* data, the contribution of the inhibitory effects of sertraline on cardiac ion channels to the therapeutic action of sertraline cannot be excluded. Therefore, the patients taking sertraline especially with risks of long QT syndrome should be cautiously monitored for clinical signs of cardiac arrhythmia.

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