

Fluoxetine Inhibits L-Type Ca^{2+} and Transient Outward K^{+} Currents in Rat Ventricular Myocytes

Kyu-Sang Park¹, In-Deok Kong¹, Ki-Chang Park², and Joong-Woo Lee¹

Abstract

The most common cardiovascular side effects of antidepressants are cardiac arrhythmias and orthostatic hypotension. Little is known, however, about the mechanisms by which these adverse reactions may occur, especially with regard to newer drugs such as fluoxetine. We hypothesized that these side effects may have an electrophysiological basis at the level of the cardiac myocyte. Thus, we investigated the effects of fluoxetine and other antidepressants on action potentials and ionic currents of rat ventricular myocytes using the amphotericin B perforated patch clamp technique. Fluoxetine (10 μM) prolonged the action potential duration (APD_{50}) to $146.7 \pm 12.9\%$ of control value without altering resting membrane potential. Fluoxetine and sertraline potently inhibited the L-type Ca^{2+} current ($\text{IC}_{50} = 2.82$ and $2.31 \mu\text{M}$, respectively), but did not significantly modify the steady-state inactivation. Amitriptyline and imipramine had similar, but slightly weaker, effects ($\text{IC}_{50} = 3.75$ and $4.05 \mu\text{M}$, respectively). Fluoxetine attenuated the peak transient outward K^{+} current and also altered current kinetics, as shown by accelerated decay. Fluoxetine did not change the voltage-dependence of the steady-state inactivation. Sertraline, amitriptyline and imipramine inhibited the transient outward K^{+} current with potencies very similar to fluoxetine. In contrast to the other antidepressants tested, trazodone weakly inhibited the Ca^{2+} and K^{+} currents and moclobemide had no detectable effect. Our comparative pharmacology data suggest that selective serotonin reuptake inhibitors, such as fluoxetine, are as potent as tricyclic antidepressants in inhibiting L-type Ca^{2+} and transient outward K^{+} currents. These inhibitory effects may contribute to cardiovascular complications such as arrhythmias and orthostatic hypotension.

Key Words: Fluoxetine, L-type Ca^{2+} currents, transient outward K^{+} currents, cardiac myocytes

INTRODUCTION

Tricyclic antidepressants (TCAs) have been widely used for the treatment of depression for over 40 years.¹ However they elicit serious cardiovascular side effects such as arrhythmia and orthostatic hypotension, which could potentially limit their therapeutic value.^{2,3} Arrhythmias induced by TCAs include bundle branch block, atrio-ventricular block, and ventricular re-entry patterns.⁴ Such rhythm disturbances can cause death. Orthostatic hypotension, the other major untoward cardiovascular effect of antidepressants, can be due to decreased myocardial contractility and impaired vasoconstriction.⁵ These side effects are elicited at therapeutic doses required for psychiatric

benefit, therefore these drugs are potentially dangerous when administered to elderly patients or patients with pre-existing heart diseases.³

The majority of studies about the cardiovascular side effects of antidepressant treatment are clinical reports, with most investigations concentrated on imipramine.⁶ For example, it has been reported that imipramine decreases systolic left ventricular pressure and heart rate in perfused rat hearts.⁷ Imipramine also reduces the action potential amplitude and V_{max} in ventricular fibres.^{8,9} In isolated guinea-pig cardiac myocytes, imipramine antagonizes fast inward sodium current in a use-dependent manner.¹⁰ Further, imipramine blocks both high threshold Ca^{2+} (i.e., L-type) and delayed rectifier K^{+} currents in guinea-pig ventricular myocytes.⁹

Fluoxetine, one of the newly developed selective serotonin reuptake inhibitors (SSRIs), has become one of the most commonly used drugs for the treatment of depression, largely because it has significantly fewer side effects than TCAs.^{3,11} However, there is little data from animal experiments to determine the effect of fluoxetine on the cardiovascular system. Recently, we have reported that SSRIs elicit undesired effects

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on the contractility of perfused rat hearts.¹² The actions of SSRIs on Ca^{2+} and K^{+} currents have not been investigated, but may be the underlying cause of associated cardiac contractile dysfunction. The purpose of our study was to determine whether changes in L-type Ca^{2+} and transient outward K^{+} currents induced by various antidepressants may provide a rational explanation for changes in cardiac electrophysiology and contractility. We have tested the effects of fluoxetine and other antidepressants on these ionic currents and membrane potentials in ventricular myocytes isolated from the rat heart. Our data may provide further insight into the ionic mechanisms of cardiovascular complications induced by antidepressants.

