Selective serotonin reuptake inhibitor sertraline inhibits voltage-dependent K^+ channels in rabbit coronary arterial smooth muscle cells

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We examined the effects of the selective serotonin reuptake inhibitor (SSRI) sertraline on voltage-dependent K^+ (Kv) channels in freshly isolated rabbit coronary arterial smooth muscle cells using the voltage-clamp technique. Sertraline decreased the Kv channel current in a dose-dependent manner, with an IC_{50} value of 0.18 μM and a slope value (Hill coefficient) of 0.61. Although the application of 1 μM sertraline did not affect the steady-state activation curves, sertraline caused a significant, negative shift in the inactivation curves. Pretreatment with another SSRI, paroxetine, had no significant effect on Kv currents and did not alter the inhibitory effects of sertraline on Kv currents. From these results, we concluded that sertraline dose-dependently inhibited Kv currents independently of serotonin reuptake inhibition by shifting inactivation curves to a more negative potential.

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1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are used as antidepressants in the treatment of depression, panic disorder, social anxiety disorder, and obsessive-compulsive disorder. Because of their safety and efficacy, SSRIs are the most widely prescribed for depressed patients in many countries, and the use of SSRIs has increased dramatically (Ninan 2003; Meijer *et al.* 2004; Mann 2005). To date, several SSRIs, such as fluoxetine, paroxetine, fluvoxamine, dapoxetine, citalopram, escitalopram and sertraline, have been developed. Among them, sertraline was the most widely prescribed antidepressant and second most prescribed psychiatric medication in 2013 (Top 25 Psychiatric medication Prescriptions for 2013 by John M Grohol). However, similar to other SSRIs, sertraline also has general side effects, including sexual dysfunction, diarrhea, nausea, dyspepsia, headache, tremor, dry mouth, dizziness, and insomnia (Edwards and Anderson 1999; Sheehan and Kamijima 2009). Sertraline also has side effects on the various ion

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channels (Maertens *et al.* 2002; Ohno *et al.* 2007; Wang *et al.* 2008; Kobayashi *et al.* 2011; Lee *et al.* 2012); however, the side effects of sertraline on vascular ion channels, specifically K^+ channels, have been ignored. In addition, these studies were performed with cultured cell lines rather than with freshly isolated cells (Maertens *et al.* 2002; Ohno *et al.* 2007; Wang *et al.* 2008; Kobayashi *et al.* 2011).

Although sertraline is the most widely used SSRI, its usefulness could be limited by unexpected effects on other targets, specifically ion channels. For example, sertraline inhibits a broad spectrum of cardiac ion channels. In detail, cardiac K^+ channels, including rapidly activated delayed rectifier K^+ (I_{Kr}), slowly activated delayed rectifier K^+ (I_{Ks}), and inward rectifying K^+ (I_{K1}) channels, were inhibited by sertraline with IC_{50} values of 0.7, 10.5, and 15.2 μM, respectively (Lee *et al.* 2012). The cardiac Na^+ and Ca^{2+} channels were also inhibited by sertraline with IC_{50} values of 6.1 and 2.6 μM, respectively (Lee *et al.* 2012). Furthermore, G-protein-activated inwardly rectifying K^+ (GIRK, Kir3) and Kir4.1 current, stably expressed in Xenopus oocytes and HEK293T cells, respectively, were effectively reduced by application of sertraline with IC_{50} values of 29~36 and 7.2 μM, respectively (Ohno *et al.* 2007; Kobayashi *et al.* 2011). Sertraline also inhibited the volume-regulated anion channels expressed in endothelial cells and the Nav1.4 channels expressed in GH3 cells (Maertens *et al.* 2002; Wang *et al.* 2008). However, to date, the side effects of sertraline on vascular Kv channels have not been addressed. Regarding the side effect of sertraline on a broad spectrum of ion channels, we hypothesize that sertraline could affect the vascular K^+ channels. Therefore, we investigated the side effect of sertraline on vascular Kv channels using freshly isolated from rabbit coronary arterial smooth muscle cells.

