Interactions of the Nonsedating Antihistamine Loratadine with a Kv1.5-Type Potassium Channel Cloned from Human Heart

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SUMMARY

The use of nonsedating antihistamines may, on rare occasions, be associated with cardiac arrhythmias. This could be due to blockade of voltage-dependent K⁺ channels in the heart, leading to a prolongation in repolarization in the human myocardium. For this reason, we examined the effects of the nonsedating antihistamine loratadine on a rapidly activating delayed-rectifier K⁺ channel (Kv1.5) cloned from human heart and stably expressed in HEK 293 cells or mouse Ltk⁻ cells. Using patch-clamp electrophysiology, we found that loratadine blocked Kv1.5 current measured from inside-out membrane patches at concentrations of ≥100 nM, resulting in an IC₅₀ value of 808 nM at +50 mV. The drug enhanced the rate of Kv1.5 current decay, and block was enhanced at membrane potentials near threshold relative to higher potentials. Loratadine did not alter the kinetics of Kv1.5 current activation or deactivation. Unitary Kv1.5 currents were recorded in cell-attached patches. At the single-channel level, the main effect of loratadine was to reduce the mean probability of opening of Kv1.5. This effect of loratadine was achieved by a reduced number of openings in bursts and burst duration. Finally, loratadine (10 μM) failed to inhibit HERG K⁺ channel currents expressed in Xenopus laevis oocytes. It is concluded that loratadine is an effective blocker of Kv1.5 that interacts with an activated state or states of the channel. This interaction suggests a potential for loratadine to alter cardiac excitability in vivo.

Voltage-dependent K⁺ channels play an important role in determining the length of the cardiac action potential. Many different types of K⁺ channels exist in the human myocardium and contribute to its electrical activity (1, 2). Recent advances in molecular biology have led to the cloning of a variety of cardiac K⁺ channel cDNAs. For example, the rapid component of the delayed-rectifier K⁺ current is thought to be subserved by the protein encoded by HERG (3). A number of voltage-dependent K⁺ channels belonging to the Shaker superfamily have also been cloned from the heart (4, 5). One of these Shaker channels, Kv1.5, is thought to underlie the ultrarapidly activating delayed-rectifier K⁺ current found in human atrial myocytes (6, 7). In addition, both Kv1.5 transcripts (6) and Kv1.5 protein (8) have been detected in human ventricular tissue, in which they may form heteromultimeric K⁺ channels in combination with other Shaker-like subunits (8).

Pharmacological blockade of voltage-dependent K⁺ channels in the heart can be associated with untoward cardiac toxicity. Such an activity may underlie the prolongation in cardiac repolarization, which has been observed with the nonsedating antihistamines terfenadine (Seldane) and astemizole (Hismanal). Under certain clinical settings, such as cases of overdose, both terfenadine and astemizole may be associated with a prolongation of the QT interval, sometimes leading to the ventricular arrhythmia torsades de pointes (9, 10). In vitro, both terfenadine and astemizole have been shown to block cardiac K⁺ channel currents, including Kv1.5 (11–14). Another nonsedating antihistamine, loratadine (Claritin), is clinically available. Although loratadine is generally believed not to cause cardiac arrhythmias (15), reports of such arrhythmias have recently begun to appear (16, 17). To date, little is known about the interaction of loratadine with human cardiac K⁺ channels; therefore, the current study was undertaken to detail the effects of loratadine on the cloned human cardiac K⁺ channel Kv1.5.

Materials and Methods

Cell culture. The HEK 293 and mouse Ltk⁻ cell lines (American Type Culture Collection, Rockville, MD) were transfected with the human cardiac Kv1.5 K⁺ channel complementary DNA as previously described (6). Cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (GIBCO BRL, Grand Island, NY) in an atmosphere of 95% air/5% CO₂. This media also contained penicillin/streptomycin/fungizone and G418 (0.5 mg/ml, GIBCO BRL).

