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Original Research

Effects of RP58866 on transmembrane K^+ currents in mammalian ventricular myocytes

YANG Bao-Feng[1], LI Gui-Rong[2], XU Chang-Qing[3], Stanley NATTEL[2]
(*[3]Department of Pathophysiology, Harbin Medical University, Harbin 150086, China; [2]Montreal Heart Institute, Montreal, Quebec, H1T 1C8 Canada*)

KEY WORDS myocardium; cultured cells; patch-clamp techniques; ion channels; potassium channels; arrhythmia; anti-arrhythmia agents; RP58866; benzopyrans; inhibitory concentration 50

ABSTRACT

AIM: To determine effects of RP58866 on inward rectifier K^+ current (I_{K1}), transient outward K^+ current (I_{to}) and delayed outward rectifier K^+ current (I_K) in isolated cardiac myocytes. **METHODS**: In isolated ventricular myocytes of guinea pig and dog, the effect of RP58866 on I_{K1}, I_{to}, and I_K were observed by the whole cell voltage-clamp technique. **RESULTS**: RP58866 decreased I_{K1} in a concentration-dependent manner, with an IC_{50} of (3.4 ± 0.8) $\mu mol \cdot L^{-1}$ ($n = 6$) at − 100 mV in guinea pig ventricular cells. In dog ventricular myocytes, RP58866 inhibited I_{to} with IC_{50} of (2.3 ± 0.5) $\mu mol \cdot L^{-1}$ at + 40 mV. In guinea pig ventricular cells, RP58866 at 100 $\mu mol \cdot L^{-1}$ decreased I_K: I_{Kstep} by (58 ± 13) % at + 40 mV, and I_{Ktail} by (86 ± 17) %, respectively. RP58866 inhibited I_{Kstep} with an IC_{50} of (7.5 ± 0.8) $\mu mol \cdot L^{-1}$, and I_{Ktail} with an IC_{50} of (3.5 ± 0.9) $\mu mol \cdot L^{-1}$. The envelope of tail analysis suggested that both I_{Kr} and I_{Ks} were inhibited. **CONCLUSION**: RP58866 inhibits I_{K1}, I_{to}, and I_K in cardiac myocytes with a similar potency, and is not a specific I_{K1} inhibitor.

[1] Correspondence to Prof YANG Bao-Feng.
Phn 86-451-667-1354 Fax 86-451-666-9576.
E-mail Yangbf@ems.hrbmu.edu.cn
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INTRODUCTION

Anti-arrhythmic agents that selectively prolong APD and ERP have been shown to be effective in the prevention or suppression of atrial and ventricular arrhythmias [1,2]. The efficacy of these agents in most cases has been attributed to their ability to block the delayed rectifier potassium current I_K [3]. I_K in guinea pig cardiac myocytes is composed of two distinct components, I_{Kr} and I_{Ks}, which are distinguished by their different kinetics, pharmacology, voltage dependence, and rectification properties [4,5]. Several anti-arrhythmic agents that prolong APD, such as dofetilide, E-4031, and MK-499, selectively block I_{Kr} with little or no demonstrable effect on I_{Ks} [6,7]. Little is known about the effects of both drugs on I_{Kr} and I_{Ks} in guinea pig ventricular cells.

Cardiac inwardly rectifying K^+ channel current (I_{K1}) and the transient outward current (I_{to}) play critical roles in the rapid repolarization process of cardiac action potentials [8]. I_K, I_{K1}, and I_{to} are major components in the process of repolarization and may therefore be important targets for anti-arrhythmic drug action.

1-[2-3(3,4-Dihydrol-2H-1-benzopyran-4-yl)ethyl]-4-(3, 4-dimethoxyphenyl)-piperidine (RP58866) is a novel benzopyran derivative which has been proved to be a class Ⅲ anti-arrhythmic agent [9,10], specifically, the inward rectifying potassium current blocker. It markedly prolongs APD in mammalian cardiac atrial and ventricular tissues dose-dependently but affects neither the upstroke of the action potential nor the diastolic potential. It has been demonstrated that the prolongation of APD induced by this compound is

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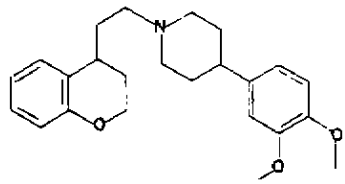
mainly due to the specific block of inwardly rectifying K^+ current (I_{K1})[9].

However, Escande *et al* reported that RP58866 blocked I_{to} in rat atrial cells. Whether this compound blocks other K^+ channels is unclear. The present study was designed to determine whether RP58866 was a specific I_{K1} blocker, and therefore effect of this compound on transmembrane K^+ currents, I_{to}, I_K (I_{Kr} and I_{Ks}) and I_{K1}, will be evaluated with a whole-cell voltage-clamp configuration in guinea pig and/or dog cardiac ventricular cells.