Several K^+ channels are expressed in vascular smooth muscle cells, including ATP-sensitive K^+ (K_{ATP}), voltage-dependent K^+ (Kv), inward rectifier K^+ (Kir), and big-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels (Nelson and Quayle 1995). Among these channels, Kv channels are regarded as the most important channels in determining resting membrane potential and agonist-induced changes in vascular tone. (Nelson and Quayle 1995; Yuan 1995). In fact, inhibition of Kv channels induced membrane depolarization and thus vasoconstriction (Shimoda *et al.* 1998; Bae *et al.* 2006). Furthermore, altered Kv channel expression and/or function was associated with several conditions such as hypoxia, hypertension, hypertrophy, and diabetes (Ko *et al.* 2010a). Therefore, the side effects of drugs on Kv channels should be clearly addressed to avoid the incorrect interpretation of experimental data when performing vascular functional studies.

In the present study, we investigated for the first time the side effects of sertraline on Kv channels using native vascular smooth muscle cells. Our results clearly demonstrated that sertraline inhibited the vascular Kv channel in a dose-dependent manner, independent of serotonin reuptake inhibition. Considering the efficacy of sertraline and the physiological relevance of vascular Kv channels, our study could evoke caution for its effects on the vasculature when applying sertraline as an SSRI.

2. Materials and methods

2.1 *Single cell isolation*

Male New Zealand White rabbits were anesthetized by simultaneous injection of pentobarbital sodium (50 mg/kg), and heparin (100 U/kg) into the ear vein. The Committee for Animal Experiments of Kangwon National University approved the experimental procedures. Their hearts were rapidly removed and were immersed in ice-cold normal Tyrode's solution. The second-order branches of left descending coronary arteries (450–550 μm diameter) were separated from the hearts under a stereomicroscope. The endothelium was eliminated by injection of air bubbles into the arteries. Two-step enzyme treatment was applied to render single smooth muscle cells from the arteries. First, the arteries were immersed in 1 ml of Ca^{2+}-free normal Tyrode's solution containing papain (1.0 mg), bovine serum albumin (BSA, 1.0 mg), and dithiothreitol (DTT, 1.0 mg) for 25 min at 37°C. After the first step, the arteries were transferred into 1 ml of Ca^{2+}-free normal Tyrode's solution containing collagenase (2.8 mg), BSA (1.0 mg), and DTT (1.0 mg) for 21–22 min at 37°C. After enzymatic treatment, single smooth muscle cells were separated by gentle agitation in Kraft-Brühe (KB) solution with a fire-polished glass pipette. The cells were stored at 4°C in KB solution and used within one day.

2.2 *Solutions and drugs*

The normal Tyrode's solution contained (mM): NaCl 135, HEPES 5, KCl 5.4, NaH_2PO_4 0.33, glucose 16.6, $CaCl_2$ 1.8, and $MgCl_2$ 0.5, adjusted to pH 7.4 with NaOH. The KB solution contained (mM): KOH 70, L-glutamate 50, KH_2PO_4 20, KCl 55, taurine 20, $MgCl_2$ 3, glucose 20, HEPES 10, and EGTA 0.5, adjusted to pH 7.3 with KOH. The pipette-filling solution contained (mM): K-aspartate 110, KCl 25, $MgCl_2$ 1, NaCl 5, Mg-ATP 4, EGTA 10, and HEPES 10, adjusted to pH 7.2 with KOH. Sertraline and paroxetine were purchased from Tocris Cookson (Ellisville, MO) and were dissolved in dimethyl sulfoxide (DMSO).

2.3 *Electrophysiology*

Whole-cell membrane currents were recorded using the whole-cell patch clamp technique with an EPC-8 amplifier (Medical System Corp., Darmstadt, Germany) and an NI-DAQ-7 digital interface (National Instruments, Union, CA). Recording electrodes were made from borosilicate capillaries (Clark Electromedical Instruments, Pangbourne, UK) using a PP-830 puller (Narishige Scientific Instrument Laboratory, Tokyo, Japan). The resistance of the recording electrodes was 2–3 MΩ when they were filled with pipette solution. Voltage signals were sampled at a rate of 1–3 kHz and were filtered at 0.5–1 kHz. The average values of membrane resistance (Rm), cell capacitance, and resting membrane potential (RMP) were 4.21 ± 0.51 GΩ (n=11), 14.22 ± 0.91 pF (n=21), and −42.85 ± 3.85 mV (n=15), respectively. We did not use the cells with Rm value below 2 GΩ and RMP value more positive than −35 mV in our experiments. In addition, cells with changes in access resistance more than 10% during recording were discarded. The average access resistance was 6.88 ± 0.76 MΩ (n=16).