Electrophysiology. For whole-cell and cell-free inside-out macropatch recordings (18), HEK 293 cells were seeded onto glass cov-

ABBREVIATIONS: HEK, human embryonic kidney; HERG, human ether-a-go-go-related gene; EGTA, ethylene glycol bis(β-aminoethyl ether)-N,N′,N″-tetraacetic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; I-V, current-voltage.
eruptions 24–72 hr before use. Electrodes (1.5–3-MΩ resistance) were fashioned from TW150 glass capillary tubes (World Precision Instruments, New Haven, CT). For inside-out patches, the electrodes were filled with a solution containing 130 mM NaCl, 5.0 mM KCl, 2.8 mM sodium acetate, 1.0 mM MgCl₂, 10 mM HEPES, 10 mM glucose, and 1.0 mM CaCl₂, pH 7.4, with 1 N NaOH. This solution served as the external solution for whole-cell recordings. The external recording solution used for inside-out patches contained 120 mM potassium aspartate, 20 mM KCl, 4.0 mM Na₂ATP, 5.0 mM HEPES, and 1.0 mM MgCl₂, pH 7.2, with KOH. This served as the internal solution for whole-cell experiments. Currents were recorded at room temperature using an Axopatch-1 D amplifier (Axon Instruments, Burlingame, CA) and were conditioned by a four-pole low-pass filter with a cutoff frequency of 500 Hz. Currents were stored and analyzed using a Compaq Deskpro computer and pCLAMP software (Axon Instruments). Linear leakage and capacity currents were corrected on-line by using the P/4 subtraction method unless stated otherwise. For steady state inactivation curves, peak currents were normalized to the first pulse in each series and fit to the Boltzmann equation 1 + exp((Vₐₐₕ − V)/k)⁻¹, where V is the membrane voltage, Vₐₐₕ is the midpoint of the curve, and k is the slope factor. The IC₅₀ value of loratadine was obtained by nonlinear least-squares fit of the data (GraphPAD Software, San Diego, CA). To obtain the apparent association and dissociation rates of loratadine, we plotted the fast, drug-induced time constants (τₚ) versus drug concentration (D), according to the equation 1/τₚ = k[D] + L, where k and L are the apparent association and dissociation constants, respectively.

For single-channel recordings, Ltk⁻ cells were seeded onto glass coverslips 24–48 hr before use, and the cell-attached mode of the patch-clamp technique (18) was used to record unitary Kv1.5 channel currents. Pipettes were fashioned from 7052 glass, and the tips were beveled before use. The bath solution consisted of 140 mM potassium aspartate, 5.4 mM KCl, 1.0 mM MgCl₂, 1.8 mM CaCl₂, 5 mM HEPES, and 10 mM glucose, pH 7.4 with KOH. Pipettes were filled with 137 mM NaCl, 5.4 mM KCl, 1.0 mM MgCl₂, 1.8 mM CaCl₂, 5 mM HEPES, and 10 mM glucose, pH 7.4 with NaOH. An Axopatch 200A and pCLAMP software (Axon Instruments) were used for recording unitary current from cell-attached patches. Data were analog-filtered with an eight-pole low-pass Bessel response filter at a cutoff frequency of 1000 Hz. Single-channel currents were corrected for leak and capacity currents by subtracting the average of records with no openings from each record in an experiment and idealized with the TRANSIT algorithm (19). Parameter estimates for single-channel probability distributions were obtained with the maximum likelihood method. For burst analysis, we used a critical closed criterion that results in equal proportions of misclassified short and long dwell times (20). This condition is satisfied for values of τᵣₑₛᵣ that satisfy the relation exp(−τᵣₑₚₜ/τᵣₑₛᵣ) = 1 − exp(−τᵣₑₛᵣ/τₑₛᵣ), where τₑₛᵣ and τₑₛᵣ are the time constants for fast and slow components, respectively, of the closed time distribution. The probability of observing a dwell time from the long closed dwell time component with duration of ≥τₑₛᵣ is 1 − exp(−τₑₛᵣ/τₑₛᵣ), and the probability for observing a dwell time from the short closed dwell time component longer than τₑₛᵣ is exp(−τₑₛᵣ/τₑₛᵣ). The value of τₑₛᵣ is obtained by using a modified Newton-Raphson root search algorithm implemented in Turbo Pascal to numerically solve for the value (τₑₛᵣ) that satisfies this equation. In two of three patches, a very rapid closed time component with time constant of <350 μsec was detected. These events are poorly resolved at the filter frequency (1 kHz) used for analysis and were not further analyzed. Values for τₑₛᵣ used to define bursts in data from three patches presented in the study were (control/loratadine) 2.665/6.449, 6.263/7.132, and 3.118/3.187 msec.

