

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

YANG Bao-Feng¹, LI Gui-Rong², XU Chang-Qing³, Stanley NATTEL²

(Department of Pharmacology, ³Department of Pathophysiology, Harbin Medical University, Harbin 150086, China; ²Montreal Heart Institute, Montreal, Quebec, HIT 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 $(3.4 \pm 0.8) \mu\text{mol} \cdot \text{L}^{-1}$ ($n = 6$) at -100 mV in guinea pig ventricular cells. In dog ventricular myocytes, RP58866 inhibited I_{to} with IC_{50} of $(2.3 \pm 0.5) \mu\text{mol} \cdot \text{L}^{-1}$ at $+40$ mV. In guinea pig ventricular cells, RP58866 at $100 \mu\text{mol} \cdot \text{L}^{-1}$ decreased I_K : $I_{K\text{step}}$ by $(58 \pm 13) \%$ at $+40$ mV, and $I_{K\text{tail}}$ by $(86 \pm 17) \%$, respectively. RP58866 inhibited $I_{K\text{step}}$ with an IC_{50} of $(7.5 \pm 0.8) \mu\text{mol} \cdot \text{L}^{-1}$, and $I_{K\text{tail}}$ with an IC_{50} of $(3.5 \pm 0.9) \mu\text{mol} \cdot \text{L}^{-1}$. 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.

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-Dihydro-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

¹ Correspondence to Prof YANG Bao-Feng.

Phn 86-451-667-1354 Fax 86-451-666-9576.

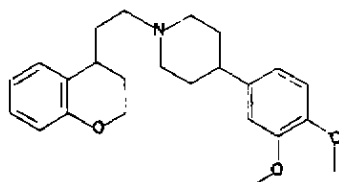
E-mail Yangbf@ems.hrbmu.edu.cn

Received 1998-12-15

Accepted 1999-06-24

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 °C) 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 $kU \cdot L^{-1}$, 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 $mg \cdot kg^{-1}$, 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 \times 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 $kU \cdot L^{-1}$ collagenase (CLS || 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 $mL \cdot min^{-1}$ with Tyrode solution. All the experiments were conducted at $(36 \pm 0.5) ^\circ C$. Only quiescent rod-shaped cells showing clear cross striations were studied.

Solutions Tyrode solution contained (in $mmol \cdot L^{-1}$): 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 $mmol \cdot L^{-1}$): KCl 20, KH_2PO_4 10, glucose 10, potassium glutamate 70, β -hydroxybutyric acid 10, taurine 10, egtazic acid 0.5, and 1.0 % albumin, pH adjusted to 7.3 with KOH. The pipette solution contained (in $mmol \cdot L^{-1}$): 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 $mmol \cdot L^{-1}$ with distilled water. $BaCl_2$ (Sigma) and $CdCl_2$ (Sigma) stock solutions were prepared as 0.2 $mol \cdot L^{-1}$, 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 Marquardt 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 $5 \mu\text{mol}\cdot\text{L}^{-1}$ and 4-aminopyridine $2 \text{mmol}\cdot\text{L}^{-1}$ 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 $0.2 \text{mmol}\cdot\text{L}^{-1} \text{Cd}^{2+}$ 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 $50 \mu\text{mol}\cdot\text{L}^{-1}$), 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 $50 \mu\text{mol}\cdot\text{L}^{-1}$ RP58866 from $(-5.27 \pm 0.66) \text{nA}$ to $(-3.1 \pm 0.3) \text{nA}$ (decrease by 49.7%, *P* < 0.01, *n* = 6) and $(-1.95 \pm 0.76) \text{nA}$ (decrease by 62.3%, *P* < 0.01, *n* = 6), whereas at -30 mV, outward component of I_{K1} was decreased from $(0.69 \pm 0.09) \text{nA}$ to $(0.41 \pm 0.07) \text{nA}$ (by 40%, *P* < 0.01) and $(0.39 \pm 0.05) \text{nA}$ (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 $3.4 \pm 0.8 \mu\text{mol}\cdot\text{L}^{-1}$ (*n* = 6). The strongest effect of RP58866 on I_{K1} was $100 \mu\text{mol}\cdot\text{L}^{-1}$, which reduced I_{K1} to $(-1741 \pm 779) \text{pA}$ from $(-5273 \pm 661) \text{pA}$ (67%).

