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Electrophysiological effects of ibutilide on the delayed rectifier K^+ current in rabbit sinoatrial and atrioventricular node cells

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Abstract

Biophysical and pharmacological characteristics of the delayed rectifier K^+ current (I_K) of rabbit sinoatrial (SA) node and atrioventricular (AV) node cells have been studied using the whole-cell patch clamp technique together with a recently developed antiarrhythmic agent, ibutilide. Ibutilide is a potent blocker of the rapid delayed rectifier K^+ current, I_{Kr}. Superfusion with ibutilide (10^{-7} M) caused a decrease in the spontaneous firing frequency, depolarization of the maximal diastolic potential and prolongation of the action potential duration in both SA and AV node cells. In whole cell voltage clamp experiments done on myocytes from SA node, ibutilide (10^{-7} M) blocked I_K strongly (40%) and had smaller effects on Ca^{2+} current (10%) and hyperpolarization-activated inward current, I_f (11%). In AV node cells, the corresponding reductions were I_K (68%), I_{Ca} (13%) and I_f (10%), respectively. A 10-fold increase in the concentration of ibutilide further decreased I_K in SA node cells (67 ± 8%), and blocked I_K almost completely in AV node cells. These results are consistent with the hypothesis that the delayed rectifier K^+ current in SA node cell is generated by both I_{Kr} and I_{Ks}, whereas I_{Kr} predominates in AV node cells. Knowledge of the differences in the distribution of I_{Kr}, as well as the different sensitivity to blockers of I_{Kr} in nodal cells, is important for understanding modifications of the automaticity, conduction velocity, and refractoriness by class III antiarrhythmic agents.

Keywords: K^+ current, Delayed rectifier; Sinoatrial node; Atrioventricular node; Antiarrhythmic agent, Class III

1. Introduction

The delayed rectifier K^+ current (I_K) in the heart plays important functional roles under both physiological and pathophysiological conditions. It is one of the major contributors to repolarization of the action potential, and also is an important target for newly developed class III antiarrhythmic agents. Sanguinetti and Jurkiewicz (1990) first demonstrated by using a selective blocker, 1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methyl-sulfonylaminobenzoyl) piperidine dihydrochloride (E-4031), that I_K in guinea-pig ventricular myocytes was composed of two distinct K^+ components currents, I_{Kr} and I_{Ks} (Sanguinetti and Jurkiewicz, 1990). Similar approaches have yielded evidence for species- and tissue-dependent differences in the components of I_K in a number of different mammalian myocyte preparations.

In rabbit pacemaker cells, Ito and Ono reported I_K in sinoatrial (SA) node cells was mainly generated by I_{Kr}, based on their observation that it was blocked almost completely by E-4031 (Ito and Ono, 1995; Ono and Ito, 1995). However, their data also suggested that I_{Ks} was present, since an E-4031-insensitive outward current was identified in some myocytes. Howarth et al. (1996) reported that I_K in rabbit atrioventricular (AV) node cells

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consists mainly I_{Kr} since I_K tail was completely blocked by 5 μM E-4031. In guinea-pig SA node, I_{Ks} appears to be the major component of the delayed rectifier K^+ current, as judged by the very similar voltage dependencies, rectification properties and gating kinetics with I_{Ks} in the guinea pig (Anumonwo et al., 1992). Since I_{Kr} and I_{Ks} are kinetically and pharmacologically quite different, it seems very important to know the patterns of expression of these K^+ currents, and their contribution to the pacemaking activity in SA and AV node cells. In the present study, we have attempted to identify the electrophysiological characteristics of I_K in SA and AV node cells of rabbits using ibutilide, a recently developed I_{Kr} blocker (Lynch et al., 1995; Yang et al., 1995). Our results show that SA node expresses both I_{Kr}, and a second very slowly developing component of I_K (probably I_{Ks}). In contrast, I_K in AV node is mainly generated by I_{Kr}, a finding which is in agreement with the recent findings of Howarth et al. (1996).