RP58866

MATERIALS AND METHODS

Preparation of guinea pig ventricular myocytes Single ventricular cells were isolated from guinea pig hearts with a modified method described previously[11]. Briefly, guinea pigs were killed by cervical dislocation, their hearts were quickly removed and cannulated on a Langendorff apparatus and perfused with Tyrode solution (36 ℃) for 5 – 10 min. After the heart was perfused with nominally Ca^{2+}-free Tyrode solution for 8-10 min, it was enzymatically digested for 15 – 20 min with a solution containing collagenase (100 – 150 kU · L^{-1}, CLS Worthington Biochemical. Fredhold NJ). Left ventricular tissue was then excised from the softened hearts, placed in a storage medium, minced, and gently swirled. The myocytes were incubated in the storage medium at room temperature.

Isolation of dog ventricular myocytes Adult mongrel dogs of either sex (21.4 ± 2.5) kg were anesthetized with sodium pentobarbital (30 mg · kg^{-1}, iv), and their hearts were quickly removed and placed in oxygenated Tyrode's solution at room temperature. The left anterior coronary artery was cannulated, and the left ventricular free wall (2 cm × 4 cm) was then separated. Ventricular myocytes were dissociated with the procedure as human ventricular cell isolation described previously[12]. Briefly, the free wall was perfused with oxygenated nominally Ca^{2+}-free Tyrode solution for 20 – 25 min, and the solution was then changed to one containing 200 – 300 kU · L^{-1} collagenase (CLS Ⅱ Worthington Biochemical) for 60 – 100 min. The digested tissue was cut into small (1 – 1.5 mm^3) pieces, placed in a storage medium, and gently triturated with a Pasteur pipette. Isolated myocytes were kept in the medium at room temperature.

A small aliquot of the solution containing the isolated cells was placed in an open perfusion chamber (1 mL) mounted on the stage of an inverted microscope. Myocytes were allowed to adhere to the bottom of the dish for 5 – 10 min and were then superfused at 2 – 3 mL · min^{-1} with Tyrode solution. All the experiments were conducted at (36 ± 0.5) ℃. Only quiescent rod-shaped cells showing clear cross striations were studied.

Solutions Tyrode solution contained (in mmol · L^{-1}): NaCl 126, KCl 5.4, $MgCl_2$ 1.0, $CaCl_2$ 1.0, NaH_2PO_4 0.33, glucose 10, and HEPES 10, pH adjusted to 7.4 with NaOH. Storage medium contained (in mmol · L^{-1}): KCl 20, KH_2PO_4 10, glucose 10, potassium glutamate 70, β-hydroxbutyric acid 10, taurine 10, egtazic acid 0.5, and 1.0 % albumin, pH adjusted to 7.3 with KOH. The pipette solution contained (in mmol · L^{-1}): KCl 20, potassium aspartate 110, $MgCl_2$ 1.0, HEPES 10, egtazic acid 5, GTP 0.1, and Mg-ATP 5.0, pH adjusted to 7.4 with KOH. Stock solutions of RP58866, (the gift from Rhne-Poulenc Rorer, France) was freshly prepared as 10 mmol · L^{-1} with distilled water. $BaCl_2$ (Sigma) and $CdCl_2$ (Sigma) stock solutions were prepared as 0.2 mol · L^{-1}, which were used to block I_{K1} and/or I_{Ca}.

Electrophysiological recording The whole-cell patch-clamp technique was employed to record ionic currents. The resistance of the borosilicate glass electrodes used was 2 to 4 megohms when filled with pipette solution, and this electrode was connected to a patch-clamp amplifier (Axopatch 1-D, Axon Instruments, Foster City, CA). A 12-bit digital-to-analog converter controlled by pCLAMP software (Axon Instruments) generated command pulses. Recordings were lowpassedly filtered at 1 kHz and data were acquired by analog-to-digital conversion at a maximum

rate of 100 kHz (Model TM 125, Scientific Solutions, Solon, OH) and stored on the hard disk of an IBM-compatible computer. Pipette tip potentials (2 - 10 mV) were corrected before the pipette touched the cell. After a tight pipette-membrane seal had been obtained (seal resistance > 10 GΩ), the membrane was ruptured with gentle suction to obtain the whole cell voltage-clamp configuration. Liquid junction potentials between pipette solution and perfusion solution (10 - 11 mV) were not corrected after membrane rupture. In all of the cells studied, the series resistance was electrically compensated to minimize the duration of the capacitive transient.