For oocyte recordings, the cRNA encoding the HERG K⁺ channel was microinjected into Xenopus laevis oocytes as previously described (14). Whole-cell currents were recorded from X. laevis oocytes by use of the conventional two-microelectrode voltage-clamp technique. Beveled microelectrodes were filled with a solution of 3 mol/liter KCl, 10 mmol/liter HEPES, and 10 mmol/liter EGTA, pH 7.4 (Tris), to give a low tip resistance of 0.2 to 0.5 MΩ. Oocytes were placed in a chamber and perfused with Ringer’s solution containing 120 mmol/liter NaCl, 2.5 mmol/liter KCl, 1.1 mmol/liter CaCl₂, 10 mmol/liter EGTA, and 10 mmol/liter HEPES-acid, pH 7.2 (NaOH). A stock solution of loratadine (50 mmol/liter) was prepared in dimethylsulfoxide and diluted to the desired test concentrations with bath solution. To avoid artifacts, the portion of dimethylsulfoxide in the perfusing solution was never allowed to exceed 0.2% (v/v).

Current records were amplified with the use of a Warner oocyte clamp (OC-725A) and low-pass filtered at 3 kHz (−3 dB, four-pole Bessel filter, Wavetech model 432, Hamden, CT). Data were stored on the hard disk of a 486 IBM-compatible computer for off-line analysis. All data acquisition and analysis were done with pCLAMP software (Axon Instruments). Currents were recorded at room temperature, and experiments in which the holding current was >−0.2 μA at a holding level of −90 mV were excluded from analysis. For all electrophysiological measurements, statistical significance was accepted at the p < 0.05 level.

Results

Fig. 1 shows the effects of loratadine on human cardiac Kv1.5 current recorded from an HEK 293 cell in the inside-out membrane patch configuration. Under these conditions, we found loratadine to be an effective blocker of this channel. At a concentration of 100 nM, loratadine produced a small but significant (16 ± 2% inhibition, n = 7; p < 0.05 paired t test) inhibition of Kv1.5 current (Fig. 1A). At higher concentrations, a more robust inhibition of Kv1.5 current was apparent, which was reversible on washing the patch with drug-free solution (Fig. 1B). The IC₅₀ value for loratadine blockade of Kv1.5 was 8.08 × 10⁻⁷ M (Fig. 1C). The main effect of loratadine was to accelerate the rate of Kv1.5 current decay during a step depolarization. In the absence of drug, Kv1.5 current decay was well fitted to a single exponential function with a time constant of ~400–500 msec (Fig. 2A) (13, 21). In the presence of loratadine, a new component of rapid inactivation was added (Fig. 2B). This rapid component of inactivation ranged from 54.4 msec at a loratadine concentration of 300 nM to 11.0 msec at 10 μM. These fast, drug-induced time constants are plotted as a function of loratadine concentration in Fig. 2C. A plot of the reciprocal of these time constants versus loratadine concentration (Fig. 3) yielded an apparent association constant rate constant of 7.5 × 10⁶ M⁻¹sec⁻¹ and an apparent dissociation rate constant of 16.5 sec⁻¹. The apparent Kᵰᵣ value was 2.2 × 10⁻⁴ M, which is in good agreement with the IC₅₀ value obtained in Fig. 1C.