2.4 *Data analysis*

Data analysis was performed using Origin software, version 7.5 (Microcal Software, Inc., Northampton, MA). As described previously, a first-order blocking scheme was used to describe the interaction kinetics between the drugs and channels (Park *et al.* 2013; Snyders and Yeola 1995). The IC_{50} value and Hill coefficient (n) were yielded by fitting concentration-dependent data (figure 2) to the following Hill equation:

$$f = 1\Big/\left\{1 + \left(\mathrm{IC}_{50}\Big/[D]\right)^{n}\right\},$$

where f is the fractional inhibition of channel current ($f = 1 - I_{drug} / I_{control}$) at the test potential, and $[D]$ is the drug concentration.

The steady-state activation curves were obtained by tail currents, which were elicited by returning the potential to −40 mV after short (20–50 ms) step-depolarizing pulses between −80 and +60 mV. The Boltzmann equation was applied to fit the activation curves:

$$y = 1\Big/\left[1 + \exp\left\{-\left(V - V_{1/2}\right)\Big/k\right\}\right],$$

where k is the slope factor, V is the test potential, and $V_{1/2}$ is the voltage of half-maximal activation.

The steady-state inactivation curves were derived from a two-pulse voltage protocol. Currents were measured with returning potential to 40 mV for 600 ms, after applying 7 s preconditioning pulses varying from −80 to +30 mV intervals of 10 mV in the absence and presence of drugs. Steady-state inactivation curves were fitted with another Boltzmann equation as described below:

$$y = 1\Big/\left[1 + \exp\left\{\left(V - V_{1/2}\right)\Big/k\right\}\right],$$

where k is the slope factor V is the preconditioning potential, and $V_{1/2}$ is the potential at the half-maximal inactivation point.

Data are represented as the means ± standard errors of the mean (S.E.M.). Statistical analysis was performed by Student's t-test. $P<0.05$ was defined as statistically significant.

3. Results

3.1 *Suppression of Kv channels by sertraline*

We investigated the effects of sertraline on Kv channels in rabbit coronary artery smooth muscle cells using the whole-cell patch clamp technique. The influences of BK_{Ca} and K_{ATP} channels were excluded by the addition of EGTA (10 mM) and ATP (4 mM) to the pipette solutions. Involvement of Kir channels was also excluded using large-diameter coronary arteries (450–550 μm) because Kir channels are only present in microvessels (<100 μm) and, not in conduit arteries (Park *et al.* 2005a). As shown in figure 1A, the Kv current rapidly reached a peak and then showed partial and slow inactivation (intrinsic inactivation). Application of 1 μM sertraline decreased the Kv current amplitude (figure 1B). This inhibition reached a steady-state within 3 min and the inhibitory effect of sertraline was partially washed out (approximately 50%). The current-voltage (I-V) relationships measured at the end of the current are shown in figure 1C. Application of 1 μM sertraline inhibited the Kv current by 56% at +60 mV (n=6, *$P<0.05$; control vs. sertraline by Student's t-test).

3.2 *Sertraline inhibits the Kv current in a concentration-dependent manner*

To evaluate the concentration-dependent inhibition of Kv channels by sertraline, various concentrations of sertraline at 0.01, 0.03, 0.3, 1, 10 and 30 μM were applied to Kv channels. Kv currents were evoked by a one-step depolarizing pulse to +60 mV from a holding potential of -60 mV. The Kv channel inhibition was increased with increasing concentration of sertraline (figure 2A). The steady-state Kv currents were normalized with a control (without sertraline) Kv current, which was fitted with the Hill equation to yield