Curve fitting was performed with a Marcquardt algorithm and TableCurve software (Jandel Scientific). Results are presented as the mean ± s. Statistical comparisons between two group means were made by t test, and a two-tailed value of $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Effect of RP58866 on I_{K1} Fig 1 displays effects of RP58866 on I_{K1} in guinea pig ventricular cells. Test pulses were applied for 300 ms (0.2 Hz) from a holding potential of -60 mV to potential ranging from -120 mV to +0 mV in 10 mV steps. Recordings were obtained 10 min after obtaining intracellular access. Nifedipine 5 μmol·L^{-1} and 4-aminopyridine 2 mmol·L^{-1} were present in the external solution. The steady-state current of I_{K1} was measured at the end of voltage step. I_{Ca} was blocked by 0.2 mmol·L^{-1} Cd^{2+} in superfusion. Panel E illustrates I - V relation of I_{K1} obtained with protocol as shown in panel A (in inset) in the absence and presence of RP58866 (5 and 50 μmol·L^{-1}), and washout of the compound. RP58866 decreased I_{K1} at all test potentials, and the effect reversible upon washout. At -100 mV, inward component of I_{K1} was decreased respectively by 5 and 50 μmol·L^{-1} RP58866 from (-5.27 ± 0.66) nA to (-3.1 ± 0.3) nA (decrease by 49.7 %, $P < 0.01$, $n = 6$) and (-1.95 ± 0.76) nA (decrease by 62.3 %, $P < 0.01$, $n = 6$), whereas at -30 mV, outward component of I_{K1} was decreased from (0.69 ± 0.09) nA to (0.41 ± 0.07) nA (by 40 %, $P < 0.01$) and (0.39 ± 0.05) nA (decrease by 44.0 %, $P < 0.01$). Inhibition of the drug on I_{K1} could be recovered by 70 % after a 30-min washout. The concentration-dependent inhibition for I_{K1} was analysed at -100 mV (panel F) with an IC_{50} of 3.4 ± 0.8 μmol·L^{-1} ($n = 6$). The strongest effect of RP58866 on I_{K1} was 100 μmol·L^{-1}, which reduced I_{K1} to (-1741 ± 779) pA from (-5273 ± 661) pA (67 %).

Effect of RP58866 on I_{to1} I_{to1} was determined in dog ventricular myocytes in the Na^+-free (replaced by equimolar choline) superfusate. Cd^{2+} at 0.2 mmol·L^{-1}, Ba^{2+} at 0.2 mmol·L^{-1} and ryanodine at 2 μmol·L^{-1} were used to block I_{Ca}, I_{K1}, and I_{ClCl}, respectively. I_{to1} was measured from the current peak to the steady-state current at the end of pulses. Fig 2 displays effects of RP58866 on I_{to1}. I_{to1} was elicited by a 300-ms depolarizing pulse from -80 mV to 60 mV at 0.1 Hz. Panel A-D shows recordings in the same cell. I_{to1} was markedly inhibited by RP58866 in the test potentials of -10 to +60 mV and partially recovered after a 30-min washout. At +40 mV, RP58866 at 1 and 10 μmol·L^{-1} inhibited I_{to1} from (926.9 ± 197) pA to (692.2 ± 79.4) pA and (236.3 ± 84.9) pA ($P < 0.01$, $n = 7$), and then recovered to (764.3 ± 103.3) pA (by 82 %, pannel D) after 30 min washout. Concentration-dependent effect of RP58866 on I_{to} (panel F) was determined at +40 mV with an IC_{50} of (2.3 ± 0.5) μmol·L^{-1}. The significant effects of RP58866 on I_{to1} was 100 μmol·L^{-1}, which decresed I_{to1} from (926.9 ± 197) pA to (119.3 ± 17.7) pA. I - V relations of I_{to1} in the absence and presence of RP58866 I_{to1} are illustrated in panel E.

Effects of RP58866 on I_K I_K was determined in guinea pig ventricular myocytes. I_{Ca} was blocked by 0.2 mmol·L^{-1} Cd^{2+}, and I_{K1} was blocked by 0.1 mmol·L^{-1} Ba^{2+}. After cell membrane rupture, a 20 - 30-min period will be needed to observe stable I_K for pharmacological study. The cells showing any I_K run-down were rejected in our experiments. Fig 3 shows effects of RP58866 on I_K. I_K was elicited by 3,000 ms depolarizing pulse at 0.1 Hz to potentials ranging from -40 to +60 mV, from a holding potential of -60 mV. Ca^{2+} currents and I_{K1} were abolished by cadmium (0.2 mmol·L^{-1}) and barium (0.2 mmol·L^{-1}) to the bath solution. I_{Kstep} and I_{Ktail} was markedly decreased after treatment with RP58866,

