Kir3-Based Inward Rectifier Potassium Current
Potential Role in Atrial Tachycardia Remodeling Effects on Atrial Repolarization and Arrhythmias

Tae-Joon Cha, MD*; Joachim R. Ehrlich, MD*; Denis Chartier, BSc; Xiao-Yan Qi, PhD; Ling Xiao, BSc; Stanley Nattel, MD

Background—We previously characterized a novel K⁺ current (IₘKH) with properties of constitutively active acetylcholine-related current in dog atrium. IₘKH is sensitive to tertiapin-Q (IC₅₀ = 10 nmol/L), a highly selective Kir3 current blocker. This study assessed the role of IₘKH in atrial tachycardia (AT)–remodeled canine left atrium (LA) with the use of tertiapin-Q as a probe.

Methods and Results—Dogs were subjected to 7 to 13 days of AT (400 bpm). Coronary-perfused LA preparations were studied intact or subjected to cardiomyocyte isolation. IₘKH was recorded with patch-clamp methods. AT pacing increased time-dependent hyperpolarization-activated current (IₘKH) at −110 mV from −1.8 ± 0.3 (control) to −3.4 ± 0.5 pA/pF (AT) and the 100-nmol/L tertiapin-sensitive component from −1.5 ± 0.4 (control) to −3.3 ± 0.6 pA/pF (AT). Prolonged atrial tachyarrhythmias could be induced with single extrastimuli in AT-remodeled, but not control, preparations, reflecting the atrial fibrillation–promoting effects of AT remodeling. In AT-remodeled preparations, tachyarrhythmia duration averaged 11.0 ± 5.2 seconds, with a cycle length of 108 ± 6 ms. Tertiapin-Q decreased tachyarrhythmia duration (to 0.6 ± 0.1 second; P < 0.001) and increased tachyarrhythmia cycle length (to 175 ± 10 ms; P < 0.001). Atrial action potential duration (APD) was increased 65 ± 6% by tertiapin in AT-remodeled hearts versus 19 ± 2% (P < 0.001) in control. In 2 AT-remodeled preparations, tachyarrhythmia lasted uninterrupted for >20 minutes; tertiapin-Q slowed and then terminated arrhythmia in both. Tertiapin had no effect on left ventricular cardiomyocyte currents or APD.

Conclusions—AT remodeling increases IₘKH and a highly selective Kir3 current antagonist, tertiapin-Q, increases APD and suppresses atrial tachyarrhythmias in AT-remodeled preparations without affecting ventricular electrophysiology. Constitutive acetylcholine-related K⁺ current contributes to AT-remodeling effects in dogs and is a potentially interesting antiarrhythmic target. (Circulation. 2006;113:1730-1737.)

Key Words: antiarrhythmia agents • arrhythmia • electrophysiology • ion channels • remodeling

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Present antiarrhythmic drug approaches for sinus rhythm maintenance suffer from limited efficacy and a significant risk of adverse effects, particularly proarhythmia.1 One potential approach to improving drug therapy is the identification of novel ionic targets.2 We have previously identified a time-dependent inwardly rectifying K⁺ current (IₘKH) in canine atrial myocytes. IₘKH is highly sensitive to the specific inward rectifier current blocking compound tertiapin.3 In cardiac tissue, tertiapin is a highly selective blocker of channels carried by the Kir3 subunits that underlie the acetylcholine-dependent K⁺ current IₘKACh. In our previous study we obtained extensive evidence indicating that IₘKH is a constitutively active form of IₘKACh.3 IₘKH is increased by β-adrenergic stimulation and appears to be enhanced by sustained atrial tachycardia.4 Because IₘKH contributes to atrial action potential repolarization,3 it is a potential ionic determinant of the occurrence of AF and could constitute a novel ionic target for AF therapy.

The only selective IₘKH blocker presently available is tertiapin-Q, but tertiapin-Q is not available in sufficient quantities for in vivo administration under conditions that can produce and maintain stable and effective plasma concentrations. We recently showed that the atrial tachyarrhythmia–promoting effect of atrial tachycardia remodeling can be demonstrated in isolated coronary artery–perfused canine left atrial (LA) preparations.4 Such preparations demonstrate accelerated atrial repolarization and readily inducible atrial tachyarrhythmias, unlike control preparations in which programmed stimulation rarely induces repetitive responses (which in turn never consist of more...
than a few beats). Tertiapin-Q can be added to the perfusate of atrial tachycardia–remodeled preparations at known and effective Kir3 current–blocking concentrations. We therefore designed the present studies to assess the actions of tertiapin-Q on atrial repolarization and tachyarrhythmias in tachycardia-remodeled atrial preparations. In addition, we evaluated the effects of atrial tachycardia remodeling on Kir3-based currents as reflected by tertiapin-Q–sensitive current and the atrial specificity of $I_{K,ACh}$ by studying the impact of tertiapin-Q exposure on ionic currents and action potential properties of canine ventricular cells.