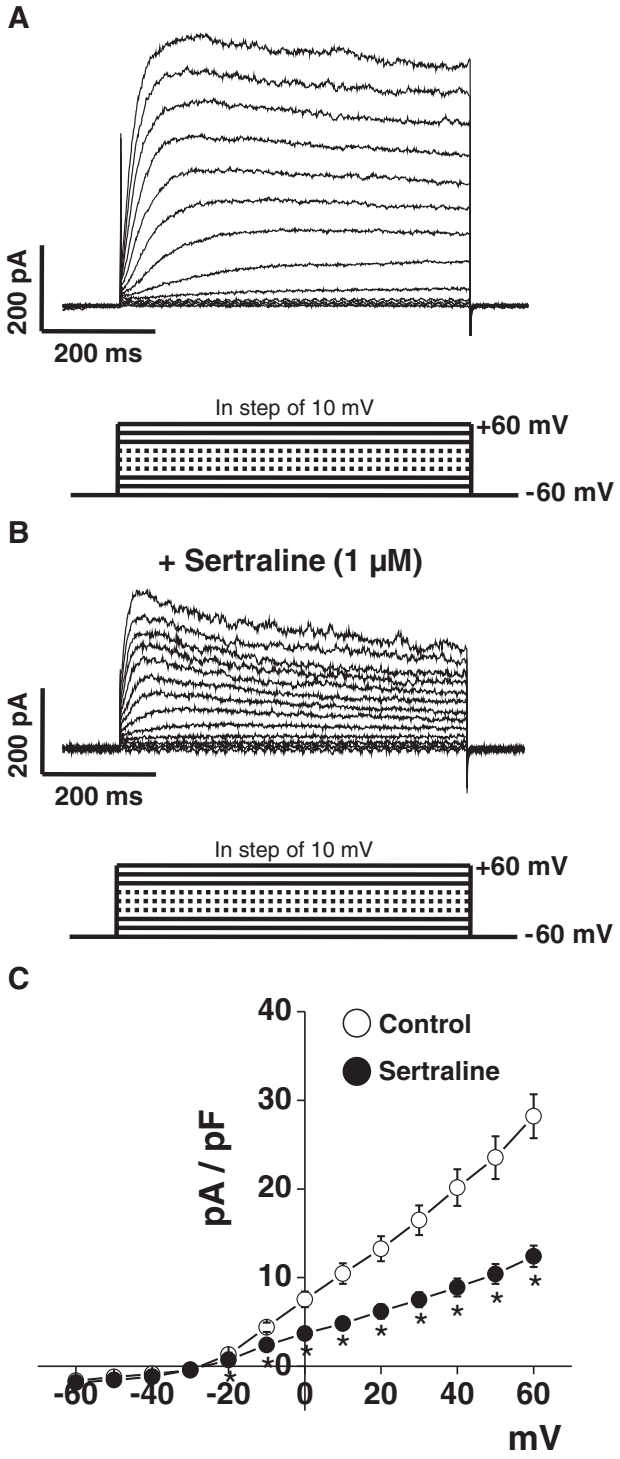

Figure 1. The effects of sertraline on Kv current in rabbit coronary arterial smooth muscle cells. The Kv current traces were elicited by a 600 ms depolarizing pulse from −60 mV to +60 mV at a holding potential of −60 mV in steps of 10 mV, in the control condition (**A**) and the presence of 1 μM sertraline (**B**). (**C**) The current–voltage (*I-V*) relationship of steady-state Kv current in the absence (○) and presence (●) of 1 μM sertraline. *n*=6. **P*<0.05 (control vs. sertraline by Student's *t*-test).

an IC_{50} value of 0.18±0.04 μM and a slope value of 0.61 ±0.06 (figure 2B, *n*=7). These results suggested that sertraline inhibited the Kv channels in a concentration-dependent manner.