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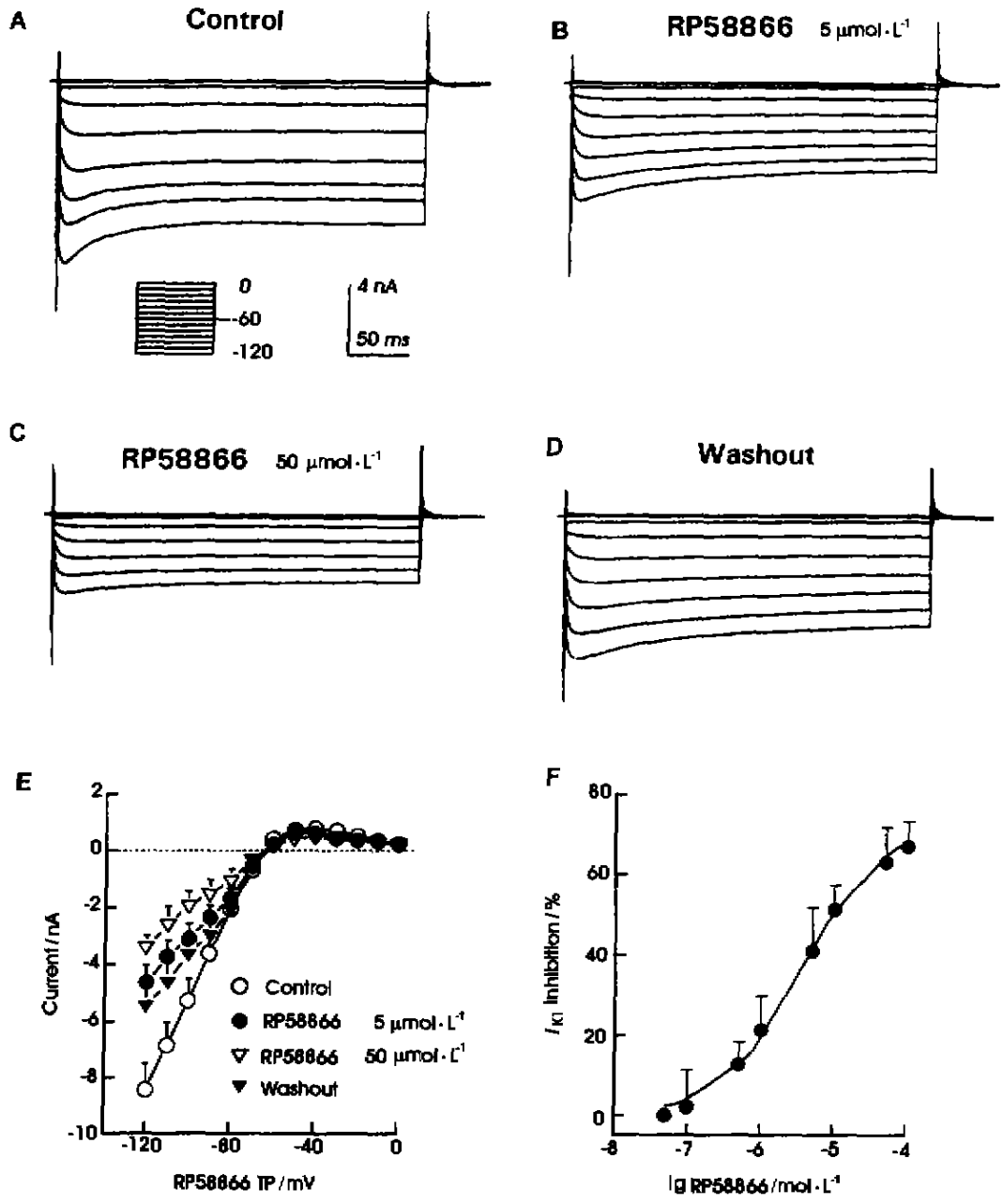

Fig 1. Whole-cell I_{K1} in guinea pig ventricular myocytes. A) Represent I_{K1} current traces in normal Tyrode solution. B) RP58866 5 μmol·L^{-1}. C) RP58866 50 μmol·L^{-1}. D) After washout of agent for 30 min. E) Plot of average steady state I – V relation (n=6). F) Percent change of I_{K1} after exposure to RP58866 0.1, 0.5, 1, 5, 10, 50, 100 μmol·L^{-1}.

especially stronger effect was seen on I_{Ktail}. Panel E shows I – V relations of I_{Kstep} determined with protocol shown in panel A (inset). I_{Kstep} was definded as a time-dependent component to exclude the contamination of nonspecific currents, which was measured from initial activation to the current at the end of steps. RP58866 at 5 and 50 μmol·L^{-1} markedly decreased I_{Kstep} at all test potentials, and the effect was reversible upon a 30-min washout. At + 40 mV, I_{Kstep} was decreased respectively from (284.8 ± 42.4) pA to

