Inhibition of Human ether-a-go-go-Related Gene K\(^+\) Channel and I\(_{\text{Kr}}\) of Guinea Pig Cardiomyocytes by Antipsychotic Drug Trifluoperazine

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ABSTRACT

Trifluoperazine, a commonly used antipsychotic drug, has been known to induce QT prolongation and torsades de pointes, which can cause sudden death. We studied the effects of trifluoperazine on the human ether-a-go-go-related gene (HERG) channel expressed in \textit{Xenopus} oocytes and on the delayed rectifier K\(^+\) current of guinea pig cardiomyocytes. The application of trifluoperazine showed a dose-dependent decrease in current amplitudes at the end of voltage steps and tail currents of HERG. The IC\(_{50}\) for a trifluoperazine block of HERG current progressively decreased according to depolarization: IC\(_{50}\) values at \(-40\), 0, and +40 mV were 21.6, 16.6, and 9.29 \(\mu\)M, respectively. The voltage dependence of the block could be fitted with a monoexponential function, and the fractional electrical distance was estimated to be \(\delta = 0.65\). The block of HERG by trifluoperazine was use-dependent, exhibiting more rapid onset and greater steady-state block at higher frequencies of activation; there was partial relief of the block with decreasing frequency. In guinea pig ventricular myocytes, bath applications of 0.5 and 2 \(\mu\)M trifluoperazine at 36\(^\circ\)C blocked the rapidly activating delayed rectifier K\(^+\) current by 32.4 and 72.9\%, respectively; however, the same concentrations of trifluoperazine failed to significantly block the slowly activating delayed rectifier K\(^+\) current. Our findings suggest the arrhythmogenic side effect of trifluoperazine is caused by a blockade of HERG and the rapid component of the delayed rectifier K\(^+\) current rather than by the blockade of the slow component.

Sudden death associated with antipsychotic drug use was first reported in the 1960s and continues to be reported with various drugs up to the present (Kelly et al., 1963; Buckley and Sanders, 2000), which raises the concern that some of these deaths may be due to drug-induced arrhythmias (Reilly et al., 2000). Polymorphic ventricular arrhythmias, known as torsades de pointes, have been recorded during antipsychotic drug overdose (Raehl et al., 1985; Witchel et al., 2003). Several antipsychotic drugs are associated with the lengthening of the rate-corrected QT interval (QTC) on the electrocardiogram (ECG) (Reilly et al., 2000), which often precedes torsades de pointes (Faber et al., 1994). Trifluoperazine, a phe-nothiazine, is used for the treatment of schizophrenia since it can block dopamine receptors in the central nervous system, particularly the D\(_2\) subpopulation (Seeman, 1980). However, trifluoperazine induces adverse effects on the cardiovascular system, such as QTC prolongation (Reilly et al., 2000), ventricular tachycardia, torsades de pointes (Raehl et al., 1985), and sudden death (Jusic and Lader, 1994). Intentional use of this drug for suicidal purposes is also common; therefore, it is important to examine the electrophysiological mechanisms of trifluoperazine-induced arrhythmias.

Repolarization of cardiac ventricular myocytes is mainly due to outward K\(^+\) currents. One of the most important currents is the delayed rectifier cardiac K\(^+\) current, I\(_{\text{Kr}}\), which has rapidly and slowly activating components (I\(_{\text{K,ra}}\) and I\(_{\text{K,sa}}\), respectively) (Sanguinetti and Jurkiewicz, 1990). Activation of I\(_{\text{Kr}}\) leads to initiation of repolarization of the cardiac action potential (Sanguinetti et al., 1995), and the human ether-a-go-go-related gene (HERG) encodes the major protein underlying I\(_{\text{Kr}}\) (Sanguinetti et al., 1995). Mutations of HERG have been shown to cause chromosome 7-linked inherited long QT syndrome (LQT2) (Curran et al., 1995), and several drugs that block I\(_{\text{Kr}}\) and HERG cause acquired LQT and torsades de pointes.