MATERIALS AND METHODS

Single ventricular cells from rat hearts were isolated by enzymatic dissociation. Adult male Sprague-Dawley rats (200–300 g) were anesthetized with sodium thiopental (50 mg/kg, *i.p.*), and heparinized (500 IU/kg) via the inferior vena cava. After opening the thoracic cavity, hearts were quickly removed and mounted on a modified Langendorff perfusion system for retrograde coronary perfusion. The hearts were perfused for 6 min. with nominally Ca^{2+} -free Tyrode solution which contained (in mM) NaCl 140, KCl 5.4, NaH_2PO_4 0.3, MgCl_2 1.0, HEPES 10, glucose 10, to pH 7.4 with NaOH. Hearts were then perfused for 12 min. with Ca^{2+} -free Tyrode solution containing 1.2 mg/ml collagenase (CLS-2, Worthington Biochemical Co., Freehold, NJ, USA) and 0.1 mg/ml protease (Type XIV, Sigma Chemical Co., St. Louis, MO, USA). Enzymes were washed out by perfusing with Tyrode solution containing 200 μM Ca^{2+} for 6 min. The hearts were then removed from the Langendorff apparatus and the ventricles dissected free. Ventricular tissue was placed in 200 μM Ca^{2+} Tyrode solution in a petri dish and gently shaken to disperse cells. Isolated myocytes were allowed to equilibrate for more than 1 hour prior to study. Only Ca^{2+} -tolerant, rod-shaped cells with clear striations were used for electrophysiology experiments.

The suspension of dissociated cells was transferred to a 0.5 ml chamber placed on the stage of an inverted microscope (IMT-2, Olympus, Tokyo, Japan). After adhering to the bottom of the chamber, cells were superfused with an external solution (2–3 ml/min) at room temperature. The membrane po-

tential and ionic currents were recorded in the whole cell configuration of the patch clamp technique using an Axopatch 1 D amplifier (Axon Instruments, Foster city, CA, USA). The action potentials were elicited by current pulses (200 pA, 2.5 msec, 0.2 Hz) and recorded in current-clamp mode. Patch pipettes were fabricated on a model P-97 Flaming/Brown micropipette puller (Sutter Instrument Co., CA, USA) from glass capillary (G-1.5, Narishige, Tokyo, Japan). Pipettes were fire-polished prior to use and had tip resistances of 1.5–2.0 $\text{M}\Omega$ when filled with internal solution. The pipette and its holder were connected to the headstage of the amplifier via an Ag/AgCl wire.

The perforated patch clamp technique with amphotericin B (Sigma) was used to record whole cell currents. Amphotericin B stock solution (120 mg/ml) was prepared in dimethyl sulfoxide and diluted in the pipette solution to give a final concentration of 480 $\mu\text{g/ml}$. Voltage-clamp command pulses were generated by an IBM computer using pClamp 6.0 software with a Digidata 1200 analog-to-digital converter (Axon Instruments Inc). An 8-pole Bessel filter was used to low-pass filter membrane currents at 5 kHz. Current amplitudes were normalized to membrane capacitance and expressed as pA/pF. Membrane capacitances (C_m) were measured by applying a 20 ms, 10 mV hyperpolarizing step from a holding potential and calculated according to the following equation: $C_m = \tau \cdot I_0 / \Delta V_m$ (I_∞ / I_0). Where τ is the time constant of the capacitive current, I_0 is the maximum capacitive current value, ΔV_m is the amplitude of a voltage step, and I_∞ is the amplitude of the steady-state current.¹³ Series resistances were calculated as $R_s = \Delta V_m / I_0$. Average membrane capacitance and series resistance of ventricular myocytes were 145.1 ± 4.5 pF and 6.2 ± 0.3 $\text{M}\Omega$, respectively ($n=50$).

To isolate Ca^{2+} currents, the pipette solution contained (in mM) Cs-Aspartate 100, CsCl 30, EGTA 0.1, MgCl_2 1.2, HEPES 10, glucose 10, titrated to pH 7.2 with CsOH. Tyrode solution with 2 mM CaCl_2 was used as an external solution for Ca^{2+} current measurements. When recording K^{+} currents, the pipette solution was (in mM) K-gluconate 110, KCl 30, EGTA 0.1, MgCl_2 1.2, HEPES 10, glucose 10, adjusted to pH 7.2 with KOH. The external solution for measuring K^{+} currents was Tyrode solution with 2 mM MnCl_2 instead of CaCl_2 . Applying a holding potential or prepulse of -40 mV eliminated the fast Na^{+} current.¹⁴ Pipette solutions were

passed through a 0.2 μm pore size filter membrane (Gelman Sciences, Ann Arbor, MI, USA) and drugs were applied to the bath via gravity-fed polyethylene tubes connected to a 6-way valve (Hamilton, Reno, NV, USA). Antidepressants used in these experiments were kindly donated as follows: imipramine and amitriptyline from Myung-In (Seoul), fluoxetine from Dae-Woong Lilly (Seoul), Sertraline from Korea Pfizer (Seoul), trazodone from Kuk-Je (Seoul) and moclobemide from Korea Roche (Seoul).