Methods

Animal Model

All animal care procedures followed Canadian Council on Animal Care guidelines and were approved by the animal research ethics committee of the Montreal Heart Institute. Mongrel dogs weighing 20 to 30 kg were studied, with 3 control dogs and 8 tachycardia-remodeled dogs used for standard microelectrode experiments in multicellular preparations, 9 control and 4 tachycardia-remodeled dogs used for measurement of $I_{K,ACh}$-sensitive and atrial tertiapin-Q–sensitive currents, and 5 control dogs used to study the effects of tertiapin-Q on ventricular ionic currents and action potentials.

Dogs (Forest & Gremier, Inc, Boucherville; Laka, St-Basile-le-Grand; and Raymond Mailloux, Ste-Angele-de-Monnoir, Quebec, Canada) subjected to atrial tachycardia remodeling were initially anesthetized with diazepam (0.25 mg/kg IV), ketamine (5.0 mg/kg IV), and halothane (1% to 2%) for transvenous insertion of right ventricular and right atrial unipolar pacing leads connected to IV), and halothane (1% to 2%) for transvenous insertion of right ventricular and right atrial unipolar pacing leads connected to ventricular and atrial pacemakers implanted in the neck. Atrioventricular block was created by radiofrequency catheter ablation, and atrial pacing was begun 24 hours after pacemaker implantation, after which the right atrium was tachypaced (400 bpm) for 7 to 13 days. The right ventricular demand pacemaker was programmed to 80 bpm to prevent excess Bradycardia after induction of atrioventricular block.

On study days, dogs were anesthetized with pentobarbital (30 mg · kg$^{-1}$ IV) and artificially ventilated. Hearts and adjacent lung tissue were excised via a left thoracotomy and immersed in oxygenated Tyrode’s solution. For atrial tachyarrhythmia induction, we used single S2 extrastimuli at multiple sites after 15 basic S1 stimuli at cycle lengths of 500, 333, 250, 200 ms, until a tachycardia rhythm was induced or until all S1S2s at all cycle lengths specified by the protocol were studied without tachycardia induction. The same protocol was performed before and after tertiapin-Q infusion. This protocol tended to minimize the inducibility differences between conditions before and after tertiapin because it did not consider the ease of tachyarrhythmia induction, which was often much greater before tertiapin (when tachyarrhythmias were often induced during the ERP determination at the first cycle length studied) versus after the drug (when tachyarrhythmias could often be induced only on completing nearly the full induction protocol).

To study ventricular action potentials, ventricular free-wall multicellular preparations were perfused via the circumflex coronary artery (as performed for cell isolation) and simultaneously superfused at 10 mL/min in a Plexiglas chamber for standard microelectrode recording. All stimuli were twice-threshold, 2-ms pulses.

Cellular Electrophysiology

Currents were recorded with whole-cell patch-clamp methods at 36±0.5°C. Borosilicate glass patch-clamp electrodes had tip resistances between 1.5 and 3.0 MΩ when filled. Compensated series resistance and capacitive time constants averaged 3.1±0.2 mol/L/Ω and 0.27±0.01 ms, respectively. In some experiments, cell access was obtained with the use of the perforated-patch technique. Rather than rupturing cell membranes by suction, the pipette tip was filled with normal intracellular solution, and then the pipette shaft was filled by injecting nystatin-containing (400 μg/mL) intracellular solution. After seal formation, the series resistance decreased progressively to reach a stable value averaging 7.7±0.6 MΩ. Atrial cell capacitance averaged 89.3±4.1 picofarad (pF), and left ventricular cell capacitance averaged 188.5±7.9 pF. To control for cell size variability, currents are expressed as densities (picoamperes [pA]/pF). Junction potentials averaged 9.7±0.7 mV and were not compensated. Currents were recorded with hyperpolarizing and depolarizing pulses (4-second duration) from a holding potential of −40 mV to selected test potentials.