Effect of RP58866 on I_{tot} I_{tot} was determined in dog ventricular myocytes in the Na^+ -free (replaced by equimolar choline) superfusate. Cd^{2+} at $0.2 \text{mmol}\cdot\text{L}^{-1}$, Ba^{2+} at $0.2 \text{mmol}\cdot\text{L}^{-1}$ and ryanodine at $2 \mu\text{mol}\cdot\text{L}^{-1}$ were used to block I_{Ca} , I_{K1} , and I_{CaCl} , respectively. I_{tot} was measured from the current peak to the steady-state current at the end of pulses. Fig 2 displays effects of RP58866 on I_{tot} . I_{tot} 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_{tot} 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 $10 \mu\text{mol}\cdot\text{L}^{-1}$ inhibited I_{tot} from $(926.9 \pm 197) \text{pA}$ to $(692.2 \pm 79.4) \text{pA}$ and $(236.3 \pm 84.9) \text{pA}$ (*P* < 0.01, *n* = 7), and then recovered to $(764.3 \pm 103.3) \text{pA}$ (by 82%, panel D) after 30 min washout. Concentration-dependent effect of RP58866 on I_{tot} (panel F) was determined at +40 mV with an IC_{50} of $(2.3 \pm 0.5) \mu\text{mol}\cdot\text{L}^{-1}$. The significant effects of RP58866 on I_{tot} was $100 \mu\text{mol}\cdot\text{L}^{-1}$, which decreased I_{tot} from $(926.9 \pm 197) \text{pA}$ to $(119.3 \pm 17.7) \text{pA}$. $I-V$ relations of I_{tot} in the absence and presence of RP58866 I_{tot} 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 $0.2 \text{mmol}\cdot\text{L}^{-1} \text{Cd}^{2+}$, and I_{K1} was blocked by $0.1 \text{mmol}\cdot\text{L}^{-1} \text{Ba}^{2+}$. 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 ($0.2 \text{mmol}\cdot\text{L}^{-1}$) and barium ($0.2 \text{mmol}\cdot\text{L}^{-1}$) to the bath solution. $I_{K\text{step}}$ and $I_{K\text{tail}}$ was markedly decreased after treatment with RP58866,