2. Materials and methods

2.1. Cell isolation

The method used for isolating single SA node cells and AV node cells was similar to that described previously (Han et al., 1994). Briefly, rabbits weighing 1.5–2.0 kg were anaesthetized with sodium pentobarbital (50 mg/kg). The heart was quickly removed and then perfused retrogradely for 5 min on a Langendorff apparatus (37°C, 80 cm H_2O) with (1) a bicarbonate buffered Tyrode's solution containing 1 mM $CaCl_2$ to remove the blood, (2) a Ca^{2+}-free Tyrode for 10 min, and (3) Ca^{2+}-free Tyrode containing 12.5 U/ml collagenase (Yakult, Tokyo, Japan) and 0.05 U/ml protease (Type 14, Sigma, St. Louis, MO, USA) with 1% bovine serum albumin (Sigma Fraction V). After 8 min of enzyme treatment, the anatomical SA and AV nodal regions were removed, and the surrounding tissues were dissected away. The final preparations were cut into small pieces and stirred in Ca^{2+}-free HEPES-buffered Tyrode solution containing 500 U/ml collagenase (Sigma type 1), 50 U/ml elastase (Sigma type 3) and 1% bovine serum albumin for SA node cells, and 500 U/ml collagenase and 1% bovine serum albumin for AV node cells. Every 3 min, aliquots of these solutions were aspirated and placed in KB solution. The isolated cells were collected by centrifugation for 5 min, and stored in KB solution with 1% bovine serum albumin at 4°C.

2.2. Solutions and drugs

Bicarbonate-buffered Tyrode solution contained (in mM): NaCl 121, KCl 5.0, sodium acetate 2.8, $MgCl_2$ 1.0, Na_2HPO_4 1.0, $NaHCO_3$ 24 and glucose 5.5. This solution was equilibrated with 95% O_2 and 5% CO_2 (pH = 7.4). The HEPES-buffered Tyrode solution contained (in mM): NaCl 145, KCl 5.4, $MgCl_2$ 1.0, $CaCl_2$ 1.8, Na_2HPO_4 1.0, HEPES 5.0, and glucose 10 (pH = 7.4 adjusted with NaOH). The KB solution contained (in mM): K glutamate 90, K-oxalate 10, KCl 25, KH_2PO_4 10, NaOH 6, $MgCl_2$ 1.0, taurine 20, HEPES 5.0, and glucose 10 (pH = 7.2 adjusted with KOH). The pipette filling solution used for nystatin perforated patches contained (in mM): KCl 140, NaCl 6.0, $MgCl_2$ 1.0, HEPES 5.0 (pH = 7.2 adjusted with KOH). The pipette filling solution used when conventional ruptured patch method were used contained (in mM): K^+-aspartate 95, KCl 25, HEPES 5.0, EGTA 10, K_2ATP 3, $CaCl_2$ 1, $MgCl_2$ 1 (pH = 7.2 adjusted by KOH).

Ibutilide (Upjohn Pharmaceutical, USA) was used in these experiments. Ibutilide was dissolved in distilled water as a 2-mM stock solution. Nifedipine (Sigma) was dissolved in dimethylsulfoxide (DMSO) to form a-10 mM stock solution.

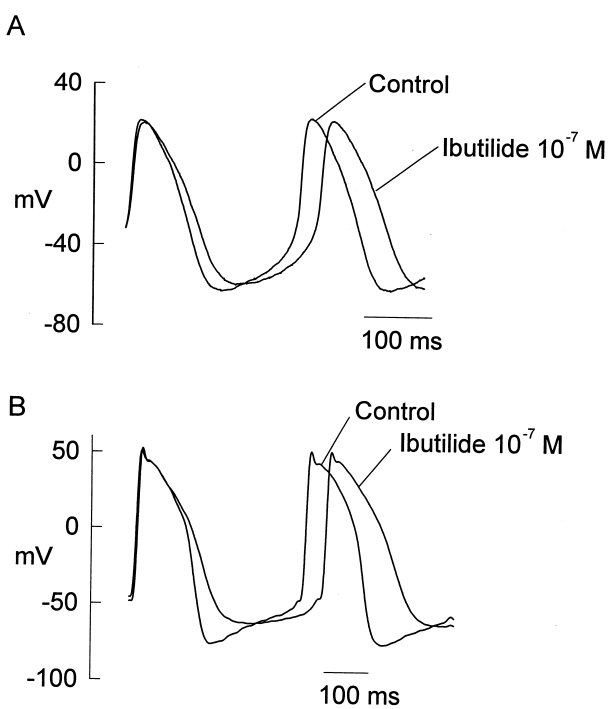

Fig. 1. Effect of ibutilide on spontaneous pacemaker activity and action potentials in nodal cells from adult rabbit heart. (A) Representative recordings of action potentials from a single rabbit SA nodal cell in the presence and absence of 10^{-7} M ibutilide. The nystatin-permeabilized patch method was used for these experiments. Temperature was 34 ± 1°C. (B) Representative recordings of action potentials from a single rabbit AV nodal cell in the presence and absence of ibutilide (10^{-7} M). Action potential upstrokes have been aligned to illustrate changes in duration, and slope of diastolic depolarization, or pacemaker potential.