Solutions

The solution for cell storage contained the following (mmol/L): KCl 20, KH₂PO₄ 10, dextrose 10, mannitol 40, L-glutamic acid 70, β-Hydroxybutyric acid 10, taurine 20, EGTA 10, and 0.1% bovine serum albumin (pH 7.3, KOH). Tyrode’s (extracellular) solution contained the following (mmol/L): NaCl 136, KCl 5.4, MgCl₂ 1, CaCl₂ 1, NaH₂PO₄ 0.33, HEPES 5, and dextrose 10 (pH 7.35, NaOH). Nifedipine (10 μmol/L) was used to inhibit L-type Ca²⁺ current. 4-Aminopyridine (2 mmol/L) was added to suppress transient outward current ($I_{to}$). Atropine (100 mmol/L) was added to extracellular solutions to suppress muscarinic receptor–activated currents. The internal solution contained the following (mmol/L): potassium aspartate 110, KCl 20, MgCl₂ 1, MgATP 5, GTP (lithium salt) 0.1, HEPES 10, sodium phosphocreatinine 5, and EGTA 5.0 (pH 7.3, KOH). Nystatin was prepared freshly each day that it was used and dissolved into intracellular solution at the desired concentration. For standard microelectrode experiments, a solution containing (mmol/L) NaCl 120, KCl 4, KH₂PO₄ 1.2, MgSO₄ 1.2, NaHCO₃ 25, CaCl₂ 1.25, and dextrose 5 (95% O₂/5% CO₂, pH 7.4) was used to perfuse the tissue. The highly selective Kir3 channel blocker tertiapin-Q and all other chemicals unless otherwise stated were obtained from Sigma-Aldrich Chemical Co (St Louis, Mo).

Data Analysis

Clampfit 6.0 (Axon Instruments, Foster City, Calif) and GraphPad Prism 3.0 (GraphPad Software, Inc, San Diego, Calif) were used for data analysis. Group data are presented as mean±SEM. Two-way repeated-measures ANOVA was used to study the behavior of the 2 groups (control and atrial tachycardia) across voltages. Two-group t
test was used to study the effect of atrial tachycardia on the tertiapin-induced percent increase in APD50 and APD90. Generalized estimating equations were used to model AF duration and tachycardia cycle length before versus after tertiapin-Q, as well as APD values before and after tertiapin. These models included before and after tertiapin-Q as factor and dog as the unit within which repeated observations were made. To analyze arrhythmia duration, which was found to have a skewed distribution, data were subjected to normalization by logarithmic transformation before statistical comparison. For atrial tachyarrhythmia inducibility analysis, the percentage of successful induction attempts (number of successes/number of attempts) was computed for each dog, and the mean percentage of success in the 8 dogs before tertiapin-Q infusion was compared with the mean percentage of success in the same dogs in the presence of tertiapin-Q with a paired \( t \) test. A 2-tailed \( P < 0.05 \) was considered to indicate a statistically significant difference.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Atrial Tachycardia–Induced Remodeling of \( I_{KH} \)**

Figure 1A shows currents elicited by 4-second pulses from a holding potential of \(-40 \) mV to voltages between \(-120 \) and \(-30 \) mV with 10-mV increments under control conditions. \( I_{KH} \) is seen as a typical time-dependent activating current with small outward tail currents. There is also an instantaneous component that includes \( I_{K1} \). Currents were increased in LA cardiomyocytes from atrial tachypaced dogs, as illustrated by the recordings from a representative cell in Figure 1B. The middle panels in Figure 1A and 1B show currents from the same cells after exposure to 100 nmol/L tertiapin-Q, which suppresses \( I_{KH} \), leaving an instantaneous current that we have previously shown to be primarily \( I_{K1} \).\(^3\) The bottom panels show tertiapin-sensitive currents from the respective cells, obtained by digitally subtracting currents in the middle panels from those in the top panels. These tertiapin-sensitive currents are essentially pure \( I_{KH} \).\(^3\) Mean data in Figure 1C show a significant increase in the time-dependent currents obtained in the absence of tertiapin (as in Figure 1A) over a broad range of voltages. Overall time-dependent current averaged \(-1.8 \pm 0.3 \) pA/pF at \(-110 \) mV in 18 control cells from 9 dogs versus \(-3.4 \pm 0.5 \) pA/pF in 10 cells from 4 tachypacing-remodeled dogs. Mean tertiapin-sensitive current–voltage relations are shown in Figure 1D. Atrial tachypacing clearly increased tertiapin-Q–sensitive current. Tertiapin-sensitive current could be measured on the basis of stable recordings from the same cells both before and after the drug in 9 cells from 6 control dogs and 8 cells from 3 atrial tachycardia–remodeled dogs. The tertiapin-sensitive current at \(-110 \) mV averaged \(-1.5 \pm 0.4 \) pA/pF in control cells compared with \(-3.3 \pm 0.6 \) pA/pF in atrial tachycardia–remodeled cells.