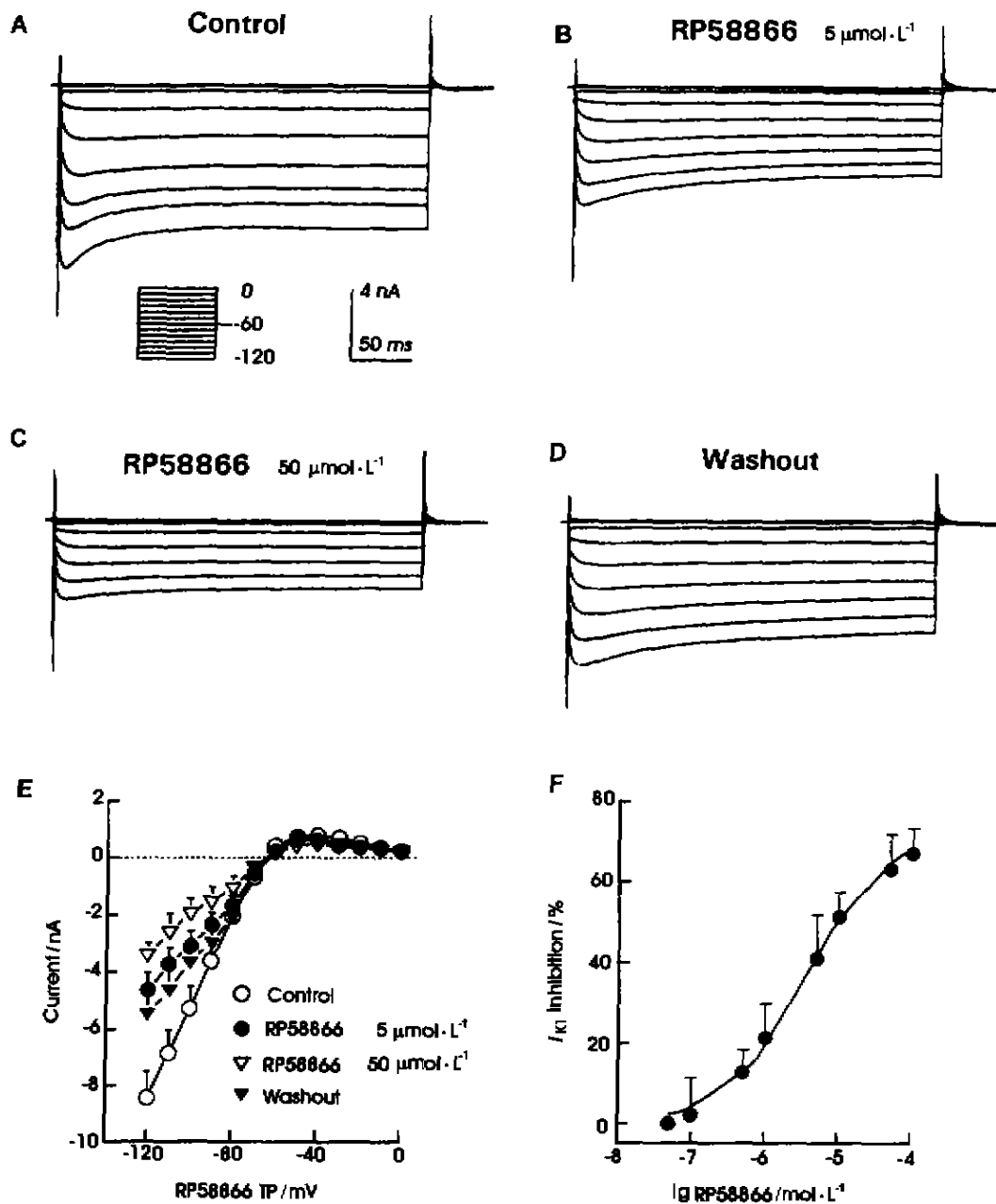


Fig 1. Whole-cell I_{K1} in guinea pig ventricular myocytes. A) Represent I_{K1} current traces in normal Tyrode solution. B) RP58866 $5 \mu\text{mol}\cdot\text{L}^{-1}$. C) RP58866 $50 \mu\text{mol}\cdot\text{L}^{-1}$. D) After washout of agent for 30 min. E) Plot of average steady state $I - V$ relation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

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 defined 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 $50 \mu\text{mol}\cdot\text{L}^{-1}$ 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