ABBREVIATIONS: QTc, rate-corrected QT interval; I\(_{\text{Kr}}\), rapidly activating delayed rectifier K\(^+\) current; I\(_{\text{K,ra}}\), slowly activating delayed rectifier K\(^+\) current; HERG, human ether-a-go-go-related gene; LQT, long QT syndrome; APD, action potential duration; I\(_{\text{h}}\), tail current(s); I\(_{\text{HERG}}\), current at the end of voltage step; E-4031, (1-[2-(6-methyl-2-pyridyl)ethyl]-4-methylsulfonylaminobenzoyl)-piperidine); BRL-32872, N-(3,4-dimethoxyphenyl)ethyl)propyl)-4-nitrobenzamide hydrochloride; TFZ, trifluoperazine.
de pointes (Suessbrich et al., 1996, 1997). In many cases, the cardiotoxicity of numerous drugs can be solely attributed to their interaction with the HERG K+ channel (Tagliatela et al., 1998). Another component of the delayed rectifier K+ channel, I\textsubscript{Ks}, is also responsible for terminating the plateau phase of the action potential-like I\textsubscript{Ks} (Sanguinetti and Jurkiewicz, 1990). The gene coding I\textsubscript{Ks} was identified from positional cloning studies that identified mutations in the most common congenital form of LQT (LQT1) (Wang et al., 1996).

Phenothiazines were reported to delay repolarization by prolonging phase 3 of the action potential (Arita and Surawicz, 1973) and to produce ECG abnormalities, such as QTc prolongation (Lathers and Lipka, 1987). This raises the possibility that trifluoperazine, a phenothiazine, may prolong APD in vivo and cause LQT by inhibiting I\textsubscript{Ks}, the HERG channel, or I\textsubscript{Ks}, eventually resulting in torsades de pointes (Suessbrich et al., 1996, 1997). In many cases, the binding site was determined with half-blocking concentrations (K\textsubscript{D}) obtained from the fractional current (f\textsubscript{o}) as the current with 20 \textmu M trifluoperazine and under control conditions at the end of the voltage step with the equation K\textsubscript{D} = f\textsubscript{o}/(1 - f\textsubscript{o}) \times 20 (in \textmu M). The value of \delta was obtained by fitting the K\textsubscript{D} values with the equation K\textsubscript{D} = K\textsubscript{D \_[0 mV]} \times \exp(-zF\textsubscript{IV}RT), where K\textsubscript{D \_[0 mV]} represents the half-blocking concentration at the reference potential of 0 mV. V represents the membrane potential, and z, R, F, and T have their usual meanings (Snyders et al., 1992).

Materials and Methods

Expression of HERG in Oocytes. Complementary HERG RNA was synthesized by in vitro transcription from 1 \mu g of linearized cDNA using T7 message machine kits (Ambion, Austin, TX) and stored in 10 mM Tris-HCl (pH 7.4) at -80°C. Stage V to VI oocytes were surgically removed from female Xenopus laevis (Nasco, Fort Atkinson, WI) and anesthetized with 0.17% tricane methanesulfonate (Sigma-Aldrich, St. Louis, MO). Theca and follicle layers were manually removed from the oocytes using fine forceps. Oocytes were then injected with 40 nl of cRNA (0.1–0.5 \mu g \cdot \mu l\textsuperscript{-1}). After injection, oocytes were maintained in modified Barth’s solution containing 88 mM NaCl, 1 mM KCl, 0.4 mM CaCl\textsubscript{2}, 1 mM MgCl\textsubscript{2}, 5 mM Hepes, and 10 mM glucose (pH 7.4 with 4 M NaOH). Inward rectifier K+ currents were inhibited by adding 5 mM CaCl\textsubscript{2} to the normal Tyrode’s solution. The patch pipette (outer diameter 1.5 mm; World Precision Instruments, Inc., Sarasota, FL) had resistances around 1 to 2 M\Omega. The pipette solution for the potassium current measurement contained 140 mM KCl, 1 mM MgCl\textsubscript{2}, 5 mM EGTA, 5 mM MgATP, 2.5 mM diTris-phosphocreatine, and 2.5 mM disodium phosphocreatine (pH 7.4 with KOH).