**Changes in APD Caused by Tachycardia Remodeling and Tertiapin Exposure**

To assess the role of \( I_{KH} \) in repolarization of atrial tachycardia–remodeled preparations, we monitored APD before and after exposure to tertiapin-Q. Figure 2A shows
Figure 2. APD changes due to atrial tachypacing and tertiapin-Q (TQ). A, Action potential recordings at 2 Hz obtained before and after tertiapin (100 nmol/L) in a preparation from a control dog. B, Action potential recordings at 2 Hz before and after tertiapin (100 nmol/L) in a preparation from an atrial tachycardia (AT)-remodeled dog. Note the strong APD abbreviation seen with atrial tachycardia remodeling and the APD increases produced by tertiapin. The dotted and dashed lines show phase 1 and phase 3 slopes, respectively. Bars indicate zero voltage. C, Mean ± SEM APD in the absence and presence of 100 nmol/L tertiapin-Q in control (CTL; left) and atrial tachycardia-remodeled (right) preparations. n = 25, 12 cells before and after tertiapin-Q, respectively, in 3 dogs for control; n = 24, 23 cells before and after tertiapin-Q, respectively, from 8 dogs in atrial tachycardia-remodeled preparations. D, Percent increase in APD caused by tertiapin-Q in control (left) and atrial tachycardia-remodeled (right) preparations based on the analysis of the data illustrated in C. *P < 0.001 vs control.

To analyze further the effects of tertiapin-Q on repolarization, we fitted the slopes of phases 1 and 3 of the action potential, as illustrated by the dotted and dashed lines, respectively, in Figure 2A and 2B. Phase 1 slope averaged 0.81 ± 0.06 mV/ms in 25 cells from 3 control dogs and increased to 3.09 ± 0.33 mV/ms (P < 0.001) in 24 cells from 8 tachycardia-remodeled dogs. Tertiapin-Q had little effect on phase 1 slope in 3 control dogs (0.72 ± 0.05 mV/ms; n = 12 cells; P = NS versus control before tertiapin-Q) but considerably decreased phase 1 slope in 23 remodeled cells from 8 dogs, to 1.12 ± 0.15 mV/ms (P < 0.001 versus values before tertiapin), almost to control levels. Phase 3 slope averaged 0.52 ± 0.01 mV/ms before and 0.51 ± 0.02 mV/ms after tertiapin-Q in control dogs (P = NS). Atrial tachycardia remodeling increased phase 3 slope to 0.74 ± 0.02 mV/ms (P < 0.001 versus control), and this value was significantly reduced by tertiapin-Q, to 0.45 ± 0.02 mV/ms (P < 0.001 versus values before tertiapin in remodeled cells), to values comparable to those of control dogs.

The very strong inward rectification of $I_{K_{ACh}}$ (Figure 1) makes it hard to understand its role in repolarization, as shown in Figure 2. One possible explanation is that dialysis of cellular contents under tight-seal patch clamp alters intracellular composition in a fashion that enhances rectification. We therefore recorded $I_{K_{ACh}}$ with perforated-patch methods before and after tertiapin-Q (100 nmol/L) in 11 cells from 5 additional dogs. The current–voltage curve between −70 and −40 mV from these cells is compared with those in 9 cells from 6 control dogs in Figure 3. The outward currents are larger in cells studied with nystatin patch. To analyze inward rectification, we expressed the current for each cell at each voltage between −70 and −40 mV as a ratio of the inward current at −120 mV. This index was significantly larger (P < 0.05, 2-factor repeated-measures ANOVA) for cells studied with the perforated-patch technique (eg, at −60 mV, 0.08 ± 0.04 versus −0.07 ± 0.07 for ruptured patch), indicat-
Effects of Tertiapin-Q on Atrial Tachyarrhythmias

Figure 4A shows the induction of an atrial tachyarrhythmia by a single extrastimulus in an atrial tachycardia–remodeled preparation. Figure 4B shows failure of tachyarrhythmia induction by an extrastimulus just beyond the refractory period in the same preparation after the addition of 100 nmol/L tertiapin-Q to the perfusate. Overall, in the absence of tertiapin, atrial tachyarrhythmias were induced by single extrastimuli in 81 of 117 attempts (65% of attempts) in preparations from 8 dogs. After tertiapin-Q infusion, atrial tachyarrhythmias could only be induced in 66 of 174 attempts (34% of attempts; P = 0.0025) in the same preparations.