2.3. Electrophysiological recordings

Electrical recordings were made using an Axopatch-1D amplifier (Axon Instruments, Foster City, CA, USA). All action potential measurements were made using nystatin permeabilized patch method. Nystatin dissolved in DMSO (0.1 mg/μl) was added to the pipette solution, giving a final concentration of 400 μg/ml. The pipette resistance, when filled with this solution was 1.5–3 MΩ. For the voltage-clamp experiments, the conventional membrane ruptured pipette method with pipettes having tip resistances of 1–2 MΩ was used. The liquid junction potential of approximately 10 mV was corrected for. In voltage clamp experiments, currents were elicited by 500-ms or 1-s depolarizing or hyperpolarizing pulses from a holding potential of −40 or −50 mV to potentials ranging from −110 to +40 or +50 mV. All recordings were made at 32–34°C. Electrical signals were sampled at 3.3 kHz with a 12-bit A/D converter board (DT 2801 A, Data Translation, Marlborough, MA, USA) which was controlled by software (CELLSOFT 2.1) developed by D. Bergman at The University of Calgary. Data are expressed as mean ± S.E., wherever this is possible. Statistical significance was determined by unpaired or paired *t*-tests, as appropriate.

3. Results

3.1. Effects of ibutilide on automaticity and spontaneous action potentials

The effects of ibutilide on the automaticity and spontaneous action potentials of SA and AV node cells were studied using the nystatin-permeabilized patch method. In these experiments, we used only small spindle-shaped cells from SA and AV nodes (Denyer and Brown, 1990; Munk et al., 1996). Fig. 1A and B shows representative data recorded before and during superfusion with 10^{-7} M ibutilide. Ibutilide caused a decrease in the spontaneous firing frequency, a small depolarization of maximal diastolic potential, and prolongation of the action potential duration in both SA and AV node cells. An increase in the concentration of ibutilide to 1 μM accentuated each of these changes, finally leading to the cessation of automatic activity in both SA and AV node cells (data not shown). A similar pattern of results was obtained in a total of six separate experiments done on SA node cells and AV node cells.

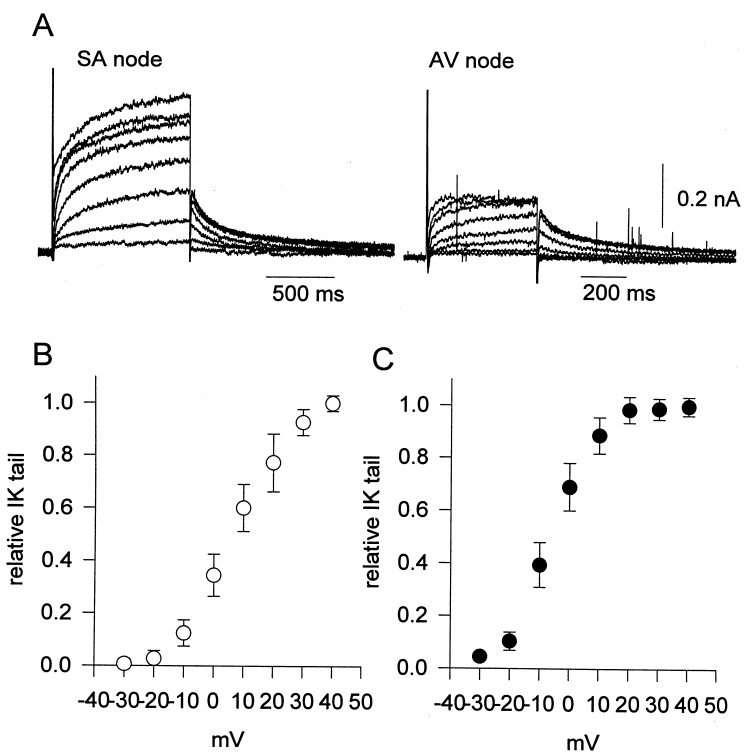

Fig. 2. Steady-state activation curve for I_K in SA node cells and AV node cells. A: Superimposed current records showing delayed rectifier, I_K and tail currents in a SA node cell (left panel) and a AV node cell (right panel). In both experiments, the cell was depolarized from a holding potential of −40 in 10 mV increments from −30 to +40 mV. Panels B and C show steady-state activation curve for I_K in SA node cells (panel B) and AV node cells (panel C) obtained by plotting normalized peak tail current amplitudes against the potential of the test depolarization. Data are expressed as means ± S.E. from six and seven experiments, respectively. L-type Ca^{2+} current was blocked by 5 M Nifedipine.