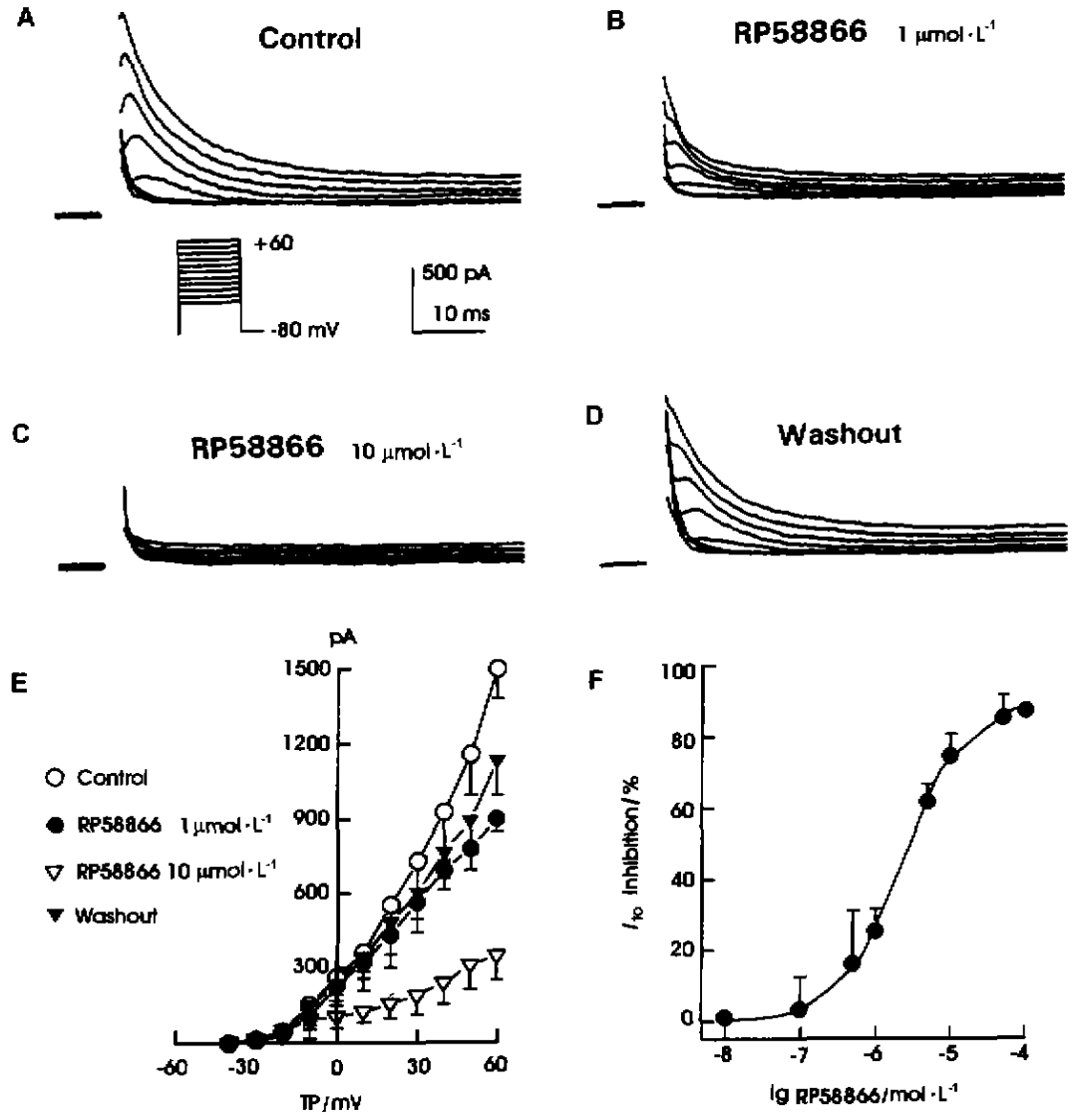

Fig 2. Effects of RP58866 on I_{to1} in dog ventricular cells. A) normal control (before exposure to RP58866). B) RP58866 1 μmol·L^{-1} for 8 min. C) RP58866 10 μmol·L^{-1} for 8 min. D) After 30 min washout. E) Examples of concentration-dependent effects of RP58866 on I_{to1}. F) Percent change of I_{to1} after exposure to RP58866 0.01, 0.1, 0.5, 1, 5, 10, 50, and 100 μmol·L^{-1}.