3.3 *Effect of sertraline on the steady-state activation and inactivation of Kv channels*

To determine whether the inhibitory effect of sertraline was due to shift in activation and/or inactivation curves, we tested the effects of sertraline on steady-state activation and inactivation curves. As described in the Materials and Methods section, a two-pulse protocol was applied to obtain tail currents. figure 3A shows the effects of sertraline on steady-state activation curves. Application of 1 μM sertraline did not cause a significant shift in the activation curve for Kv channels. Indeed, the half-maximal activation potential ($V_{1/2}$) and slope value (*k*) were 3.42±1.91 mV and 9.28±1.31, respectively, under control conditions, and −0.50±1.98 mV and 10.51±2.13, respectively, in the presence of 1 μM sertraline (*n* = 6).

We also investigated the effects of sertraline on steady-state inactivation curves. The inactivation curves were obtained from another two-pulse protocol as described in Materials and Methods. As shown in figure 3B, application of 1 μM sertraline caused a significant negative shift in the inactivation curves. The half-maximal potential ($V_{1/2}$) and slope value (*k*) were −21.64±1.42 mV and 9.55±0.94, respectively, in the control condition, and −35.85±2.25 mV and 11.50±1.05, respectively, in the presence of 1 μM sertraline (*n*=6, **P*<0.05; control vs. sertraline, at each voltage by Student's *t*-test). These results suggested that sertraline could interact with the Kv channel in the closed (inactivated) state.

3.4 *Effect of another SSRI on the inhibition of Kv channels by sertraline*

To confirm that the inhibitory effect of sertraline on the Kv channel was not related to its serotonin reuptake inhibition, we tested the effects of sertraline on Kv channels in the presence of another SSRI, paroxetine. Paroxetine has also been widely used as highly potent SSRI that binds with high affinity to the serotonin transporter with a K_i value of 0.05 nM (Owens *et al.* 1997). Therefore, we applied 0.5 μM paroxetine (10,000 times higher than the K_i value for serotonin transporter inhibition) to inhibit serotonin transporter completely. As shown in figure 4A and B, treatment with paroxetine only slightly affected the Kv current (NS = not significant; control vs. paroxetine by Student's *t*-test), and did not alter the inhibitory effects of sertraline on Kv channels (*n*=5, **P*<0.05; control vs. paroxetine + sertraline by Student's *t*-test). These results strongly suggested that the