3.2. Delayed rectifier K^+ current (I_K) in SA and AV nodes

Fig. 2A shows representative delayed rectifier K^+ current records obtained from SA and AV node cells, respectively. The superimposed membrane currents in Panel A were elicited by applying 500 or 1000 ms depolarizing pulses in 10 mV increments from a holding potential of −40 mV. Note that there is a clear difference between the current configuration in SA and AV node cells. I_K in the SA node cell was characterized by relatively large and slowly activating time-dependent outward current, while I_K in the AV node cell exhibited relatively small and rapidly activated outward current. This suggested that components of I_K are different in SA and AV node cells. Fig. 2B and C shows steady-state activation curves for I_K from 6 SA node cells and 7 AV node cells, respectively.

3.3. Block of I_K by ibutilide

The effect of ibutilide on I_K in SA and AV nodes was investigated using conventional membrane-ruptured method. Fig. 3A consists of representative current traces in the presence and absence of ibutilide in an SA node cell. 10^{-7} M ibutilide inhibited the steady state outward current and corresponding tail current by 11% and 20%, respectively. An increase in the concentration of ibutilide to 1 μM caused an additional block of the time-dependent outward current (13%). The initial amplitude of the I_K tail was reduced by an additional 42% in this experiment.

Fig. 3B demonstrates strong inhibition of I_K in an AV node cell following ibutilide 10^{-7} M application. Fig. 3C and D shows a summary of the inhibition of the I_K tail by ibutilide in SA node cells (Fig. 3C) and AV node cells (Fig. 3D). Note that ibutilide at 1 μM blocked I_K tail in AV node nearly completely, whereas it had less effect on I_K tails in SA node cells. These findings demonstrate that the distribution of I_{Kr} in these two pacemaker cell types is different, and suggest that I_K in AV node is mainly composed of I_{Kr}, while I_K in SA node is composed of I_{Kr} and another component, probably, I_{Ks}. Fig. 4A shows examples of ibutilide-sensitive currents obtained by digital subtraction of currents recorded in the presence of drug, from corresponding control records. Fig. 4B shows current–voltage relationships for activating current and relative I_K tail values (Fig. 4C) of ibutilide-sensitive currents.

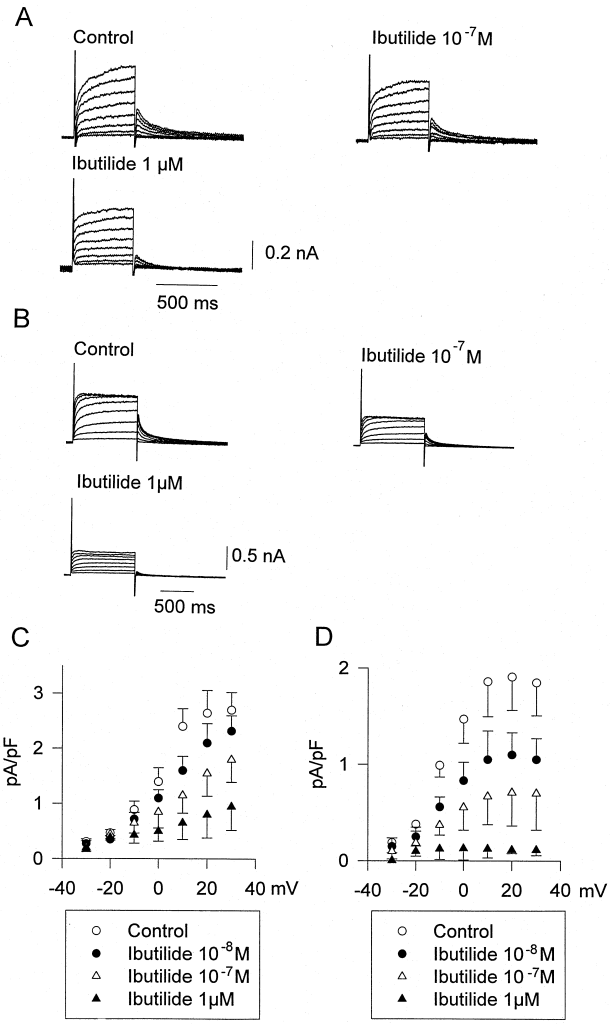

Fig. 3. Effects of ibutilide on delayed rectifier K^+ current in a SA node cell and an AV node cell. (A) Representative recordings of delayed rectifier K^+ currents before (upper left) and after (upper right, lower left) superfusion with 10^{-7} M and 1 μM ibutilide in a SA node cell. Currents were activated from a holding potential of −40 mV by voltage steps ranging from −30 to +50 mV in 10 mV increments. (B) Superimposed currents recorded before (upper left) and during (upper right, lower left) superfusion with 10^{-7} and 1 μM ibutilide. Each cell was held at −40 mV and voltage steps from −30 to +40 mV were applied in 10 mV increments. Panels C and D are plots of peak amplitude of deactivating tail currents in the absence and presence of ibutilide in SA node cells (panel C) and AV node cells (panel D). Data are presented as means ± S.E. from six experiments for SA node cells, and seven for AV node cells.