After oral administration, loratadine is extensively metabolized, with descarboethoxyloratadine as the major metabolic product (22). Fig. 4 illustrates the effects of this metabolite on Kv1.5. Descarboethoxyloratadine was ~7-fold less potent at blocking Kv1.5 than the parent compound, displaying an IC₅₀ value of 5.60 × 10⁻⁴ M (Fig. 4B). Also, unlike loratadine, descarboethoxyloratadine reduced Kv1.5 current amplitude with no apparent effect on the rate of current decay (Fig. 4A). Fig. 5 illustrates the effects of loratadine on Kv1.5 current recorded over a wide range of test potentials. Currents in the absence and presence of 1 μM loratadine are shown in Fig. 5, A and B, respectively. The resultant steady state I-V relationships for these data are shown in Fig. 5C. Interestingly, we found that the blocking effects of loratadine on Kv1.5 were more potent at lower membrane potentials relative to...
higher ones. This was true even over potentials in which channel conductance is saturated (±20 to +50 mV, Ref. 6, slope significantly different from zero, \( p < 0.05, t \) test). This inverse relationship between Kv1.5 current blockade and test potential is plotted in Fig. 5D.

Fig. 6 shows the effects of loratadine on Kv1.5 current deactivation. Using the whole-cell configuration of the patch-clamp, outward tail currents were recorded at a potential of −45 mV after a 100-msec step depolarization to +30 mV (Fig. 6A). In the absence of drug, Kv1.5 currents deactivated with a time constant of 10.83 ± 1.56 msec (five experiments). In the presence of 3 μM loratadine, this value was 9.85 ± 1.19 msec (five experiments), which was not significantly different from the control value (\( p > 0.05, \) paired \( t \) test). Loratadine also failed to alter the time course of Kv1.5 current activation. In the absence of drug, Kv1.5 current activated at +30 mV with a time constant of 3.24±0.25 msec (five experiments). In the presence of 3 μM loratadine, this value was not significantly different and was 3.49±0.49 msec (five experiments).
Fig. 7 illustrates the effects of loratadine on the steady state inactivation properties of Kv1.5. Inactivation was determined by measuring current evoked by depolarizing pulses to $+50 \, mV$ while the holding potential (20-sec duration) was increased in 7-mV increments from $-270$ to $7 \, mV$. In the absence of drug, the midpotential ($V_{0.5}$) and slope value ($k$) of the steady state inactivation curve was $21.5 \pm 1.9 \, mV$ and $-8.2 \pm 0.4 \, mV$, respectively (four experiments). In the presence of $3 \, \mu M$ loratadine, the slope value was not significantly changed and was $-9.0 \pm 0.5 \, mV$, whereas a small but significant ($p < 0.05$, paired $t$ test) hyperpolarizing shift in the midpotential ($-27.5 \pm 1.4 \, mV$, four experiments) was observed.

We next examined the effects of loratadine on Kv1.5 at the single-channel level. Because the very high channel density in the HEK 293 cell line made single-channel experiments difficult, we used a mouse $Ltk^-$ cell line expressing a lower density of Kv1.5 channels for single-channel recordings. This system has previously been used for recording Kv1.5 currents (23). Fig. 8 shows typical Kv1.5 channel activity recorded at a test potential of $+60 \, mV$. In the absence of drug, Kv1.5 channel openings appeared throughout the duration of a $190-\text{msec}$ test pulse (Fig. 8, A and B). In the presence of $3 \, \mu M$ loratadine (Fig. 8B), channel openings were largely confined to an abbreviated burst at the beginning of each test depolarization, followed by longer closed times relative to control (Fig. 8A). This resulted in an acceleration of Kv1.5 current decay when these single-channel sweeps were summed (Fig. 8C), similar to that found for the macroscopic currents.

Fig. 2. Effects of loratadine on Kv1.5 current decay. A, Kv1.5 current recorded from an inside-out patch was elicited by a 1-sec test depolarization to $+50 \, mV$ from a holding potential of $-80 \, mV$ in the absence and presence of $1 \, \mu M$ loratadine. B, Control current was well fitted to a single exponential decay. C, After the addition of loratadine, current decay was enhanced and could be fit as the sum of two exponentials. D, The fast drug-induced time constants are plotted as a function of loratadine concentration. The deviation from linearity noted at $10 \, \mu M$ may be due to difficulty in measuring the fast rate constant produced by loratadine at this high concentration combined with potential contamination from the slower component observed in the absence of drug. Error bars, mean ± standard error (three to eight experiments).