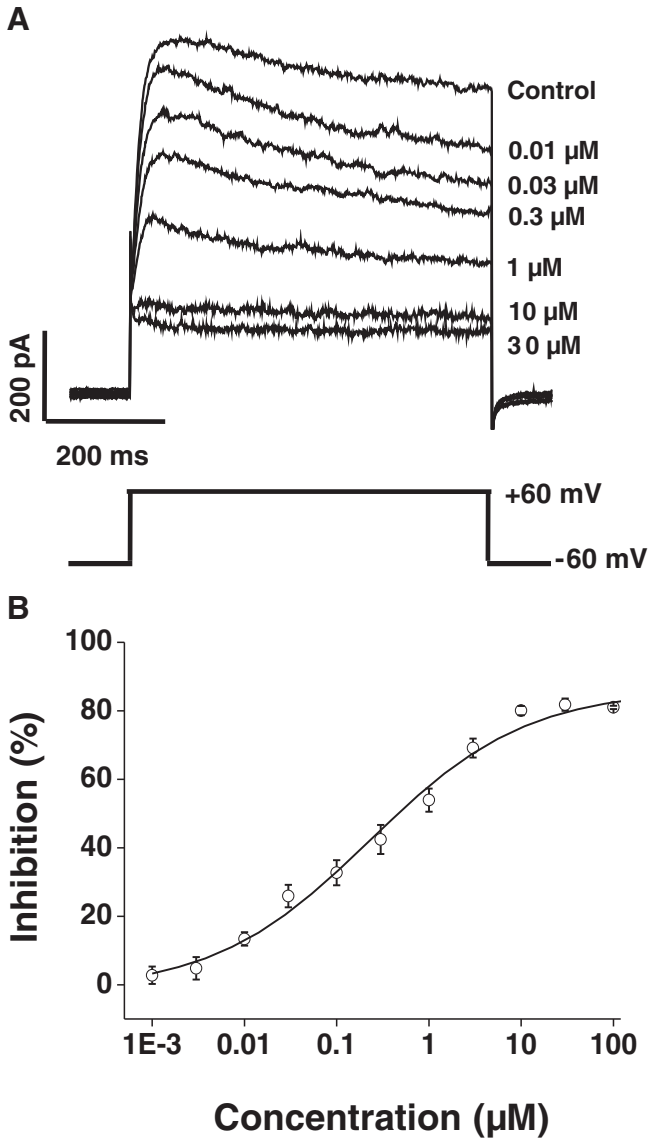

Figure 2. Concentration-dependent inhibition of Kv current by sertraline. (**A**) Representative current traces obtained in the absence and presence of 0.01, 0.03, 0.3, 1, 10 and 30 μM sertraline. One-step 600 ms depolarizing pulses to +60 mV from a holding potential of −60 mV were applied to generate current traces. (**B**) Dose-response curve for sertraline-induced inhibition of Kv channels. The percentage inhibition of Kv current is plotted by various concentrations of sertraline. All *n*=7.

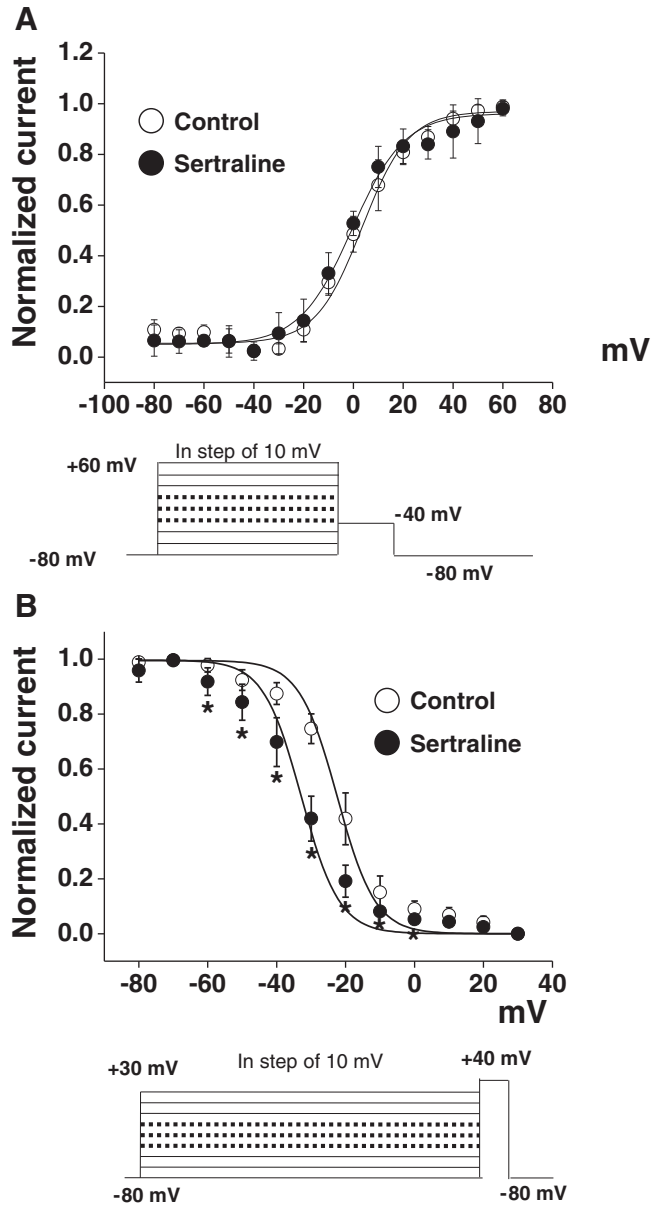

Figure 3. Influence of sertraline on steady-state activation and inactivation curves. (**A**) Activation curves obtained in the absence (○) and presence of 1 μM sertraline (●). Tail currents were elicited by returning the potential to −40 mV after short depolarizing step pulses (20–50 ms) between −80 mV to +60 mV in steps of 10 mV at a holding potential of -80 mV. The recorded tail currents at each potential were normalized by the maximal tail current. n = 6. (**B**) Inactivation curves obtained in absence (○) and presence of 1 μM sertraline (●). The current was elicited by a test pulse to +40 mV after 7-s pre-pulses of different voltages, and then the steady-state currents of the test pulse were normalized by the peak current. n=6. *P<0.05 (control vs. sertraline, at each voltage by Student's t-test).

inhibitory effects of sertraline on Kv channels are independent of serotonin reuptake inhibition.