In addition to suppressing the induction of tachyarrhythmias in tachycardia-remodeled preparations, tertiapin-Q substantially reduced their persistence. In the absence of tertiapin-Q, mean tachyarrhythmia duration for nonsustained episodes was 11.0 ± 5.2 seconds, with a mean cycle length of 108 ± 6 ms. In the presence of 100 nmol/L tertiapin-Q, tachyarrhythmia duration was decreased significantly to 0.6 ± 0.1 second (P < 0.001), and tachyarrhythmia cycle length increased to 175 ± 10 ms (P < 0.001). In 2 separate tachycardia-remodeled preparations, tachyarrhythmias were spontaneously sustained for >20 minutes. An example of action potential recordings during a sustained tachyarrhythmia from 1 such preparation is shown in Figure 5A. In both cases, the addition of tertiapin-Q during sustained tachyarrhythmia caused progressive slowing of the tachycardia, with termination occurring on equilibration of the drug in the bath (within 4 minutes), as illustrated in Figure 5B.

Assessment of Potential Ventricular Effects of Tertiapin-Q

The aforementioned experiments indicate that tertiapin produces prominent APD increases in tachycardia-remodeled atrial preparations and alters the properties of tachyarrhythmias by decreasing their inducibility, reducing their duration, prolonging their cycle length, and terminating sustained episodes. To establish the atrial selectivity of tertiapin-Q and its target current, we performed the experiments illustrated in Figure 6. Currents were recorded from single ventricular myocytes (Figure 6A) with the same voltage protocol as used for atrial I_{Ks} recording (Figure 6A). A representative set of recordings from 1 ventricular myocyte is shown in the top panel. In no cases was current with the
significant effect of tertiapin-Q was observed. For example, after tertiapin-Q in 10 ventricular myocytes from 2 dogs. No concentration of tertiapin-Q. There was no apparent change. Figure 6B shows mean current density–voltage relations before and after tertiapin-Q. Tom panel shows currents from the same cell after administration of tertiapin-Q. Figure 6C shows typical ventricular action potentials recorded before (top) and after (bottom) tertiapin-Q exposure in one multicellular ventricular preparation. In contrast to its clear effect on atrial tissues (Figure 2), tertiapin had no apparent effect on ventricular action potentials. Mean APD data (Figure 5D) confirm the lack of any significant effect of tertiapin-Q on ventricular repolarization.

Discussion

In this study we found that atrial tachycardia remodeling increases the tertiapin-Q–sensitive atrial current I_{KH}. In addition, tertiapin-Q importantly prolonged repolarization, prevented tachyarrhythmia induction, and suppressed sustained tachyarrhythmias in tachycardia-remodeled atrial preparations. In contrast to its important atrial effects, tertiapin-Q produced no detectable changes in ventricular ionic currents or action potentials.

