Wide Spectrum of Inhibitory Effects of Sertraline on Cardiac Ion Channels

Hyang-Ae Lee¹², Ki-Suk Kim¹, Sung-Ae Hyun¹, Sung-Gurl Park¹, and Sung Joon Kim²

¹Next-Generation Pharmaceutical Research Center, Korea Institute of Toxicology, Korea Research Institute of Chemical Technology, Daejeon 305-600, ²Department 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 Ca²⁺ channels in rat ventricular myocytes. According to the results, sertraline is a potent blocker of cardiac K⁺ channels, such as hERG, I_Ka, and I_Ks. The rank order of inhibitory potency was hERG > I_K1 > I_Ka, with IC_{50} values of 0.7, 10.5, and 15.2 μM, respectively. In addition to K⁺ channels, sertraline also inhibited I_Ka and I_Ks, 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 Ca²⁺ 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 Ca²⁺ channel current (I_{Ca}), the inward rectifying potassium channel current (I_K), 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_{hERG} 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_Ka, I_Ks, and I_{Ca} to evaluate the potential effects of the drug on cardiac repolarization.

ABBREVIATIONS: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; hERG, human ether-a-go-go-related gene; AP, action potential.
KOH). The internal solution for ethyl)-1-piperazineethanesulfonic acid, 0.33 NaH₂PO₄, MgCl₂, 5 Mg-ATP (pH adjusted 7.25 with KOH), and for KCl, 5 ethylene glycol tetracetic (EGTA), 10 HEPES, 10 glucose and 1.8 CaCl₂ (pH adjusted to 7.4 with NaOH). The external solution for recording the ionic solution (in mM) NaCl, 5.4 KCl, 1.8 CaCl₂, 0.5 MgCl₂, 5 HEPES (4-(2-hydroxymethyl)-1-piperazineethanesulfonic acid ), 0.33 NaH₂PO₄ and 16.6 glucose (pH adjusted to 7.4 with NaOH). The internal solution for IKo contained the following (in mM): 130 KCl, 5 ethylene glycol tetracetic (EGTA), 10 HEPES, 1 MgCl₂, 5 Mg-ATP (pH adjusted 7.25 with KOH), and for IKs in the KCNQ1/KCNE1-cotransfected Human Embryonic Kidney 293 (HEK293) cells, 150 KCl, 5 EGTA, 10 HEPES, 2 MgCl₂, 1 CaCl₂ and 5 Na₂-ATP (pH adjusted 7.25 with KOH). The internal solution for IKr in KCNQ2-transfected HEK293 cells contained (in mM): 130 K-Asp, 15 KCl, 10 HEPES, 1 MgCl₂, 5 Na₂-ATP, 5 EGTA (pH adjusted 7.25 with KOH), and for the IKs in SCN5A-transfected HEK293 cells, 105 CsF, 35 NaCl, 10 EGTA, 10 HEPES (pH adjusted to 7.25 with NaOH). The IC₅₀ in native rat ventricular myocytes, cells were superfused with an external solution that consisted of (in mM): 137 cholin-Cl, 5 CaCl₂, 5 CsCl, 2, 4-Aminopyridine (4-AP), 10 HEPES, 10 glucose and 1.8 CaCl₂ (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 was used for storage of the freshly isolated rat ventricular myocytes contained (in mM): 70 K-glutamate, 55 KCl, 10 HEPES, 3 MgCl₂, 20 taurine, 20 K₂HPO₄, 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 IKo), KCNQ1/KCNE1 (the gene corresponding to IKs), KCNJ2 (the gene corresponding to IKr), SCN5A (the gene corresponding to IK1) or SCN5A (the gene corresponding to IKs) 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 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=xH/(IC₅₀Hⁿ); H=Hill coefficient, IC₅₀=IC₅₀, x=concentration, f=Inhibition ratio] using the SigmaPlot 2000 program. The half-maximum inhibiting concentration (IC₅₀) was calculated with this function.

RESULTS

Effect of sertraline on hERG, IKo and IKr currents

Fig. 2 shows the effects of sertraline on hERG K⁺ channel
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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 IC50 and Hill coefficient were 0.7±0.01 μM and 1.3±0.02, respectively.

Fig. 3. The effect of sertraline on I\textsubscript{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\textsubscript{Ks} by serial application of 1, 3, 10, and 30 μM sertraline. The relationship was fitted to a Hill equation. The IC50 and Hill coefficient were 12.3 μM and 2.5, respectively (n=4). And we also investigated the effects of sertraline on I\textsubscript{Kr} in KCNQ1/KCNE1 cDNA-transfected HEK293 cells (Fig. 4). Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the I\textsubscript{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\textsubscript{50}) of sertraline. The IC\textsubscript{50} and Hill coefficient were 0.7±0.01 μM and 1.3±0.02, 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\textsubscript{Kr} amplitude by 7.9±1.9%, 24.2±1.9%, 60.1±2.7%, and 86.4±1.4%, respectively (n=4).

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Fig. 4. The effect of sertraline on I\textsubscript{K1} expressed in HEK293 cells. (A) The I\textsubscript{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\textsubscript{K1} by serial application of 1, 3, 10, and 30 μM sertraline. The relationship was fitted to a Hill equation. The IC\textsubscript{50} and Hill coefficient were 10.5±0.5 μM, and the Hill coefficient was 2.1±0.2.

And we also investigated the effects of sertraline on I\textsubscript{K1} in KCNQ2 cDNA-transfected HEK293 cells (Fig. 4). Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the I\textsubscript{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\textsubscript{50} value calculated from the concentration-response curve was 10.5±0.5 μM, and the Hill coefficient was 2.1±0.2.
Effect of sertraline on $I_{Ca}$

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 were 6.1±1.7 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.

**Effect of sertraline on $I_{Na}$**

Fig. 6 shows the effects of sertraline on the $I_{Na}$ in freshly isolated rat ventricular myocytes. Sertraline at concentrations of 1, 3, 10, and 30 μM reduced the $I_{Na}$ amplitude by 6.7±3.5%, 18.6±3.6%, 55.3±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 $I_{Ks}$), KCNQ1/KCNE1 (for $I_{Ks}$), KCNJ2 (for $I_{Ks}$), and SCN5A DNA-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 $I_{Ca}$ (Fig. 3) and $I_{K1}$ (Fig. 4) as well. The rank order of potency was hERG-$I_{Ks}$-$I_{Na}$-$I_{K1}$ 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 ($I_{Ks}$) 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 hERG block has been suggested as margin of safety relative to the risk of TdP for all drugs with hERG-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 $I_{Ks}$, the $I_{Ks}$-related heart rhythm disturbances also known [29] but it’s less prevalent than those associated with $I_{K1}$ 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
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cells, the malfunction of the IA, 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 disorders [31].

Although SSRIIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and venlafaxin) are considered to be free from the cardiotoxicity, there are increasing numbers of case reports on various arrhythmias and syncope associated with the use of SSRIIs 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 Ca2+ 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 sertraline therapy was also reported on several cases.

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 currents by antidepressant sertraline and paroxetine. The inhibition of 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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