4. Discussion

In the present study, we demonstrated for the first time the inhibitory effect of sertraline on the vascular Kv channel.

Sertraline inhibited the Kv current in a concentration-dependent manner, independently of its serotonin reuptake inhibition. In addition, sertraline shifted the steady-state inactivation curves to more negative potentials, suggesting that sertraline interacted with Kv channels in the closed (inactivated) state of the channels.

The inhibitory effects of sertraline on Kv channels do not appear to be mediated via serotonin reuptake inhibition, supported for the following reasons. First, pretreatment with another SSRI, paroxetine, did not affect the basal Kv current and did not change the inhibitory effects of sertraline on Kv channels (figure 4). This finding strongly suggested that the inhibitory effect of sertraline was not mediated by serotonin reuptake inhibition. Second, serotonin was reported to inhibit the vascular Kv current (Bae *et al.* 2006). Therefore, application of SSRI could result in an increase in the concentration of serotonin in the circulation, inducing inhibition of the Kv current and thereby increasing the cardiovascular risk in hypertensive patients (Watts 2005). However, SSRI-induced increases in serotonin were impossible in our experimental system using single smooth muscle cells. Therefore, sertraline-induced inhibition of Kv current was not mediated by a sertraline-induced increase in serotonin level but was independent of serotonin reuptake inhibition. Third, based on our experiments, the IC_{50} value for the inhibition of Kv currents by sertraline was 0.18 μM (figure 2), which was 200 times greater than the IC_{50} value (0.85 nM) for serotonin reuptake inhibition (Shank *et al.* 1988). This evidence also supported that the inhibitory effect of sertraline was not related to its serotonin reuptake inhibition. Fourth, the steady-state inactivation curves shifted toward more negative potential (figure 3), suggesting that sertraline could interact with the voltage sensors of Kv channels in a closed state of the channels. Fifth, the inhibition of Kv channels by sertraline occurred instantaneously and reached a steady-state within 3 min. This rapid interaction between sertraline and Kv channels could suggest that Kv channel inhibition by sertraline was not involved in its serotonin reuptake inhibition but was perhaps a direct interaction.

Vascular Kv channels are among the major channels determining resting membrane potentials and, consequently resting tone (Nelson and Quayle 1995; Yuan 1995). Indeed, inhibition of Kv channels by 4-aminopyridine induced membrane depolarization and vasoconstriction in some arteries (Shimoda *et al.* 1998; Bae *et al.* 2006). Furthermore, alterations of Kv channels have been closely correlated with cardiovascular and metabolic diseases, such as hypoxia, hypertension, hypertrophy, and diabetes (Ko *et al.* 2010a). In these pathological conditions, expression and function of Kv channels were decreased in most systemic arteries. Therefore, the recovery of Kv channel function or increased expression of Kv channels has been noted as a crucial therapeutic target to overcome cardiovascular and metabolic diseases. Considering the physiological and pathological relevance of vascular Kv channels, the elucidation of the side effects of some chemicals on Kv channels is essential to the correct interpretation of experimental results.