Fig. 3. Determination of association and dissociation rate constants for loratadine. The reciprocal of the fast drug-induced time constants obtained at $+50 \, mV$ is plotted against loratadine concentration. Least-squares fit of the data resulted in an apparent association rate constant ($k$) of $7.5 \times 10^6 \, \text{m}^{-1}\text{sec}^{-1}$ and an apparent dissociation rate constant of $16.5 \, \text{sec}^{-1}$. Error bars, mean ± standard error (three to eight experiments).

Fig. 7 illustrates the effects of loratadine on the steady state inactivation properties of Kv1.5. Inactivation was determined by measuring current evoked by depolarizing pulses to $+50 \, mV$ while the holding potential (20-sec duration) was increased in 7-mV increments from $-70$ to $7 \, mV$. In the absence of drug, the midpotential ($V_{0.5}$) and slope value ($k$) of the steady state inactivation curve was $-21.5 \pm 1.9 \, mV$ and $-8.2 \pm 0.4 \, mV$, respectively (four experiments). In the presence of $3 \, \mu M$ loratadine, the slope value was not significantly changed and was $-9.0 \pm 0.5 \, mV$, whereas a small but significant ($p < 0.05$, paired $t$ test) hyperpolarizing shift in the midpotential ($-27.5 \pm 1.4 \, mV$, four experiments) was observed.

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Because the time dependence of loratadine block resembles the kinetics of open-channel block we examined the open time distribution for evidence of a reduction in channel open time. Fig. 9 illustrates the lack of effect of loratadine on the open time distribution of Kv1.5 unitary currents. Mean values are $2.56 \pm 0.38 \, \text{msec}$ for control and $2.71 \pm 0.66 \, \text{msec}$ for
loratadine (mean ± standard error, three experiments; \( p > 0.05 \), Student's paired \( t \) test). The probability of open state occupancy at the end of the voltage step was reduced significantly by loratadine. The ratio of the mean to the peak probability of open state occupancy was 0.73 ± 0.05 in control and was significantly reduced to 0.43 ± 0.06 in the presence of loratadine (mean ± standard error, three experiments; \( p < 0.05 \), Student's paired \( t \) test).

Comparison of burst duration in control and in the presence of 3 \( \mu \)M loratadine revealed a statistically significant reduction: 52 ± 3 msec for control and 27 ± 3 msec for loratadine (mean ± standard error, three experiments; \( p < 0.05 \), Student's paired \( t \) test). The shorter burst duration was due to a reduction in the number of openings in a burst: 14 ± 2 for control and 7 ± 2 for loratadine (mean ± standard deviation, three experiments; \( p < 0.05 \), Student’s paired \( t \) test), whereas closed times within bursts were unchanged.

We next examined the effects of loratadine on the HERG cardiac K\(^+\) channel with a protocol previously used to examine the blocking effects of terfenadine on this channel (14). Briefly, HERG current was activated at a potential of \( > -40 \) mV by an 800-msec depolarizing pulse from a holding potential of \( -80 \) mV. The steady state I-V relationship had a typical bell-shaped wave form that peaked at 0 mV and revealed large outward tail currents at \( -50 \) mV due to fast recovery from inactivation and slow deactivation characteristic of this channel (3, 14). Fig. 10 shows the effects of 10 \( \mu \)M loratadine on whole-cell HERG channel currents recorded from a \( X. \) laevis oocyte over a wide range of test potentials. Under these conditions, loratadine failed to significantly alter HERG currents. Conversely, using the same experimental protocol, the non-sedating antihistamine terfenadine has previously been shown to block HERG currents with an \( IC_{50} \) value of 350 nM (14).