Concentration-response curves and IC_{50} values of antidepressants on Ca^{2+} and K^{+} currents were obtained from least-squares non-linear regression. IC_{50} is defined as the concentration of antidepressant, which reduced the Ca^{2+} or K^{+} current by 50%. The steady-state inactivation data were fitted by a Boltzmann distribution of the following equation: $I / I_{\text{max}} = 1 / \{1 + \exp[(V - V_{1/2}) / k]\}$ where I_{max} is maximal current, $V_{1/2}$ is the membrane potential producing 50% inactivation, and k is the slope factor. All data, including percent inhibition, were expressed as the mean \pm S.E.M. Statistical analysis was done with Student's t-test, and differences were considered significant when $p < 0.05$.

RESULTS

Effects of fluoxetine on action potential characteristics

The effects of fluoxetine on the action potential characteristics of ventricular myocytes stimulated at a frequency of 0.2 Hz were studied. Fluoxetine (10 μM) prolonged the action potential duration measured at 50% of the repolarization (APD_{50} ; from 74.0 ± 16.2 msec to 109.1 ± 25 msec) ($n=6$, $p < 0.05$). Fluoxetine also significantly lengthened the final phase of repolarization measured as APD_{90} from 114.9 ± 22.9 msec to 168.1 ± 35.5 msec ($p < 0.05$). Action potential amplitude was decreased slightly by fluoxetine (113.3 ± 3.2 mV vs. 108.9 ± 3.6 mV). However, the resting membrane potential was not affected by fluoxetine (-68.4 ± 2.3 mV vs. -68.5 ± 2.5 mV).

Effects of fluoxetine on L-type Ca^{2+} current

The representative traces shown in Fig. 1a were obtained using depolarizing test pulses between -30 and $+50$ mV from holding potential of -40 mV.

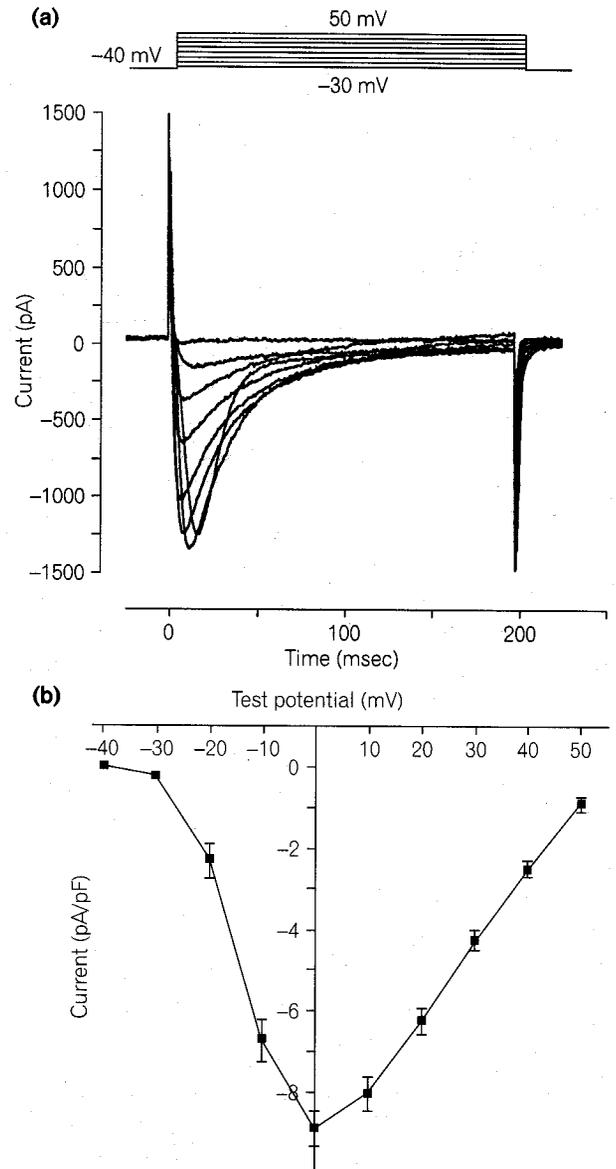


Fig. 1. L-type Ca^{2+} currents in isolated rat ventricular myocytes. Ca^{2+} currents were recorded using the perforated whole cell patch clamp technique. The cells were dialyzed with Cs^{+} to block outward current and held at -40 mV to inactivate voltage-dependent Na^{+} channels. (a) A representative family of Ca^{2+} current traces in a single isolated myocyte at room temperature. The cell was held at -40 mV and then stepped up to the indicated voltages for 200 msec. (b) Current-voltage relationship of the Ca^{2+} current in rat cardiac myocytes. Group data ($n=14$) for the peak current at each voltage are shown. Currents were normalized to membrane capacitance.