The “pipette-to-bath” liquid junction potential was small (-3.5 mV) and was uncorrected. Membrane capacitance (the time integral of the capacitive response to a 10-mV hyperpolarizing pulse from a holding potential of 0 mV, divided by the voltage drop) averaged 121.5 ± 24.5 pF (n = 10). Measurements were made using an Axopatch 200A amplifier (Axon Instruments Inc.) and a CV-201 headstage. Voltage-clamp commands were generated using “WinWCP” (John Dempster, Strathclyde University, Glasgow, Scotland) or pClamp (version 5.1; Axon Instruments). The current signals were filtered via a 1- to 10-kHz, eight-pole Bessel-type low-pass filter and digitized by an AD/DA converter (Digidata 1200; Axon Instruments Inc.) for subsequent analysis (pClAMP software 6.0.3). All chemicals were from Sigma-Aldrich except E-4031, which was kindly provided by Eisai Co., Ltd (Tokyo, Japan).

Results

The effect of trifluoperazine on the HERG current was studied using a Xenopus oocyte expression system. Throughout the experiments, holding potential was adjusted between -60 and -70 mV to obtain the minimum leak current, but the repolarization potential was held constant at -60 mV for the analysis of tail currents (I\textsubscript{tail}). Figure 1A shows an example of voltage-clamp recording from the Xenopus oocyte cell and representative current traces under the control condition and after exposure to 10 \mu M trifluoperazine. In the control condition, depolarizing steps activated time-dependent outward currents. The amplitude of outward currents measured at the end of the pulse (I\textsubscript{HERG}) increased with more positive voltage steps and reached a maximum value at -10 mV. Depolarizing steps toward even more positive values caused a current decrease, resulting in a negative slope of the IV curve (Fig. 1B). Current-voltage relationships for I\textsubscript{HERG} obtained at various concentrations of trifluoperazine are plotted in Fig. 1B. As the concentration of trifluoperazine progressively increased, the amplitude of I\textsubscript{HERG} showed a dose-dependent decrease.

After the depolarizing steps, repolarization to -60 mV induced outward I\textsubscript{tail}; its amplitude was even larger than the amplitude of I\textsubscript{HERG} observed during depolarization. This is a characteristic property of HERG current, and it is known to be due to the rapid recovery from inactivation and slow deactivation mechanism (Sanguinetti et al., 1995). The am-
amplitude of \( I_{\text{tail}} \) increased with depolarizing steps from -60 to +10 mV and was then superimposed on further depolarizing steps to +40 mV. When 10 \( \mu \)M trifluoperazine was added to the perfusate, not only \( I_{\text{HERG}} \) but also \( I_{\text{tail}} \) was suppressed, as shown in the bottom panel of Fig. 1A. The amplitude of \( I_{\text{tail}} \) was normalized to the peak amplitude obtained in the control condition at a maximum depolarization and was plotted against the potential of the step depolarization (Fig. 1C). The normalized \( I_{\text{tail}} \) reflects a voltage-dependent activation of the HERG channels. Data obtained in control conditions were well fitted by the Boltzmann equation with half-maximal activation (\( V_{\text{1/2}} \)) at -20.8 mV. When the concentration of trifluoperazine increased, the peak \( I_{\text{tail}} \) amplitude decreased, indicating the maximum conductance of HERG channels is decreased by trifluoperazine. Also, note that in the presence of trifluoperazine, \( I_{\text{tail}} \) does not reach the steady-state level but declines with more positive potentials, indicating the blocking effect is more pronounced at more positive potentials.