3.4. Selectivity of ionic channel block by ibutilide

To test the selectivity of ibutilide as an I_{Kr} blocker, its effects on L-type Ca^{2+} current, and the hyperpolarization-activated inward current, I_f in SA node cells were investigated. Fig. 5A shows representative current traces recorded before and after exposure to 10^{-7} M ibutilide. Fig. 5B and D shows current voltage relationships for I_{Ca}. 10^{-7} M ibutilide resulted in a small reductions of I_{Ca} (10%) in SA node cells, and 13% in AV node cells, respectively. Fig. 5C and E shows the I–V relationships for I_f in the presence of absence of ibutilide. These result show that, in this experiment I_f was reduced by 11% in SA node cells

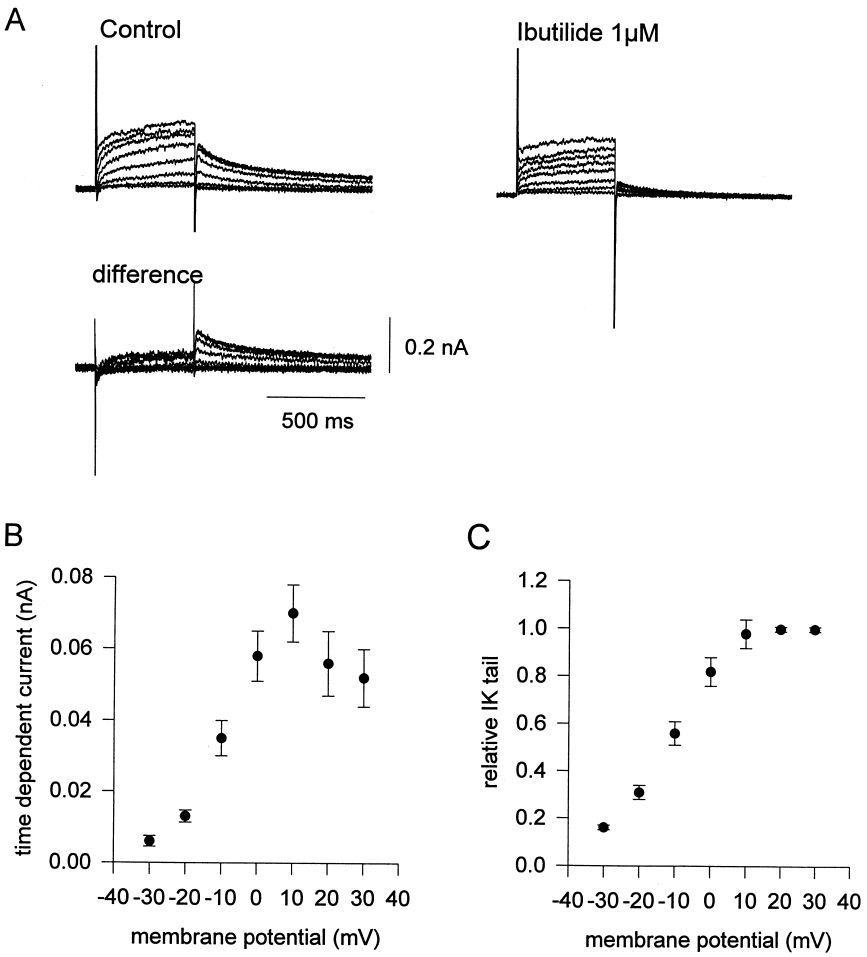

Fig. 4. Ibutilide-sensitive currents in myocyte from SA node. Currents were elicited by 1-sec depolarizing pulses from a holding potential of −50 mV to potentials ranging from −30 to +40 mV. (A) Ibutilide-sensitive currents obtained by digital subtraction of currents in upper right (control) from those in upper left (1 μM ibutilide). Current–voltage relationships for activating currents (panel B) and relative I_K tail values (panel C) of ibutilide-sensitive currents are contained in the lower panel. Data are expressed as means ± S.E. from five experiments. 5 μM Nifedipine was applied to block L-type Ca^{2+} current.

and by 10% in AV node cells by 10^{-7} M ibutilide, respectively.