**Discussion**

We previously used the Kv1.5 channel as a model to explore the interactions of another non-sedating antihistamine, terfenadine, with human cardiac K\(^+\) channels (13). We have shown that terfenadine blocks Kv1.5 channel current in a time-dependent manner with an \( IC_{50} \) value of \( ~400 \) nM (13). Like terfenadine, loratadine blocked Kv1.5 currents in a time-dependent fashion with approximately equal affinity. Also like terfenadine, the major metabolite of loratadine was far less potent at inhibiting Kv1.5 compared with the parent compound. However, we noted some important differences in the apparent mode of action of these two drugs. Terfenadine, which is mainly positively charged at physiological pH (\( p_{Ka} = 8.6 \)), slows Kv1.5 deactivation and displays a greater block at more depolarized potentials, including potentials in which channel conductance is saturated. This presumably reflects blockade of the open channel state of Kv1.5 from the intracellular face of the channel (13, 24) and that the channel must wait for the drug to unbind before closing. Loratadine, on the other hand, showed no appreciable effect on Kv1.5 current deactivation, suggesting that the channels can close with the drug bound. Furthermore, the blocking effects of loratadine displayed an inverse relationship to voltage, with significantly less inhibition occurring at depolarized potentials, relative to membrane potentials closer to the threshold of activation of Kv1.5. We found this type of voltage-dependent behavior especially interesting in light of the fact that loratadine is uncharged at physiological pH (\( p_{Ka} = 5.0 \)). Finally, we found that loratadine had little effect on the cardiac HERG channel, whereas terfenadine blocks this channel with an \( IC_{50} \) value of 350 nM (14).

We used single-channel analysis to further explore the mechanism of action of loratadine on Kv1.5 and found the main effect of loratadine was to decrease the probability of opening of Kv1.5. However, even at a near-maximal inhibitory concentration, loratadine failed to alter the mean open time of Kv1.5. Furthermore, we found that loratadine significantly reduced Kv1.5 burst duration. Taken together with the macroscopic currents, the data suggest an interaction of loratadine with an activated state of the Kv1.5 channel. This could take the form of an interaction with the open state of Kv1.5. Our single-channel data rule out a simple open-channel block mechanism in which loratadine interacts with the open state of the channel at a rate sufficient to reduce the...
open time of individual openings because no change in mean open time was observed with exposure to loratadine. From the concentration dependence of the kinetics of channel block, we calculated an on-rate for loratadine of $7.5 \times 10^3$ M$^{-1}$sec$^{-1}$, and at a concentration of 3 μM, the channel-blocking rate becomes $0.0225$ msec$^{-2}$. Channel open time is defined kinetically as the reciprocal of the sum of transitions leaving the open state and measured 2.56 msec in control and 2.71 msec in the presence of loratadine. The expected value for the open time in the presence of loratadine can be calculated from the closing rate determined in control conditions ($\lambda_o = 1/t_o$), and the additional closing transition introduced by loratadine interaction with the open state can be calculated as $t_o,loratadine = 1/(\lambda_o - k_{on,loratadine} \cdot \text{[loratadine concentration]})$. Using the estimated value for the loratadine blocking rate at 3 μM ($0.0225$ msec$^{-1}$), the expected open time for a simple open-channel block mechanism with a 2.56-msec open time in control is $(0.390$ msec$^{-2} + 0.0225$ msec$^{-1})^{-1}$, or 2.42 msec in the presence of 3 μM loratadine (25). This small reduction in open time is below the precision of our open time measurements; consequently, we observed no significant difference in open times between measurements in control and after exposure to loratadine. Although changes in mean open time were negligible, our data predict the interaction of loratadine with Kv1.5 to be sufficiently fast and of a duration to alter burst kinetics. The mean sum of individual open state dwell times occurring within single bursts (mean total open time in a burst) is much longer than an individual dwell time in the open state for Kv1.5. Similar to the relation for individual open times, the reciprocal of the mean total open time in a burst gives an estimate for the mean exit rate from the open state within a burst. This rate is similar in magnitude.
to the calculated blocking rate for loratadine and should be observable. In our case, the calculated off-rate for loratadine (16.5 sec\(^{-1}\); see above) predicts a mean shut interval (61 msec) much longer than the critical closed time used to distinguish bursts (\(5 \text{ msec in all cases}\)), so essentially all blocking events will terminate a burst and be reflected in the data as a reduction in the mean total open time in a burst.