The fast Na^{+} current was eliminated by holding at -40 mV, while outward K^{+} current was blocked by dialyzing the cell with Cs^{+} . The current under these conditions was therefore carried mainly by Ca^{2+} . This was confirmed by the observation that voltage-dependent current was completely blocked by 0.1 mM

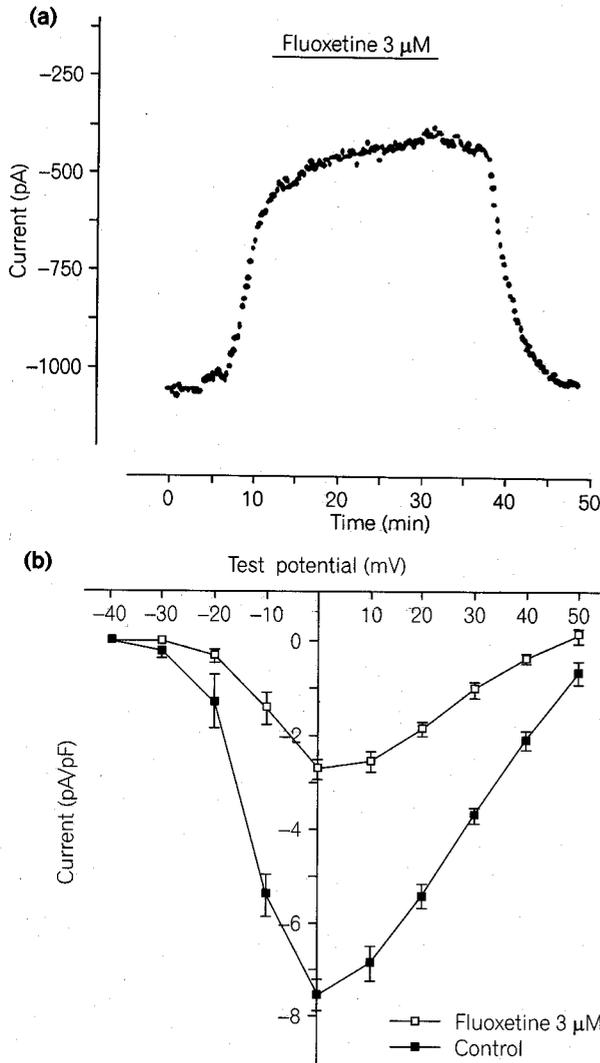


Fig. 2. Fluoxetine inhibits L-type Ca^{2+} current in ventricular myocytes. (a) A representative time course illustrates the inhibitory effect of fluoxetine on peak Ca^{2+} current. The cell was held at -40 mV and stepped up repeatedly to 0 mV to determine peak I_{Ca} . Application of $3 \mu\text{M}$ fluoxetine blocked Ca^{2+} current (application of drug indicated by horizontal bar). This inhibitory effect was reversible. (b) Group data ($n=6$) for the current-voltage relationship in the absence (■) and presence (□) of $3 \mu\text{M}$ fluoxetine. Fluoxetine significantly attenuated L-type Ca^{2+} current. Asterisks indicate significant differences from control by unpaired *t*-test (* $p < 0.05$, ** $p < 0.01$).

CdCl_2 (data not shown). Inward Ca^{2+} currents were detected at a threshold voltage of -20 to -30 mV, while peak currents occurred at 0 mV (Fig. 1b). These observations are in broad agreement with previous reports.^{15,16} Average peak current amplitude was 8.91 ± 0.45 pA/pF ($n=14$).

Fluoxetine inhibited peak Ca current in a rapid and reversible manner (Fig. 2a). Whole cell Ca^{2+} current was measured every 15 sec by applying a 200 msec

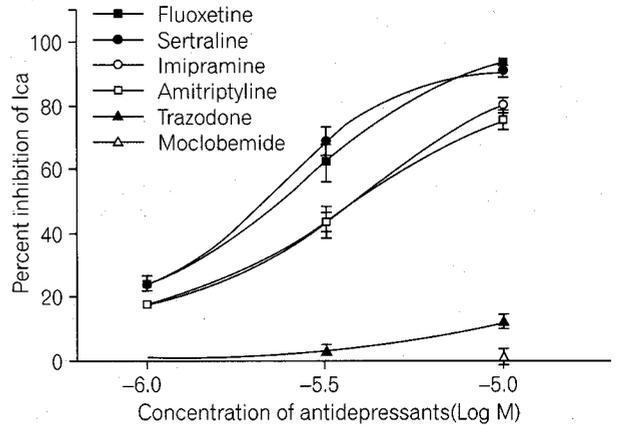


Fig. 3. Effects of various antidepressants on L-type Ca^{2+} current in rat ventricular myocytes. Concentration-response curves show antagonism of L-type Ca^{2+} current by antidepressants. Data are expressed as percent inhibition of peak I_{Ca} . The inhibitory effects of antidepressants were determined by repeatedly depolarizing to 0 mV from a holding potential of -40 mV while drugs were added in a cumulative manner. Data are the mean \pm S.E.M. from at least 5 cells.

test pulse to 0 mV. Using the same ionic conditions described above. When the extracellular solution contained $3 \mu\text{M}$ fluoxetine, peak Ca^{2+} current was decreased to less than 60% of its original value within 5 min. The current recovered fully after washing out the drug (Fig. 2a). As indicated in the group current-voltage relationship (Fig. 2b; $n=6$), fluoxetine significantly attenuated current at between -30 and $+50$ mV. Fluoxetine did not, however, alter the threshold potential and the potential at which current was maximal.