4. Discussion

The clinical utility of ibutilide for the termination of atrial fibrillation and flutter has been established in several randomized, placebo-controlled studies (Ellenbogan et al., 1996). Since ibutilide causes a significant prolongation of the QTc interval and in clinical studies this prolongation has been shown to correlate directly with the plasma concentration, the antiarrhythmic effect of this drug is thought to be due to class III actions (Ellenbogan et al., 1996). Recent studies have confirmed that ibutilide blocks I_{Kr} in guinea-pig ventricular cells, and in an atrial tumor cell line (Lynch et al., 1995; Yang et al., 1995).

In the present study, we have identified significant differences in the inhibitory effect of ibutilide on the delayed rectifier K^+ currents in SA and AV node cells from rabbit hearts. These results provide the first description of the effects of ibutilide in mammalian cardiac pacemaker tissue. This interpretation, in terms of a selective block of I_{Kr} is compatible with previous studies which provided the evidence for expression of I_{Kr} and to a lesser extent I_{Ks} in rabbit SA node (Ito and Ono, 1995) and for I_{Kr} in rabbit AV node (Howarth et al., 1996).

The characteristics of I_K in AV node cells have been described in some detail by Howarth et al. (1996). They reported half-maximal activation for I_K at −4.1 mV, and a slope factor of the steady state activation curve of 12.4, and concluded that I_K in AV node cells was largely, if not completely, comprised of I_{Kr}. This findings is in good agreement with our original work and the results of this study. I_{Kr} in SA node cells was also investigated in the recent work by Ito and Ono (1995) and Verheijck et al.