The mean total open time in a burst obtained as the product of the mean open dwell time (2.56 and 2.71 msec for control and in the presence of loratadine, respectively) and the mean number of openings in a burst (14 and 7 for control and in the presence of loratadine, respectively) were 35.84 msec in control and 18.97 msec in the presence of 3 \(\mu M\) loratadine. Using the calculated blocking rate constant for 3 \(\mu M\) loratadine and the reciprocal of the experimentally determined mean total open time in a burst in control conditions, the predicted mean total open time in a burst for the case in which all loratadine blocking events terminate a burst is \((35.84 \text{ msec}^{-1} + 0.0225 \text{ msec}^{-1})^{-1}\), or 19.84 msec, which compares favorably to our experimentally observed value of 18.97 msec. The mechanism for this block would be similar to that proposed for open-channel block of Kv1.5 by clofilium (26). However, the inverse voltage dependence of block produced by the uncharged loratadine molecule is difficult to reconcile with blockade of only the open state. Thus, we cannot exclude a secondary interaction of loratadine with another nonconducting state of Kv1.5 that may be favored at potentials near threshold.

Use of the nonsedating antihistamines terfenadine and astemizole may, on occasion, be associated with a prolongation of cardiac repolarization (9, 10). Presumably, this reflects an interaction of these drugs with one or more voltage-dependent K\(^+\) channels in the human myocardium (11–14).

After the normal therapeutic dose of loratadine (10 mg), peak serum plasma levels of the drug average \(\sim 12 \text{ nM}\) (22, 27). However, after a dose of 40 mg, peak serum levels of loratadine can reach \(\sim 150 \text{ nM}\) in normal volunteers and \(\sim 200 \text{ nM}\) in the elderly (22, 28). One case report has linked loratadine use with QT prolongation and ventricular tachycardia in a patient with a history of such arrhythmias (16, but see also 29). More recently, a cluster of adverse drug reactions involving palpitations and arrhythmias after loratadine administration was reported to the Australian ADR Advisory Committee (17). In the United States, a number of adverse drug reactions associating loratadine use with various supraventricular tachycardias are on file with the Food and Drug Administration (30), and some adverse drug reactions involv-

Fig. 7. Effects of loratadine on the steady state inactivation properties of Kv1.5. Currents from inside-out membrane patches were elicited as described in Results. Peak currents, uncorrected for leak, were used to generate the inactivation curves shown. Error bars, mean ± standard error (four experiments).

Fig. 8. Loratadine block of Kv1.5 unitary currents. Cell-attached patch recording from an L cell stably expressing Kv1.5. A, Control recordings show a characteristically high \(P_\text{o}\), with most activity occurring in bursts of openings. Fifty records at 60-mV step potential and 190-msec duration were obtained at a frequency of 0.125 Hz from a holding potential of \(-80 \text{ mV}\). B, Superfusion of the cell with 3 \(\mu M\) loratadine produced a clear decrease in \(P_\text{o}\) mainly due to reduction of burst duration. Forty-eight records with the same voltage-clamp protocol as in A were obtained in the presence of loratadine. Consecutive single-channel records are shown in all cases. C, Average currents were constructed from 50 and 48 records in control and during superfusion of the cell with loratadine, respectively, with the voltage protocol described in A. The rising phase of the currents overlapped similar to the macroscopic data.
Loratadine Block of Human Kv1.5

In summary, we described the interaction of the nonsedating antihistamine loratadine with the human cardiac K\(^+\) channel Kv1.5. The blocking effects of loratadine on Kv1.5 occurred at concentrations of \(\geq 100\) nM. Loratadine enhanced the rate of Kv1.5 current decay and was more potent at membrane potentials near the threshold of channel activation. At the single-channel level, loratadine reduced the probability of opening of Kv1.5 and decreased the number of openings in a burst and the burst duration. Loratadine failed to alter the mean open time of Kv1.5. The results show that like terfenadine and astemizole, loratadine can block at least one type of cardiac K\(^+\) channel at submicromolar concentrations. It is possible that such an interaction could contribute to altered cardiac repolarization in vivo.

Note Added in Proof

After this article was accepted for publication, we obtained a mammalian cell line expressing HERG and found the IC\(_{50}\) value of loratadine to be 2.8 mM.

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References


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