This result may suggest that the effect of trifluoperazine is voltage-dependent. We tested this possibility by comparing the decrease of \( I_{\text{tail}} \) by trifluoperazine at different potentials (Fig. 2). Indeed, a higher degree of blockade was present at more positive voltages (Fig. 2A). At -40 mV, 20 \( \mu \)M trifluoperazine reduced the amplitude of normalized \( I_{\text{tail}} \) by 46.6% (from 0.07 \pm 0.02 to 0.04 \pm 0.01; \( n = 7, P < 0.05 \)), whereas at +40 mV it reduced the amplitude of normalized \( I_{\text{tail}} \) by 68.4% (from 1.00 \pm 0.01 to 0.32 \pm 0.05; \( n = 7, P < 0.05 \)). Dose-response relationships were obtained at +40 mV and -40 mV and are plotted in Fig. 2B. Data were fitted by Hill equations, and IC\(_{50}\) values for trifluoperazine blockade of HERG current were obtained at different membrane potentials. IC\(_{50}\) values at -40, 0, and +40 mV were 21.6, 16.6, and 9.29 \( \mu \)M, respectively (\( n = 7 \)). These results indicate that the trifluoperazine block of HERG current exhibits voltage dependence.

For further analysis, the relative current under 20 \( \mu \)M trifluoperazine was calculated for each potential (Fig. 3, filled squares; \( n = 7 \)). The relative currents with the drug, as fractions of the control current, were found to decrease steadily with positive trending potentials and from 0.534 \pm 0.089 at -40 mV reached 0.316 \pm 0.054 at +40 mV (\( n = 7, P < 0.05 \)). The voltage dependence of the block was fitted with a monoeponential function (Fig. 3, solid line). Since the relative conductance of the HERG control current reached more than 90% of its maximal value at potentials positive to 0 mV (Fig. 3, dashed line; mean open probability at 0 mV obtained by Boltzmann fit, 0.91), the range between 0 and +40 mV was taken to estimate the fractional electrical distance (\( \delta \)), i.e., the fraction of the transmembranous electrical field sensed at the receptor site of trifluoperazine. From the fraction of control current achieved with trifluoperazine, half-blocking concentrations (\( K_p \)) were calculated. Fitting the mean \( K_p \) values in the potential range from 0 to +40 mV with the mean \( K_p \) at the reference potential of 0 mV (\( K_p^0 \)) \( = 20.6 \mu \)M yielded a fractional electrical distance of \( \delta = 0.65 \).

In addition to the voltage dependence of the trifluoperazine effect, a time-dependent block was found. We activated currents using a protocol with a single depolarizing step to 0 mV for 8 s (Fig. 4A). After having obtained the control measurement, we applied 10 \( \mu \)M trifluoperazine and then recordings with the drug were performed. Analysis of the test pulse after...
trifluoperazine application revealed a time-dependent increase of block to 44% at 1700 ms in a representative cell (Fig. 4A). The fractional sustained current (obtained by normalizing the currents with trifluoperazine to the control currents) decreased with ongoing depolarization (Fig. 4B). The fractional current at the beginning of the pulse was 0.928 ± 0.053 of the control and declined to 0.531 ± 0.074 after 2 s at a test potential of 0 mV (Fig. 4B; n = 6), thus indicating that HERG channels are only slightly blocked by trifluoperazine while remaining at the holding potential.

Next, we examined the use dependence of the trifluoperazine effect (Fig. 5). To analyze this, HERG channels were activated by 0.5-s depolarizing steps to −30 mV at intervals of 3, 12, or 36 s in the presence of 5 μM trifluoperazine (n = 8). Figure 5A shows that the time course of the channel blockade is dramatically dependent on the activation frequency; HERG-blockade by trifluoperazine occurred much faster at higher activation frequency. In Fig. 5B, the data shown in Fig. 5A were plotted as a function of the number of test pulses. After the same number of test pulses, the block by 5 μM trifluoperazine was stronger at high activation frequency than at lower activation frequency, indicating favored binding of the drug at higher frequency. In additional experiments, the steady-state HERG channel block by trifluoperazine was initially obtained with depolarization at 3-s intervals (Fig. 5C). Subsequent increase of the depolarization intervals to 36 s resulted in a partial relief of the HERG channel blockade (n = 5). These results indicate that the
blockade of HERG channels by trifluoperazine is strongly use-dependent.