The effects of various kinds of antidepressants on peak Ca^{2+} current are shown in Fig. 3. SSRIs (fluoxetine and sertraline) and TCAs (imipramine and amitriptyline) inhibited peak Ca^{2+} current in a concentration-dependent manner. The IC_{50} values for fluoxetine and sertraline were 2.82 and $2.31 \mu\text{M}$, respectively. These values were slightly lower than those of imipramine ($3.75 \mu\text{M}$) and amitriptyline ($4.05 \mu\text{M}$). However, trazodone (atypical antidepressant) and moclobemide (monoamine oxidase inhibitor) did not inhibit the Ca^{2+} current at the concentrations tested.

Effects of fluoxetine on transient outward K^+ current

To study the effect of fluoxetine on K^+ current, experiments were performed with equimolar replacement of Ca^{2+} with Mn^{2+} to block Ca^{2+} current and

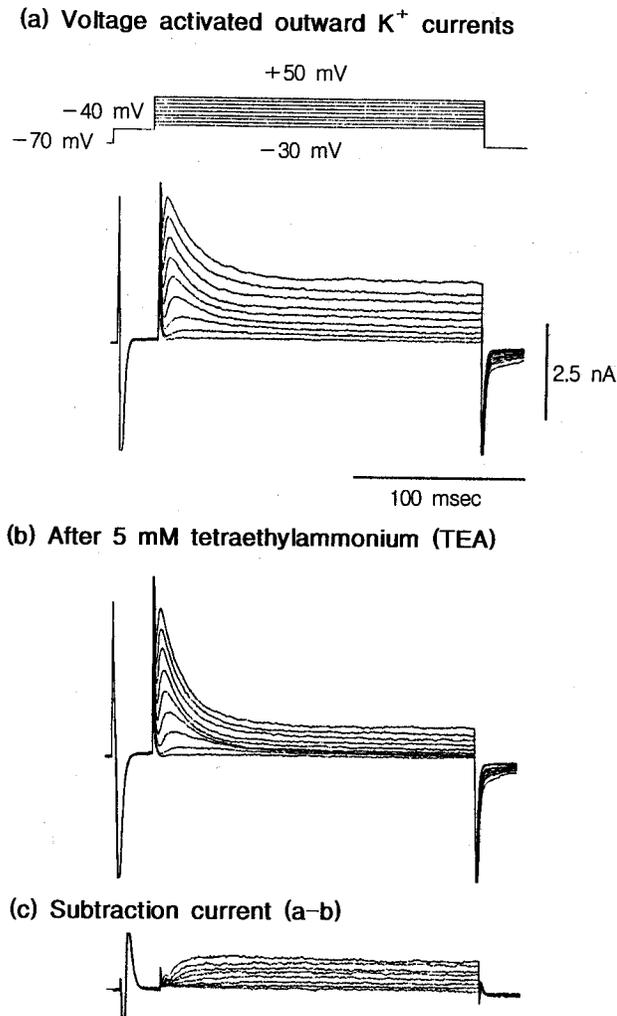


Fig. 4. TEA-sensitive and -insensitive components of the voltage-activated outward current in ventricular myocytes. Outward currents were elicited during depolarization to potentials between -30 and $+50$ mV from a holding potential of -70 mV. I_{Ca} was limited by replacing extracellular Ca^{2+} with Mn^{2+} , while a 30 msec prepulse to -40 mV was used to inactivate Na^+ current. (a) Voltage-activated outward currents from a representative cell. (b) TEA (5 mM) was applied to the same cell to antagonize delayed rectifier K^+ channels and thus reveal the rapidly inactivating I_{to} . TEA markedly attenuated the sustained current. (c) The TEA-sensitive component, i.e., the delayed rectifier current, was determined by subtracting the current in (b) from that in (a).

a prepulse to -40 mV to eliminate Na^+ current. Under these conditions, depolarizing pulses to -30 or -40 mV evoked voltage-activated outward currents (Fig. 4a), which are known to reflect a combination of transient outward and delayed rectifier currents.¹⁷ To isolate the transient outward K^+ current (I_{to}), we applied 5 mM tetraethylammonium (TEA), which blocked the delayed rectifier current (Fig. 4, b and c). The remaining current was assumed