(215.8 ± 50.6) pA and (148.6 ± 75.8) pA ($n = 6$, $P < 0.01$). After a 30-min washout, the current was recovered to (237.9 ± 43.8) pA (recovered by 61 % with washout). Concentration-dependent inhibition of RP58866 on I_{Kstep} and I_{Ktail} was determined at + 40 mV, and the results are displayed in panel F. RP58866 100 μmol·L^{-1} inhibited I_{Ktail} by (86 ± 17) %, while I_{Kstep} by (58 ± 13) %. Clearly, maxmium effect of RP58866 on I_{Ktail} was markedly stronger than that of I_{Kstep} ($P < 0.01$). IC_{50} was (7.5 ± 0.7) μmol·L^{-1} for I_{Kstep}, (3.5 ± 0.9) μmol·L^{-1} for I_{Ktail} ($P < 0.01$).

The results indicate that RP58866 inhibits I_{Kstep} and I_{Ktail} in a dose-dependent manner. Fig 4 displays the envelope of tail tests for RP58866. Test pulses were applied from a holding potential of − 60 to 50 mV for durations ranging from 60 to 3540 ms. I_{tail}/I_k was calculated in the absence and in the presence of 5 μmol·L^{-1} RP58866. In cells perfused with cadmium 200 μmol·L^{-1}, barium 100 μmol·L^{-1} and dofitilide-free solution. I_{tail}/I_k was dependent on the duration of the pulse. Thus, activation of I_k during short depolarizing

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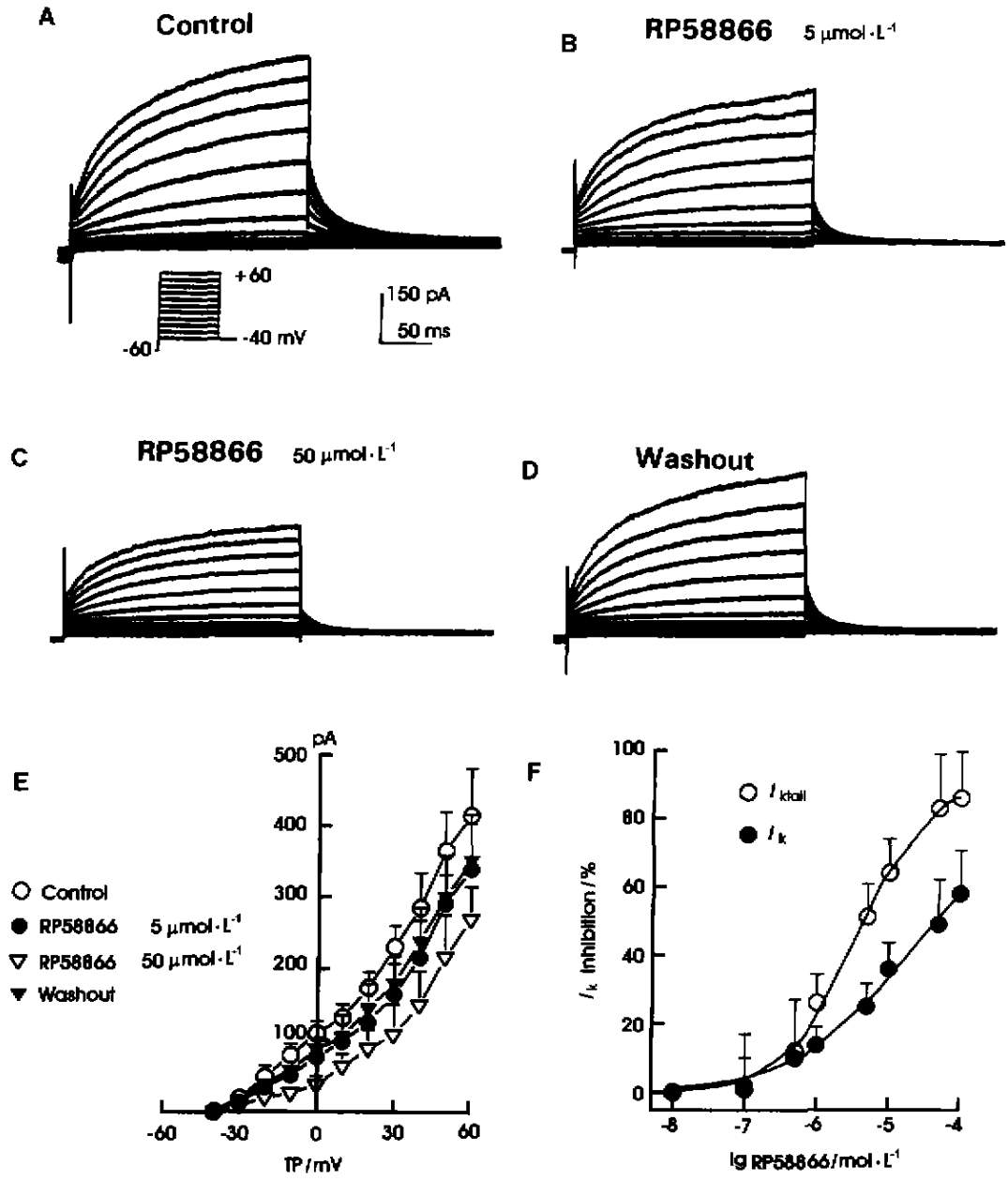