Ionic Changes in AT Remodeling

Atrial tachycardia–induced electric remodeling plays a significant role in the pathophysiology of AF.6,7 Alterations in ion channel function (“ionic remodeling”) are believed to be important in the AF-promoting consequences of atrial tachycardia.6–8 Ionic changes that have been reported include decreased transient outward current (I_{to}),9–11 L-type Ca^{2+} current (I_{L})9,11,12 and Na^{+} current (I_{Na}),13,14 and increased inward rectifier K^{+} currents.10,11,15 Bosch et al16 reported that atrial myocytes from AF patients show increases in both the background inward rectifier current I_{KH} and the acetylcholine-induced component. In contrast, Dobrev et al15 showed that in myocytes from AF patients the background inward rectifier current is increased, but the acetylcholine-induced component is reduced. We also found that the additional current induced by cholinergic stimulation is reduced in atrial myocytes from tachycardia-remodeled dog atria but that the constitutive I_{KH} component (I_{KH}) is enhanced.3 In previous work, we quantified the constitutive component in tachycardia-remodeled myocytes on the basis of its time dependence and found it to be enhanced relative to time-dependent constitutive current in control dogs.3 In that study the response of currents to tertiapin was not examined in remodeled preparations. In the present investigation we show that atrial tachycardia significantly enhances the current component sensitive to tertiapin-Q, accounting for the increased APD response to tertiapin seen in remodeled preparations. Tertiapin-Q is a highly selective blocker of currents encoded by Kir1 and Kir3 subunits,16 and in the heart (which lacks Kir1 currents) tertiapin-Q blocks the Kir3-based channels that carry I_{KH} very selectively at concentrations up to 1 μmol/L.17,18 I_{KH} channels can be constitutively active in the absence of cholinergic agonist stimulation,19,20 as must be the case for I_{KH}, because the current is robust in the presence of the muscarinic antagonist atropine. Furthermore, cholinergic K^{+} currents with kinetic properties similar to those of I_{KH} have been observed previously in human atrial myocytes.21

AF-promoting conditions like atrial tachycardia–induced remodeling produce a wide range of functional alterations. It is a significant challenge to determine the role of specific changes in AF promotion.22 Such knowledge is needed to appreciate therapeutic implications and to develop effective new therapeutic approaches. I_{KH} reduction clearly contributes to action potential abbreviation in atrial tachycardia remodeling.9,11,12 The potential importance of inward rectifier current changes10,11,15 has remained speculative. In the present study we provide strong evidence for a role of increased constitutively active I_{KACH}/I_{KH} by showing that tertiapin-Q at highly selective Kir3-blocking concentrations suppresses K^{+} current and increases APD in tachycardia-remodeled atria to
a greater extent than in control atria and suppresses tachyarrhythmia induction and maintenance in tachycardia-remodeled preparations.

**Potential Importance of Our Findings**

The pathophysiological relevance and potential therapeutic importance of atrial tachycardia remodeling are well recognized.\(^a\) Insights into underlying mechanisms are therefore of considerable significance. Our study is the first, to our knowledge, to demonstrate experimentally a role for Kir3-based inward rectifier currents in the ionic current changes, action potential alterations, and arrhythmia promotion caused by atrial tachycardia remodeling. Furthermore, these findings support the results of recent modeling work, which predicts a significant role of inward rectifying currents in stabilizing atrial reentrant arrhythmias.\(^{23}\)

The therapeutic options for AF are presently suboptimal, and there is an ongoing search for drugs that can suppress AF without promoting ventricular tachyarrhythmias. In the present study we found that tertiaripin-Q suppresses atrial tachyarrhythmias in atrial tachycardia-remodeled preparations at concentrations that have no effect on ventricular myocyte currents or action potentials. Thus, Kir3-based \(I_{KACCH}\) is a potentially interesting target for atrial-selective antiarrhythmic drug development. A variety of traditional antiarrhythmic agents have \(I_{KACCH}\)-blocking ability.\(^{24\text{-}26}\) The investigational compound AVE-0118 also blocks \(I_{KACCH}\)\(^{27}\) and has interesting efficacy in experimental AF.\(^{28}\) Thus, \(I_{KACCH}\) inhibition can apparently be achieved safely in vivo and may contribute to antiarrhythmic efficacy. Furthermore, there is evidence of constitutive \(I_{KACCH}\) activation in AF patients,\(^{29}\) which can be unmasked by its tertiaripin-sensitive properties.\(^{30}\)

In view of the results of the present study, the development of selective \(I_{KACCH}\) blockers may be an interesting new approach to consider for AF therapy.

**Potential Limitations**

Our experiments were performed in LA cardiomyocytes and multicellular preparations. The extent to which right atrial tissue would manifest similar properties is uncertain. However, given the apparent importance of LA drivers in AF,\(^{31\text{-}33}\) our results would likely be of potential importance even if similar phenomena were absent in the right atrium. In fact, there is evidence that \(I_{KACCH}\) may be greater in the left than the right atrium,\(^{34}\) which in combination with the findings of the present study would provide a candidate ionic mechanism for the role of the left atrium in AF associated with atrial tachycardia remodeling.