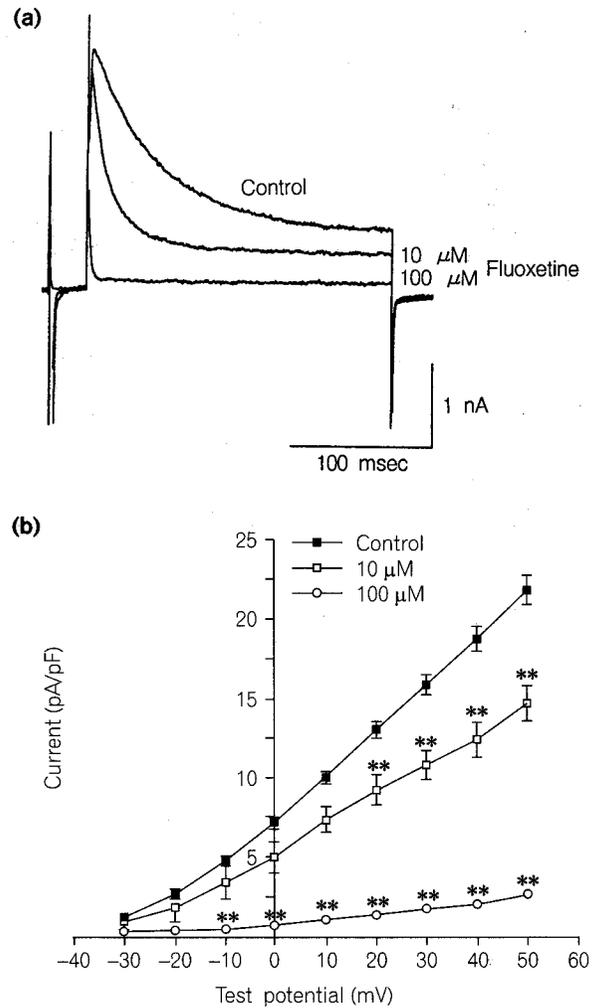


Fig. 5. Fluoxetine inhibits transient outward K^+ currents on ventricular myocytes. (a) Superimposed transient outward K^+ current traces in the absence and presence of 10 and 100 μ M fluoxetine. Currents elicited by a depolarizing pulse to $+50$ mV from a holding potential of -70 mV. TEA (5 mM) was present to antagonize delayed rectifier K^+ channels, and thus isolate I_{to} . (b) Group data ($n=7$) for the current-voltage relationship in the absence (■) and presence of 10 μ M (□) and 100 μ M (○) fluoxetine. Asterisks indicate significant differences from control by unpaired *t*-test (* $p < 0.05$, ** $p < 0.01$).

to be I_{to} , as it was completely inhibited by 3 mM 4-aminopyridine.

Rat ventricular myocytes possess a prominent I_{to} , and we tested the effects of antidepressants on this current. Fluoxetine (10 μ M) decreased the amplitude of the peak and sustained outward current and also accelerated its decay (Fig. 5, a and b). These effects were concentration-dependent (Fig. 6, a and b). The IC_{50} values for peak and sustained current inhibition by fluoxetine were 40 μ M and 12.4 μ M, respectively. These values are significantly higher than the IC_{50} for

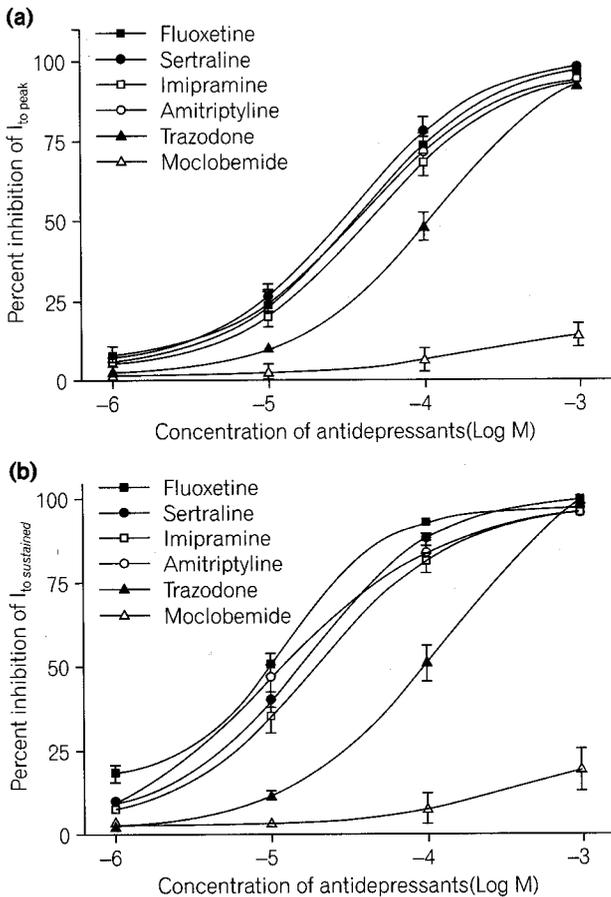


Fig. 6. Effects of various antidepressants on the peak and sustained amplitude of the transient outward K^+ current (I_{to}). Concentration-response curves show the percent inhibition of the peak (a) and sustained (b) components of outward current. The sustained current was measured 200 msec after onset of a depolarizing pulse to +50 mV. Cells were held at -70 mV and stepped up to 50 mV. I_{Ca} and I_{Na} were minimized by Mn^{2+} and a depolarizing prepulse to -40 mV, respectively. Data represent the mean \pm S.E.M. from at least 6 cells in each case.