In further experiments, we tested the effect of trifluoperazine on the rapid and slow components of delayed rectifier in guinea pig ventricular myocytes at 36°C using electrophysiological separation of the currents with a voltage-clamp protocol (Carmeliet, 1992; Heath and Terrar, 1996) shown in the inset of Fig. 6A (stimulation frequency of 0.03 Hz). Depolarization to +40 mV activates both $I_{Kr}$ and $I_{Ks}$, and repolarization to −10 mV revealed $I_{Ks}$ as deactivating $I_{tail}$, whereas subsequent repolarization to −50 mV showed the deactivation of $I_{Kr}$. We confirmed that 2 μM E-4031, a selective blocker of $I_{Kr}$ (Sanguinetti and Jurkiewicz, 1990), blocked the rapid component of delayed rectifier $K^+$ current; however, it did not change $I_{Ks}$ (Fig. 6B). As shown in Fig. 6, A and B, 0.5 and 2 μM trifluoperazine dose-dependently inhibited $I_{Kr}$ by 32.4 ± 6.10 and 72.9 ± 3.23%, respectively (n = 12–21; P < 0.05), suggesting native $I_{Kr}$ is more sensitive to the drug than the HERG channel expressed in Xenopus oocytes, considering that the IC$_{50}$ value for the HERG channel blockade was about 10 μM. However, 0.5 and 2 μM trifluoperazine did not block $I_{Ks}$ significantly (n = 12–21) in our experimental condition (e.g., 36°C). This result shows that trifluoperazine

Fig. 5. Use-dependent HERG channel blockade by 5 μM trifluoperazine. A, tail currents were recorded at −60 mV after a 0.5-s depolarizing prepulse to +30 mV from a holding potential of −70 mV every 3 (●), 12 (▲), and 36 s (●), respectively. B, the HERG channel blockade data from A were plotted against the number of test pulses. C, steady-state HERG channel blockade by 5 μM trifluoperazine after 16 pulses at 3-s intervals (■). Increasing the depolarization intervals to 36 s in the presence of trifluoperazine (□) resulted in a partial relief, and changing back to 3-s intervals increased the HERG channel blockade again. Symbols with error bars in A and B represent mean ± S.E.M.; each data point was obtained from eight cells. Symbols in C are representative of five experiments.
preferentially blocked the rapid component of delayed rectifier K+ current rather than the slow component, suggesting that trifluoperazine may prolong APD primarily by blocking \( I_{Kr} \) and not \( I_{Ks} \).

In addition, we tested the effects of trifluoperazine on the activation curve of \( I_{Kr} \) using a voltage protocol that requires only short depolarization steps and allows the recording of the current-voltage relationship for \( I_{Kr} \), deactivating at \(-40\) mV (Fig. 7A, inset) (Sanguinetti and Jurkiewicz, 1990; Heath and Terrar, 1996). To prevent possible contamination by \( I_{Ks} \), we treated each myocyte with 2 \( \mu \)M E-4031 after trifluoperazine experiments and then used the E-4031-sensitive component for data analysis by subtracting the amplitude of E-4031-insensitive tail current from that obtained in the absence or presence of trifluoperazine (Fig. 7A). Trifluoperazine at 0.5 \( \mu \)M significantly reduced \( I_{Kr} \) only at prepulses positive to 0 mV; however, 2 \( \mu \)M trifluoperazine significantly inhibited the current at all prepulses (\( n = 5-7 \); Fig. 7B). Also, the degree of blockade increased with more positive voltages; 2 \( \mu \)M trifluoperazine blocked \( I_{Kr} \) at \(-30\) and \(+30\) mV by 53.6 \( \pm \) 2.51 and 80.4 \( \pm \) 1.94\%, respectively (\( n = 5-7 \), \( P < 0.05 \); Fig. 7B). The results show that a higher degree of blockade was present at more positive voltages, which is consistent with the data from the HERG channel.