The current–voltage relations of \(I_{K1}\) indicate very small currents at voltages positive to \(-30\) mV, but we saw apparent action potential prolongation by tertiaripin-Q at more positive voltages. Furthermore, we saw a significant decrease in phase 1 slope with the compound. It is difficult to extrapolate directly from patch-clamp ion current recordings to ionic current properties in vivo. The conditions needed to record selected currents in native cells with tight-seal patch clamp involve a variety of factors that can significantly distort subtle current properties, including voltage dependence. Such factors include dialysis of intracellular contents with the patch pipette solution (which removes a variety of macromolecules and important cellular constituents), the need for strong intracellular buffering to prevent cytotoxic \(Ca^{2+}\) overload, and the use of interventions (which can have significant effects on current amplitude, kinetics, and current–voltage relations) to block potential contaminating currents. We therefore relied on the use of a highly selective blocking compound (tertiaripin-Q) in coronary artery–perfused multicellular preparations to provide information about the potential importance of \(I_{K1}\) on repolarization and arrhythmia generation under the most physiological conditions possible. In previous studies with cardiac tissue, tertiaripin blocked \(I_{KACCH}\) very potently, with an \(IC_{50}\) of 8 to 30 mmol/L and no significant effect on rapid or slow delayed-rectifier \(K^{+}\) current, \(I_{Ks}\), adenosine triphosphate–dependent \(K^{+}\) current, sustained end-pulse outward current, \(Na^{+}\) current, or \(L\)-type \(Ca^{2+}\) current.\(^{17,18}\) However, we cannot fully exclude an action of tertiaripin-Q on some unknown current that differs from \(I_{KACCH}\)-related current and from others on which the drug has been tested previously.

**Acknowledgments**

The authors thank the Canadian Institutes of Health Research, the Quebec Heart and Stroke Foundation, and the Mathematics of Information Technology and Complex Systems Network of Centers of Excellence for research funding. Dr Cha received a fellowship from Kosin University, Busan, South Korea. The authors thank Nathalie L’Heureux and Chantal Maltais for technical assistance, Annik Fortier and Marie-Claude Guertin of the Montreal Heart Institute Biostatistics Service for expert statistical advice and execution of analyses, and France Thériault for secretarial help.

**Disclosures**

Dr Nattel is listed as co-inventor on a patent for acetylcholine-dependent potassium current as a target for atrial fibrillation therapy, ownership of which belongs to the Montreal Heart Institute and University of Montreal.

**References**

Atrial fibrillation remains an arrhythmia that is difficult to treat, and there is considerable interest in developing new therapies that target underlying mechanisms. This study addresses a novel mechanism associated with atrial tachycardia remodeling, the process by which atrial fibrillation promotes its own perpetuation. In isolated tissue preparations from dogs with remodeling caused by 7 days of atrial tachycardia, tachycardia remodeling was found to enhance a current that behaves like the current activated by acetylcholine, the vagal neurotransmitter, but can be seen even in the absence of acetylcholine. Blockade of the current with a specific acetylcholine-induced current blocker partly reverses the action of this current on the activation phase of the ACh-response in guinea-pig atrial cells. In contrast to its importance in the atrium, the current is absent in the ventricle. Thus, this new model of sustained atrial fibrillation may provide a new therapeutic target for atrial fibrillation.

**CLINICAL PERSPECTIVE**

Atrial fibrillation is a common cardiac arrhythmia that affects millions of people worldwide. It is characterized by an irregular and rapid heart rate, which can lead to increased risk of stroke, heart failure, and other serious health conditions. Current treatments for atrial fibrillation include antiarrhythmic medications, cardioversion, and rhythm-control procedures, but many patients continue to experience recurrent or persistent atrial fibrillation. New therapeutic approaches are needed to improve outcomes in these patients.

This study presents a novel mechanism that could potentially be targeted for the treatment of atrial fibrillation. The study found that a current, induced by acetylcholine, plays a significant role in the atrial proarrhythmic effect of atrial tachycardia remodeling. This current is not found in the ventricle, suggesting that targeting this current in the atrium could be a promising therapeutic strategy.

The findings of this study open up new avenues for the development of atrial fibrillation treatments. Further research is needed to confirm the role of this current in clinical settings and to investigate the potential of blocking this current as a therapeutic strategy for atrial fibrillation. This could lead to the development of new medications or other interventions that could improve outcomes for patients with atrial fibrillation.
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Circulation. 2006;113:1730-1737; originally published online April 3, 2006;
doi: 10.1161/CIRCULATIONAHA.105.561738

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/14/1730

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