Ca^{2+} current inhibition. The time constant of decay for I_{to} in control conditions was 16.02 ± 0.55 msec ($n=33$). This time constant was shortened to 8.0 ± 0.6 and 3.3 ± 0.3 msec by 10 μ M and 100 μ M fluoxetine, respectively (Fig. 7). TCAs attenuate the amplitude of I_{to} and the time constant of decay with potencies similar to those of SSRIs. Trazodone inhibits I_{to} at a higher concentration than SSRIs, while moclobemide did not have any detectable effect.

Fluoxetine does not alter inactivation of voltage-dependent channels

To obtain more information about the possible mechanisms of the fluoxetine-induced voltage block-

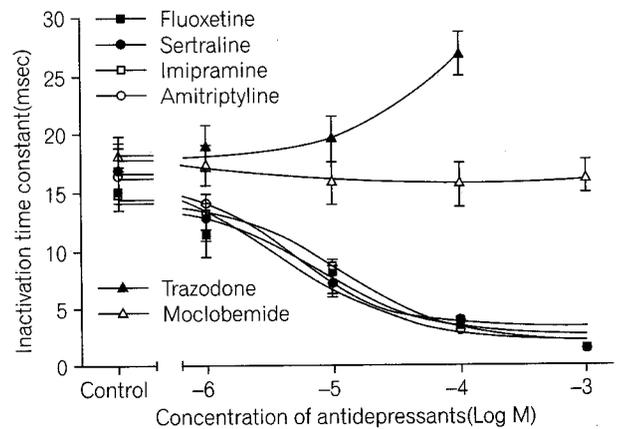


Fig. 7. Effects of various antidepressants on the time constant of decay for transient outward K^+ current (I_{to}). The fast decay time constant (τ_{fast}) of the control myocytes was 16.02 ± 0.55 msec, and the graph shows the concentration-response curve for the changes of time constant by antidepressants. Each point represents the mean \pm SEM of at least 6 cells.

ade of Ca^{2+} and K^+ currents, the effect on steady-state inactivation was examined. The voltage-dependence of steady-state inactivation was determined by using a standard double-pulse protocol. This included a 500 msec conditioning step of varying voltage, which was followed by a 200 msec test pulse to 0 mV. Under control conditions, the voltage required for half-inactivation ($V_{1/2}$) and slope factor (k) for the Ca^{2+} currents were -16.9 mV and -4.97 (mV per e -fold change). Fluoxetine did not significantly alter these values, as $V_{1/2}$ and k were -16.7 and -4.60 mV, respectively (Fig. 8a). The voltage-dependence of inactivation for I_{to} was also not significantly changed by fluoxetine (control $V_{1/2}$ -42.8, k -6.1 mV; fluoxetine $V_{1/2}$: -43.1 mV, k : -5.3; Fig. 8b).

DISCUSSION

The present study demonstrates that SSRIs, as well as TCAs, possess potent antagonistic properties for voltage-dependent ion channels in rat ventricular myocytes. These drugs inhibited both L-type Ca^{2+} and transient outward K^+ currents. The inhibitory concentrations of SSRIs and TCAs on Ca^{2+} current were slightly higher than therapeutic plasma levels (0.57–1.07 μ M).⁶ However, it is difficult to relate *in vivo* plasma concentrations to those of drug-perfused isolated cells.⁹ It is known that TCAs and SSRIs are lipophilic drugs, so they have a greater affinity for tissues where they may reach higher concen-