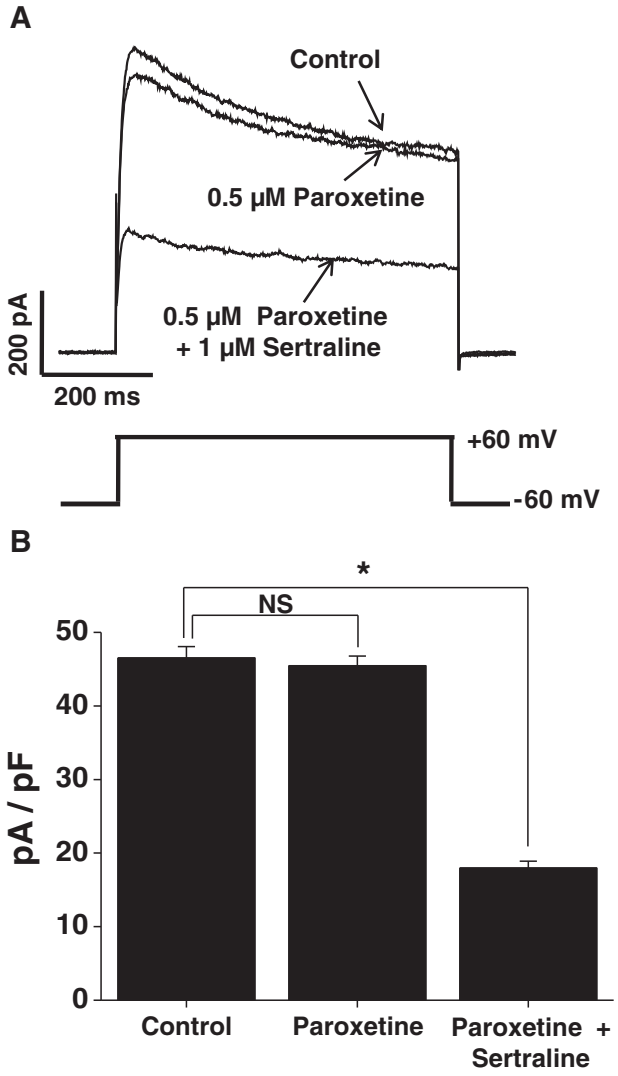

Figure 4. Effect of an alternative SSRI on sertraline-induced inhibition of the Kv current. (**A**) Representative current traces in the control condition, presence of paroxetine, and presence of paroxetine + sertraline. Currents were obtained by a one-step depolarizing pulse to +60 mV with a holding potential of −60 mV. (**B**) Summary of panel (**A**). $n = 5$. $^*P < 0.05$ (control vs. paroxetine + sertraline by Student's *t*-test). NS = not significant (control vs. paroxetine by Student's *t*-test).

To date, several drugs or chemicals have been reported to affect the vascular Kv channels irrespective of their own functions. For example, several protein kinase inhibitors/activators,

such as bisindolylmaleimide (I) (a PKC inhibitor), staurosporine (a PKC inhibitor), H-89 (a PKA inhibitor), genistein (a tyrosine kinase inhibitor), LY 294002 (a PI3 kinase inhibitor), and YC-1 (a guanylyl cyclase activator), have directly inhibited the vascular Kv channels regardless of their own targets (Park *et al.* 2005b,c, 2010; Son *et al.* 2006; Ko *et al.* 2009; Hong *et al.* 2013). Several types of Ca^{2+} channel inhibitors, including efonidipine, mibefradil, verapamil, and NNC 55-0396, have also inhibited vascular Kv currents independently of their Ca^{2+} channel inhibition (Ko *et al.* 2010b; Hong *et al.* 2012; Park *et al.* 2013; Son *et al.* 2014). In addition, calmodulin inhibitors, such as trifluoperazine, W-7, and CGS 9343B, have been reported to inhibit vascular Kv currents, unrelated to calmodulin inhibition (Hong *et al.* 2014; Li *et al.* 2015a, b). Recently, our group revealed that another SSRI, fluvoxamine, inhibited vascular Kv channels independently of serotonin reuptake inhibition. Similar to the results with sertraline, fluvoxamine shifted the inactivation curves to negative potential without alteration of the activation curve (Hong *et al.* 2015). In the present study, we clearly demonstrated the side effects of sertraline on vascular Kv channels. Considering the significance of vascular Kv channels and efficacy of sertraline, the side effects of sertraline on Kv channels should be considered when using sertraline as an SSRI.

In this study, we demonstrated for the first time the inhibitory effects of sertraline on Kv channels using freshly isolated rabbit coronary arterial smooth muscle cells. Although we could not address the detailed binding mechanisms between sertraline and Kv channels, sertraline inhibited the vascular Kv current in a concentration-dependent manner, independently of its serotonin reuptake inhibition, and this inhibition occurred in the closed state of the Kv channels.

Acknowledgements

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