### Discussion

Our results indicate that trifluoperazine is an inhibitor of HERG channels. Blockade of HERG channels heterologously expressed in *Xenopus* oocytes displayed an IC\(_{50}\) value of 9.29 \( \mu \)M (at \(+40\) mV), whereas 2 \( \mu \)M trifluoperazine inhibited \( I_{Kr} \) of guinea pig ventricular myocytes by 73\%. Due to specific properties of the *Xenopus* oocyte expression system, higher concentrations of drug are necessary when applied to the extracellular surface of whole oocytes. For example, the blocks of HERG by doxetilde (Kiehn et al., 1996) and by the antiarrhythmic drug BRL-32872 (Thomas et al., 2001) gave IC\(_{50}\) values that were 10- to 20-fold higher when the drug was applied to the bath compared with the application of the drug to the internal membrane surface in inside-out patches. One possible explanation for this observation is that the vitelline membrane and yolk reduce the concentration of drugs at the cell membrane.

In patients using trifluoperazine, the plasma concentration of the drug was estimated to be in the range of \( 10^{-7} \) and \( 10^{-6} \) M in therapeutic use (Buckley and Sanders, 2000). Trifluoperazine was shown to be toxic to 0.5 to 10 \( \mu \)M in the myocardium (Hull and Lockwood, 1986) and 25 \( \mu \)M in T-lymphocytes (Stavitsky et al., 1984). In cases of sudden unexpected death, the postmortem blood concentration of trifluoperazine was 0.1 and 2 \( \mu \)M (Jusic and Lader, 1994), and the use of antipsychotic drugs in therapeutic doses has been associated with sudden death (Kelly et al., 1963). The drug is metabolized through an oxidative process mediated by hepatic cytochrome P450 microsomal oxidase and by conjugation processes with an elimination half-life of \(-18\) h (Ereshefsky, 1996). However, the half-life may be prolonged in patients with hepatic disease and renal insufficiency (Buckley and Sanders, 2000). Our results demonstrated that trifluoperazine blocked the HERG channel with an IC\(_{50}\) value of 9.29 \( \mu \)M (at \(+40\) mV) and \( I_{Kr} \) of mammalian cardiomyocytes at a value of \(-1\) \( \mu \)M, which is a similar level to the serum concentration under normal conditions (Buckley and Sanders, 2000) and to the postmortem drug concentration of sudden death (Jusic and Lader, 1994). Furthermore, we observed that trifluoperazine inhibited the \( I_{tail} \) of the HERG channel stably expressed in HEK cell (Zhou et al., 1998) dose-dependently, and the result gives us IC\(_{50}\) value of 0.23 \( \mu \)M (\( n = 4 \), data not shown), suggesting that serological levels of the drug can inhibit HERG currents. Therefore, the present study strongly indicates that the blockade of HERG current may underlie the proarrhythmic effect of trifluoperazine in psychiatric patients, like LQT and torsades de pointes, which could induce sudden death.

Several drugs that cause acquired LQT and torsades de pointes also have been shown to block the HERG channel in a voltage-dependent manner, suggesting that the drugs bind to the open or inactivated state of HERG channels. Haloperidol, an antipsychotic drug (Suessbrich et al., 1997), and two histamine receptor antagonists, terfenadine and astemizole (Suessbrich et al., 1996), have been known to bind the inactivated-state of HERG preferentially. In contrast, a gastrointestinal prokinetic agent, cisapride has been shown to block the channel in its open state (Rampe et al., 1997). In the