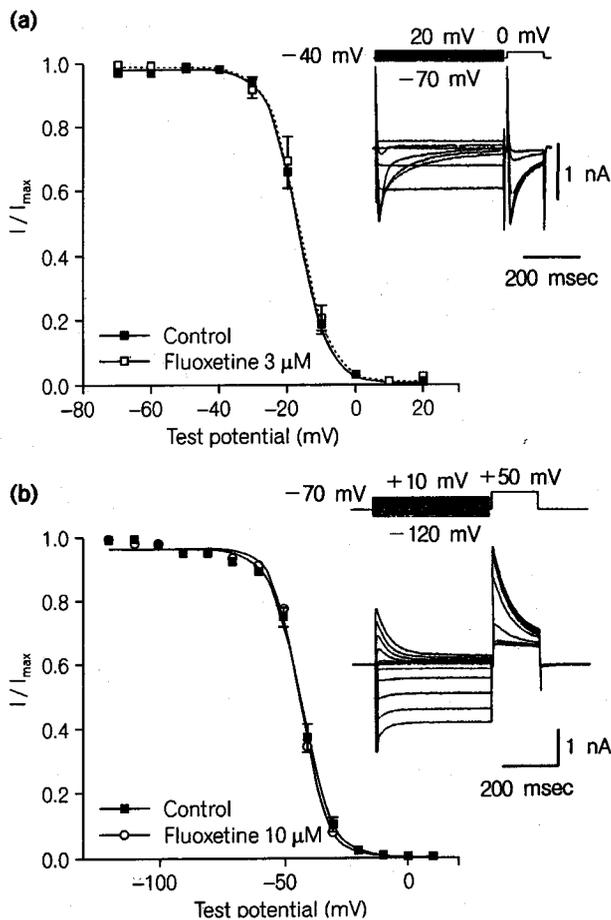


Fig. 8. Effects of various antidepressants on the voltage-dependence of steady-state inactivation of Ca^{2+} and K^{+} currents. Voltage-dependence of steady-state inactivation of L-type Ca^{2+} (a) and transient outward K^{+} current (b). Insets illustrate the double-pulse protocols used and the representative traces obtained. The amplitudes of the currents evoked by test potentials were normalized to their respective maximal amplitudes. The curves through the data points were drawn according to the Boltzmann equation: $I/I_{\max} = 1 / \{1 + \exp[(V - V_{1/2})/k]\}$.

trations than plasma.^{6,18} Furthermore, antidepressants are typically prescribed to depressed patients for an extended period of time, so it is possible that the inhibitory effects of SSRIs could be elicited at lower concentrations if drug exposure was lengthened.

We have reported previously that SSRIs and TCAs have potent cardiodepressive effects on the perfused rat heart.¹² In the present study, we provide evidence that inhibition of L-type Ca^{2+} current could play an important role in reducing cardiac contractility and heart rate. Importantly, the rank order potency of the drug which decreases cardiac contractility and heart rate is similar to that for Ca^{2+} current inhibition. In addition, the effective concentration ranges, which induce cardiac depression, are also consistent with

those for Ca^{2+} current inhibition. It is well known that Ca^{2+} influx is one of the most important factors in eliciting cardiac contraction. As well, Ca^{2+} current plays an essential role in spontaneous depolarization of the sino-atrial node and atrio-ventricular node.¹⁹ Thus, the Ca^{2+} current inhibition induced by antidepressants could potentially decrease heart rate and delay atrio-ventricular conduction. This proposed mechanism may explain the prolonged PR interval and AV block which are common cardiovascular complications of antidepressant therapy.

It has been reported that antidepressants reduce the action potential amplitude and the rate of depolarization in isolated atrial and ventricular tissues.^{8,20,21} The effects of antidepressants on the action potential duration are species-specific. For example, imipramine shortened the action potential duration in guinea-pig^{8,22} and bovine ventricular myocytes.^{20,23} However, in rat²⁴ and rabbit²⁵ cardiac myocytes, imipramine delayed repolarization and prolonged the duration of action potential. In the present study, fluoxetine (10 μM) also increased the action potential duration (APD₅₀ and APD₉₀) to $146.7 \pm 12.9\%$ and $145.4 \pm 14.0\%$ of control value in rat ventricular myocytes without altering the resting membrane potential. Such an effect may be due to the inhibition of voltage-activated outward K^{+} channels as described here.

Cardiac voltage-activated outward K^{+} current consists of transient outward current (I_{to}) and delayed rectifier current (I_{K}), which are sensitive to 4-aminopyridine and tetraethylammonium, respectively.¹⁷ In frog, guinea pig, and bovine ventricular myocytes, it has been reported that most voltage-activated outward K^{+} current is I_{K} .²⁵ However in rat, dog, rabbit, and human myocytes, I_{to} is prominent and plays a significant role in the repolarization phase of the action potential.²⁵⁻²⁷ Thus, inhibition of I_{to} could be the mechanism by which action potential duration is prolonged in rat ventricular myocytes. These antagonistic effects may also increase the probability of arrhythmogenesis, resulting in premature ventricular contraction or ventricular tachycardia.²⁸

In this study, SSRIs and TCAs not only decreased the peak amplitude of I_{to} but also accelerated the time constant of decay. These changes probably reflect a time-dependent open channel block similar to that of quinidine.²⁹ In addition, SSRIs and TCAs changed neither the current-voltage relationship nor the voltage-dependence of steady-state inactivation. Recently, it has been suggested that imipramine

blocks the transient outward K^+ channel in the open state of the channel with very little block in the resting or inactivated states or both.^{30,31} However, it is impossible to infer the exact mechanism of drug action from the results of the present study.

In conclusion, SSRIs such as fluoxetine are as potent as TCAs in inhibiting the L-type Ca^{2+} current and transient outward K^+ current. Blocking L-type Ca^{2+} channels with SSRIs may decrease cardiac contractility and heart rate. In contrast, blocking the transient outward K^+ current could increase the propensity to develop arrhythmias. Further studies to elucidate the precise effects of antidepressants may help reduce the occurrence of the serious cardiovascular side effects associated with SSRI therapy.

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