Fig 3. Effects of RP58866 on I_K in guinea pig ventricular cells. A) Current under control condition. B) Currents recorded after a perfusion of RP58866 5 μmol·L^{-1}. C) Currents recorded after a perfusion of RP58866 50 μmol·L^{-1}. D) After washout. E) Examples of concentration-dependent effects of RP58866 on I_K. F) Percent change of I_K after exposure to RP58866 0.1, 0.5, 1, 5, 10, 50, and 100 μmol·L^{-1}.

pulses (<0.5 s) is characterized by tail currents that are equal to or larger than the time-dependent outward currents during the depolarizing pulse. However, as the duration of the test pulse was lengthened, the magnitude of I_{tail} became less than that of I_k. This demonstrates the existence of two different components of I_k in guinea pig ventricular myocytes as the result of the activation of two different types of K^+ channels: a rapidly activating K^+ channel, I_{Kr}, and a slowly activating one, I_{Ks}. If RP58866 completely blocked the fast activating component of I_k, the envelop-of-tail tests should be satisfied after exposure to RP58866, ie,

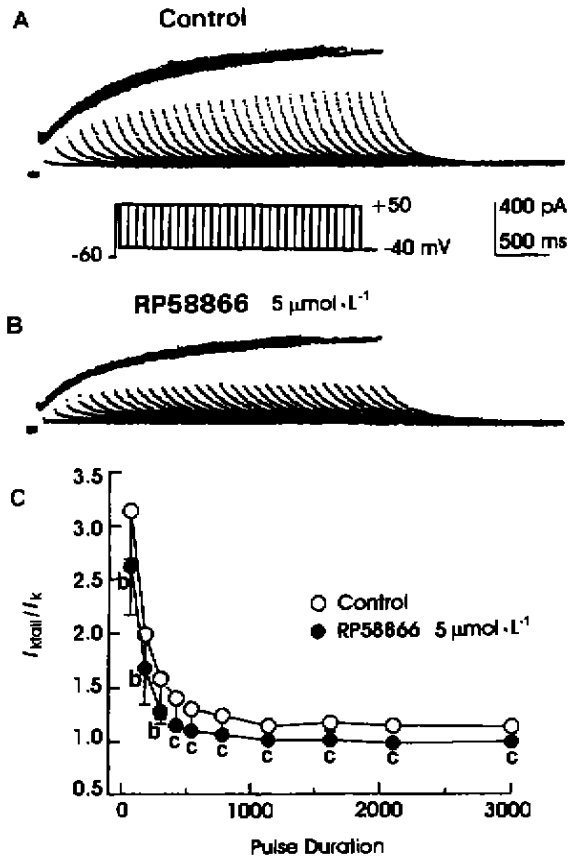

Fig 4. Envelope of tails test for the delayed rectifier (I_K) in the absence A) and presence B) of RP58866 5 μmol·L^{-1}. Protocol in C (in inset) was used to elicit current with depolarizing pulse durations ranging from 60 to 3540 ms, Step and tail currents were defined as time-dependent currents during depolarization and upon repolarization, respectively. Ratio of tail current to step current (I_{Ktail}/I_{Kstep}; $\bar{x} \pm s$, $n = 6$, $^bP < 0.05$, $^cP < 0.01$ *vs* control) is plotted as a function of pulse duration in C.

I_{tail}/I_k would be constant regardless of the duration of the pulse. Time-dependent current during the test pulse was measured at the end of the depolarizing pulse.

Fig 4 shows typical recordings elicited after depolarizing pulses to 50 mV of different durations (between 0.1 and 5 second) from holding potential −60 mV in the presence of cadmium 200 μmol·L^{-1}, barium 200 μmol·L^{-1} under the control condition. The envelop of tails test showed that I_k consisted of more than one component, whereas after exposure to RP58866 5 μmol·L^{-1} (Fig 4B), which blocked I_{Kr}, and I_{Ks}. The value of I_{tail}/I_k was not constant in the different test pulse duration (Fig 4C). The results indicated that RP58866 inhibited either I_{Kr} or I_{Ks} in guinea pig ventricular myocytes non-selectively.