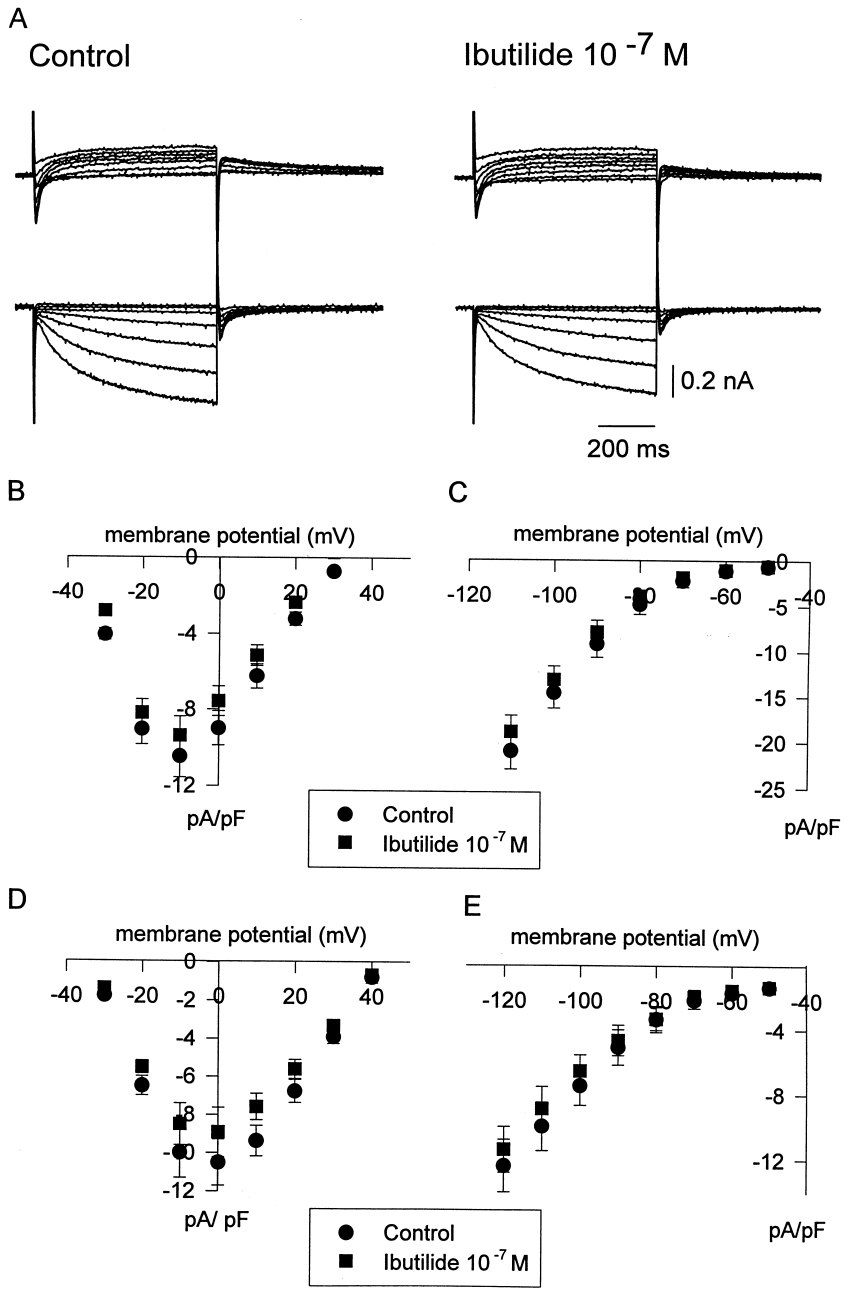

Fig. 5. Effect of ibutilide on Ca^{2+} and hyperpolarization-activated inward currents in SA node and AV node. (A) Representative recordings of whole cell currents from a rabbit SA node cell. Panel A (top) shows records in response to depolarizing pulses from −30 to +30 mV in 10 mV increments from a holding potential of −40 mV. Panel A (bottom) shows currents elicited by hyperpolarizing pulses from −50 to −110 mV in 10 mV increments. Current–voltage relationships for I_{Ca-L} and I_f in SA node are plotted in Panels B and C, those for AV node are plotted in panels D and E, respectively. Data are presented as means ± S.E. from six experiments for SA node cells, and six for AV node cells. The nystatin permebialized method was used for these experiments. Temperature was maintained at 34 ± 1°C.

(1995). Ito and Ono demonstrated that I_K tail current on repolarization was largely due to an E-4031-sensitive component of I_K, but that this component made only a small contribution to the outward whole cell current. They also suggested that the outward current remaining after I_{Kr} was blocked, consisted of a 4-AP-sensitive transient outward current in addition to the time-independent background currents. This study also provided evidence that I_{Ks} might contribute to the large outward current, since the I_K tail was suppressed strongly but not completely by 3 μM E-4031. We have found 3 μM E-4031 blocked I_K tail in SA node cells by 45%, whereas it abolished I_K tail in AV node cells nearly completely (Habuchi and Giles, unpublished data). Verheijck et al. (1995) also found that a

considerable amount of outward current remained after 10 μM E-4031 treatment. These investigators, however, speculated that the residual tail currents after the application of 10 μM E-4031 were due to recovery from inactivation of I_{Ca}, or a Ca^{2+}-dependent outward current. Their interpretation was based on the finding that the tail currents were diminished after the administration of 5 μM Nifedipine (Verheijck et al., 1995). At present, we have no convincing explanation for these different findings. In fact, in our experiments 5 μM Nifedipine was present when we studied I_K. This was done to block I_{Ca} and ensure the K^+ current were Ca^{2+}-independent. It is possible that high concentrations (10 μM) of E-4031 partially block I_{Ks}. Alternatively, differences in the isolation procedures might affect I_{Ks} channel in SA node cells, as reported for I_{Ks} in rabbit ventricular myocytes (Salata et al., 1996).

Block of I_{Kr} by ibutilide (10^{-7} M or 1 μM) caused a decrease in the spontaneous firing frequency, and eventually led to the cessation of automaticity in both SA and AV node cells. Since pacemaker depolarization is generated by the net effect of a number of different ionic currents (e.g., deactivation of I_{Kr} and I_{Ks}, and activation of I_{Ca}, I_f, and I_{st}), it is not possible to identify unambiguously the main determinant of the cycle length after the application of an I_{Kr} blocker. However, the observations that ibutilide produced a marked prolongation in the action potential duration and a significant decrease in the maximum diastolic potential indicate the contribution of I_{Kr} to the rate of repolarization, and the slow diastolic depolarization is quite large. Further experiments as to the deactivation properties of I_{Kr} and I_{Ks} will be required to elucidate the contribution of I_{Kr} to pacemaker activity and automaticity more closely.

It has been reported that ibutilide can also increase an inward Na^+ current in guinea-pig ventricular cells (Lee, 1992; Lee et al., 1993; Lee and Lee, 1998). Recent results have been interpreted in term of ibutilide promoting Na^+ influx through a nifedipine-sensitive inward channel, thus causing APD prolongation in human atrium (Lee and Lee, 1998). These investigators have concluded that the inhibition of I_{Kr} by ibutilide in these preparations play only a minor role in increasing the duration of the action potential (Lee, 1992; Lee and Gibson, 1995; Lee and Lee, 1998). One possibility for these different effects of ibutilide is that there are marked differences in current density in myocytes, depending on the cardiac tissue (atrium, ventricle, pacemaker) and/or species being studied. In our whole cell voltage clamp experiments, the possibility of ibutilide promoting of Na^+ influx through a nifedipine-sensitive channel was ruled out since 5 μM Nifedipine was present in most experiments (the exception was recordings of I_{Ca}).