![Fig. 7. Effect of trifluoperazine on \( I_{Kr} \) of guinea pig ventricular myocytes. A, superimposed recordings showing decay of \( I_{Kr} \) tail currents in the absence and presence of 0.5 or 2 \( \mu \)M TFZ and 2 \( \mu \)M E-4031 at prepulses of \(+40\) mV. B, activation curves for \( I_{Kr} \), measured as E-4031-sensitive tail currents at \(-40\) mV before and after exposure to 0.5 or 2 \( \mu \)M TFZ. \( I_{Kr} \) normalized to that following a depolarizing prepulse to \(+40\) mV in the absence of drug. Symbols with error bars represent mean \( \pm \) S.E.M. (\( n = 5-7 \)).](image-url)
present study, the amount of block increased with more positive voltages, which increase the open probability and enhance the inactivation (Figs. 1, 2, and 3). Also, the fraction of block was very low at the beginning and increased with the duration of the voltage step (Fig. 4), suggesting the channel was not blocked in the resting state at hyperpolarized potentials but during opening at depolarization. Therefore, these voltage and time dependences of the trifluoperazine block support that the drug preferentially blocks HERG channels either in the open state or in the inactivated state.

It is possible that trifluoperazine could prolong APD by blocking not only the rapid component of delayed rectifier K⁺ current but also the slow component, because Herzer et al. (1994) reported that trifluoperazine blocked human depolarization-activated very slowly activating voltage-gated K⁺ current (I₅K) expressed in Xenopus oocytes with an EC₅₀ value of 76.9 μM. The guinea pig I₅K protein has been suggested to underlie the K⁺ conductance of I₅K in guinea pig cardiomyocytes due to its electrophysiological and pharmacological properties, characteristic of I₅K (Varnum et al., 1993). The present study shows that trifluoperazine inhibited E-4031-sensitive I₅K current and the expressed major component of I₅K, HERG. However, the drug did not reduce I₅K significantly even at 2 μM (Fig. 6), suggesting that trifluoperazine preferentially blocked the rapid component of delayed rectifier K⁺ current rather than the slow component in our condition. It is still possible that cardiac arrhythmia by trifluoperazine is due to other K⁺ channels, such as the inward rectifier K⁺ channel or the transient outward K⁺ channel, which are important channels determining cardiac APD. The possible effect of the drug on each molecular equivalent of various K⁺ channels other than HERG awaits future investigation.

The present study showed that trifluoperazine blocks HERG and possibly I₅K more at positive voltage and at high frequency, which may not be consistent with reverse use-dependent repolarization lengthening by other I₅K blockers in cardiac cells. Reverse use dependence has been implicated in the bradycardia-dependent proarrhythmic effects of various class III antiarrhythmic agents, and this effect has been demonstrated with various I₅K blocking agents, including E-4031, defetilide, sotaxol, and (4-methylsulfonyl)amidobenzensulfonylamide (Hondeghem and Snyders, 1990). The possibility trifluoperazine prolongs action potential duration of cardiomyocytes in a frequency-dependent manner should be examined in future investigation.

Our present study suggested that trifluoperazine directly inhibited the HERG channel and I₅K, possibly resulting in prolongation of APD and cardiac arrhythmia. This hypothesis of the drug’s direct action on myocardial channels in sarcoidema can be supported by the study showing that phenothiazine-induced arrhythmia and death were not produced via the central nervous system (Lipka et al., 1988). Also, it can be speculated that many effects of trifluoperazine on channels are due to nonspecific membrane effects such as general perturbation of membrane proteins because trifluoperazine changes the membrane fluidity (Menetti and Di Stasi, 1987). However, those studies have shown the drug increased the freedom of membrane lipid motion, which would be related to phenothiazine-induced toxic cardiomyopathy (Hull and Lockwood, 1986) rather than inhibition of I₅K or HERG by trifluoperazine. Also, the concentration used in this study was lower than those associated with nonspecific membrane effects (Weiss et al., 1982). Therefore, it is likely that trifluoperazine interacts directly with the HERG channel proteins or HERG channel-structure relation.

In summary, the present study shows that an antipsychotic drug, trifluoperazine, at near-physiological levels, blocks the HERG channel and I₅K, but not I₅K of guinea pig cardiomyocytes, suggesting that the drug-induced arrhythmia observed in psychiatric patients would be due to, at least in part, inhibition of I₅K.

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References


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