DISCUSSION

Comparison with previous studies of these compounds Other research indicated that RP58866 was a specifical blockade of I_{K1} in guinea pig myocytes [10]. At concentration upto 50 μmol·L^{-1}, RP58866 did not markedly affect the delayed rectifier K^+ current elicited by 10 s depolarizing pulses to +40 mV[10]. This is different form our results, which proved that RP58866 inhibited markedly I_{step} and I_{Ktail}. Escande found that RP58866 (< 30 μmol·L^{-1}) did not block markedly I_{to1} in rat. We proved that this drug inhibited markedly I_{to1} in dog ventricular myocytes. This difference may be related with different animals.

Potential significance of our findings Several new class Ⅲ anti-arrhythmic drugs block markedly the rapid component of I_K with relatively high selectivity[3]. The more potent effects of these agents on I_{Kr} will produce strong reverse use-dependent actions on repolarization[2,7]. The more potent effects of agents on I_{Kr} are thought to be important risks of proarrhythmic reactions, due to excessive delays of repolarization at slow heart rates. Class Ⅲ anti-arrhythmic agents without selectivity for I_{Kr} may be a more beneficial profile of rate-dependent actions[13]. Our experiments proved that RP58866 was less selective for I_{Kr}. I_{to1} has been shown to play important roles in repolarization. Therefore, blockade of I_{to1} may be an advantageous property for class Ⅲ agents.

Mechanisms of channel blocking action. The whole cell voltage clamp measurements demonstrated the direct blocking actions were quick in onset and strong in amplitude with total block amounting to 67 % at −100 mV ($P < 0.01$) and to 57 % at −30 mV ($P < 0.01$). I_{K1} blocks by this drug was different during depolarization velocity −100 mV to −30 mV, suggesting that this block is a voltage-dependent phenomenon. The present study shows that RP58866 exerts an inhibitory effect on I_{to1} in a dose-dependent and reversible manner. This agent

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has been shown to prolong APD in mammalian tissues[10]. I_{to} plays a major role in action potential repolarization. Although a calcium-dependent component of this outward current has been described in some preparations[13], only a calcium-independent component was reported in rat ventricular myocytes[14,15]. In our experiments, I_{to2} has been blocked by Cd^{2+} due to the I_{to2} is a calcium-dependent chloride current[12].

The results of the present study showed that in isolated guinea pig ventricular myocytes RP58866 blocked the aggregate time-dependent I_K. Drug actions in the absence and in the presence of dofetilide indicated that the agent inhibited unselectively at least two components of this time-dependent I_K. The result was more closely associated with the actions of amiodarone[12] rather than *d*-sotalol or many of the newer selective Class Ⅲ agents[16]. Evidence for nonselective block is demonstrable in several ways: the drug blocks of the tail current was very constant for longer depolarization between 3 and 5 s and becomes less with a short depolarization.

The inhibitory effects of RP58866 on I_{to1}, I_{K1}, and I_K are its major mechanisms of anti-arrhythmic actions.

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RP58866 对哺乳动物心室肌细胞跨膜钾电流的作用

R972.3

杨宝峰[1], 李贵荣[2], 徐长庆[3], Stanley NATTEL[2] (哈尔滨医科大学药理教研室, [3]病生教研室, 哈尔滨市 150086, 中国; [2]加拿大蒙特利尔心脏研究所, 蒙特利尔, H1T1C8, 加拿大)

关键词 心肌; 培养的细胞; 膜片箝技术; 离子通

RP58866 抗心律失常药 药理

道；钾通道；心律失常；抗心律失常药；RP58866；苯吡喃类；半数抑制浓度

目的：研究 RP58866 对于豚鼠或犬分离心室肌细胞 I_K，I_{to}，和 I_{KI}的影响．**方法**：采用全细胞膜片箝技术．**结果**：在 −100 mV 时，RP58866 以浓度依赖方式明显减少了豚鼠心室肌细胞 I_{KI}，其 IC_{50} 为(3.4±0.8) μmol·L^{-1}(n=6)．在犬心室肌细胞，RP58866 可明显抑制 I_{to}，其 IC_{50}为 (2.3±0.5) μmol·L^{-1}．RP58866 100 μmol·L^{-1}阻断豚鼠的心室肌细胞 I_K，在 +40 mv 时使 I_{Kstep} 减少 (58±13) %，其 IC_{50}为 (7.5±0.8) μmol·L^{-1}，I_{Ktail}减少(86±17) %，其 IC_{50}为(3.5±0.9) μmol·L^{-1}．尾电流分析表明，RP58866 对 I_{Kr}和 I_{Ks}均有阻断作用．**结论**：RP58866 对心肌细胞的 I_{KI}和 I_{to}，I_K 均有抑制作用，而不是一种特殊的 I_{KI}抑制剂．

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