In summary, our results demonstrate that ibutilide blocks I_{Kr} in rabbit pacemaker cells. This pattern of results is consistent with the delayed rectifier K^+ current in SA node cell is composed of both I_{Kr} and I_{Ks}, whereas that in AV node is mainly composed of I_{Kr}. These new findings may be helpful for understanding antiarrhythmic drug effect in pacemaker tissue.

Acknowledgements

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References

Anumonwo, J.M.B., Freeman, L.C., Kwok, V.M., Kass, R.S., 1992. Delayed rectification in single cells isolated from guinea-pig sinoatrial node. Am. J. Physiol. 262, H921–H925.

Denyer, J.C., Brown, H.F., 1990. Rabbit sino-atrial node cells: isolation and electrophysiological properties. J. Physiol. 428, 405–424.

Ellenbogan, K.A., Stambler, B.S., Wood, M.A., Wesley, R.C., Meissner, M.D., Zoble, R.G., Wakefield, L.K., Perry, X., Vanderlugt, T., 1996. Efficacy of intravenous ibutilide for acute termination of atrial fibrillation and atrial flutter: a dose response study. J. Am. Coll. Cardiol. 28, 130–136, for the ibutilide Investigators.

Han, X., Shimoni, Y., Giles, W.R., 1994. An obligatory role for nitric oxide in automatic control of mammalian heart rate. J. Physiol. 476, 309–314.

Howarth, F.C., Levi, A.J., Hancox, J.C., 1996. Characteristics of the delayed rectifier K current compared in myocytes isolated from the atrioventricular node and ventricle of the rabbit heart. Pfluegers Arch. 431, 713–722.

Ito, H., Ono, K., 1995. A rapidly activating delayed rectifier K^+ channel in rabbit sinoatrial node cells. Am. J. Physiol. 269, H443–H452.

Lee, K.S., 1992. Ibutilide, a new compound with potent class III antiarrhythmic activity, activates a slow inward Na^+ current in guinea pig ventricular cells. J. Pharmacol. Exp. Ther. 262, 96–108.

Lee, K.S., Tsai, T.D., Lee, E.W., 1993. Membrane activity of class III antiarrhythmic compounds: a comparison between ibutilide, D-sotalol, E-4031, sematilide and dofetilide. Eur. J. Pharmacol. 234, 43–53.

Lee, K.S., Gibson, J.K., 1995. Unique ionic mechanism of action of ibutilide on freshly isolated heart cells. Circulation 92, 2755–2757.

Lee, K.S., Lee, E.W., 1998. Ionic mechanism of ibutilide in human atrium: evidence for a drug-induced Na^+ current through a nifedipine inhibited inward channel. J. Pharmacol. Exp. Ther. 286, 9–22.

Lynch, J.J. Jr., Baskin, E.P., Nutt, E.M., Guinosso, P.J., Hamill, T., Salata, J.J., Woods, C.M., 1995. Comparison of binding to rapidly activating delayed rectifier K^+ channel, I_{Kr}, and effects on myocardial refractoriness for class III antiarrhythmic agents. J. Cardiovasc. Pharmacol. 25, 336–340.

Munk, A.A., Adjemian, R.A., Zhao, J., Ogbaghebriel, A., Shrier, A., 1996. Electrophysiological properties of morphologically distinct cells isolated from the rabbit atrioventricular node. J. Physiol. 493, 801–818.

Ono, K., Ito, H., 1995. Role of rapidly activating delayed rectifier K^+ current in sinoatrial node pacemaker activity. Am. J. Physiol. 269, H453–H462.

Salata, J.J., Jurkiewicz, N.K., Jow, B., Folander, K., Guinosso, P.J., Raynor, B., Swanson, R., Fermini, B., 1996. I_K of rabbit ventricle is composed of two currents: evidence for I_{Ks}. Am. J. Physiol. 271, H2477–H2489.

Sanguinetti, M.C., Jurkiewicz, N.K., 1990. Two components of cardiac delayed rectifier K^+ current, differential sensitivity to block by class III antiarrhythmic agents. J. Gen. Physiol. 96, 195–215.

Verheijck, E.E., van Ginneken, A.C.G., Bourier, J., Bouman, L.N., 1995. Effects of delayed rectifier current blockade by E-4031 on impulse generation in single sinoatrial nodal myocytes of the rabbit. Circ. Res. 76, 607–615.

Yang, T., Synders, D.J., Roden, D.M., 1995. Ibutilide, a methanesulfonanilide antiarrhythmic, is a potent blocker of the rapidly activating delayed rectifier K^+ current (I_{Kr}) in AT-1 cells, concentration, time-, voltage, and use-dependent effects. Circulation 91, 1799–1806.