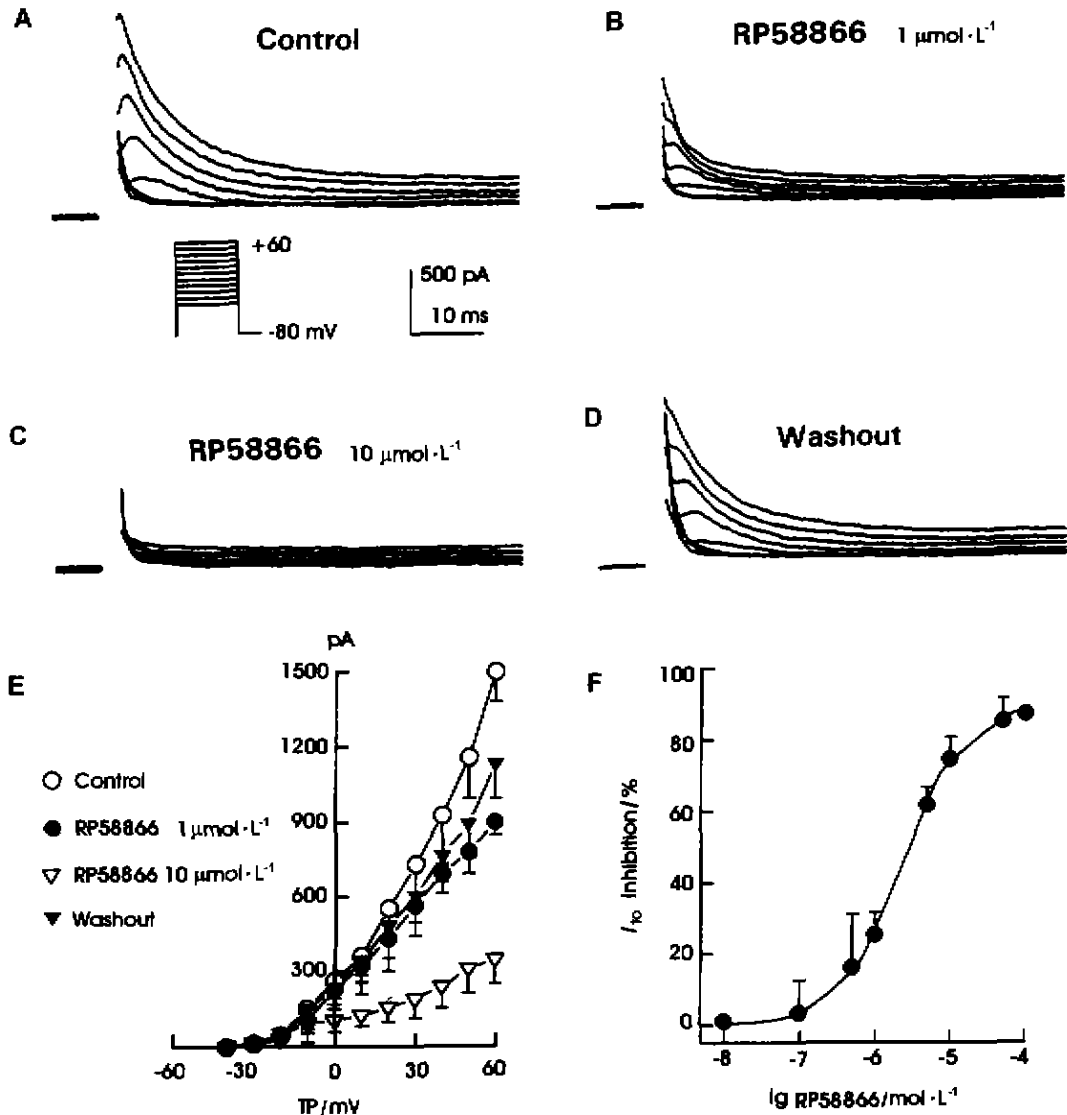


Fig 2. Effects of RP58866 on I_{tot} in dog ventricular cells. A) normal control (before exposure to RP58866). B) RP58866 $1 \mu\text{mol}\cdot\text{L}^{-1}$ for 8 min. C) RP58866 $10 \mu\text{mol}\cdot\text{L}^{-1}$ for 8 min. D) After 30 min washout. E) Examples of concentration-dependent effects of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

(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 $100 \mu\text{mol}\cdot\text{L}^{-1}$ inhibited I_{Ktail} by (86 ± 17) %, while I_{Kstep} by (58 ± 13) %. Clearly, maximum effect of RP58866 on I_{Ktail} was markedly stronger than that of I_{Kstep} ($P < 0.01$). IC_{50} was (7.5 ± 0.7) $\mu\text{mol}\cdot\text{L}^{-1}$ for I_{Kstep} , (3.5 ± 0.9) $\mu\text{mol}\cdot\text{L}^{-1}$ 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 $5 \mu\text{mol}\cdot\text{L}^{-1}$ RP58866. In cells perfused with cadmium $200 \mu\text{mol}\cdot\text{L}^{-1}$, barium $100 \mu\text{mol}\cdot\text{L}^{-1}$ and dofetilide-free solution. I_{tail}/I_k was dependent on the duration of the pulse. Thus, activation of I_k during short depolarizing

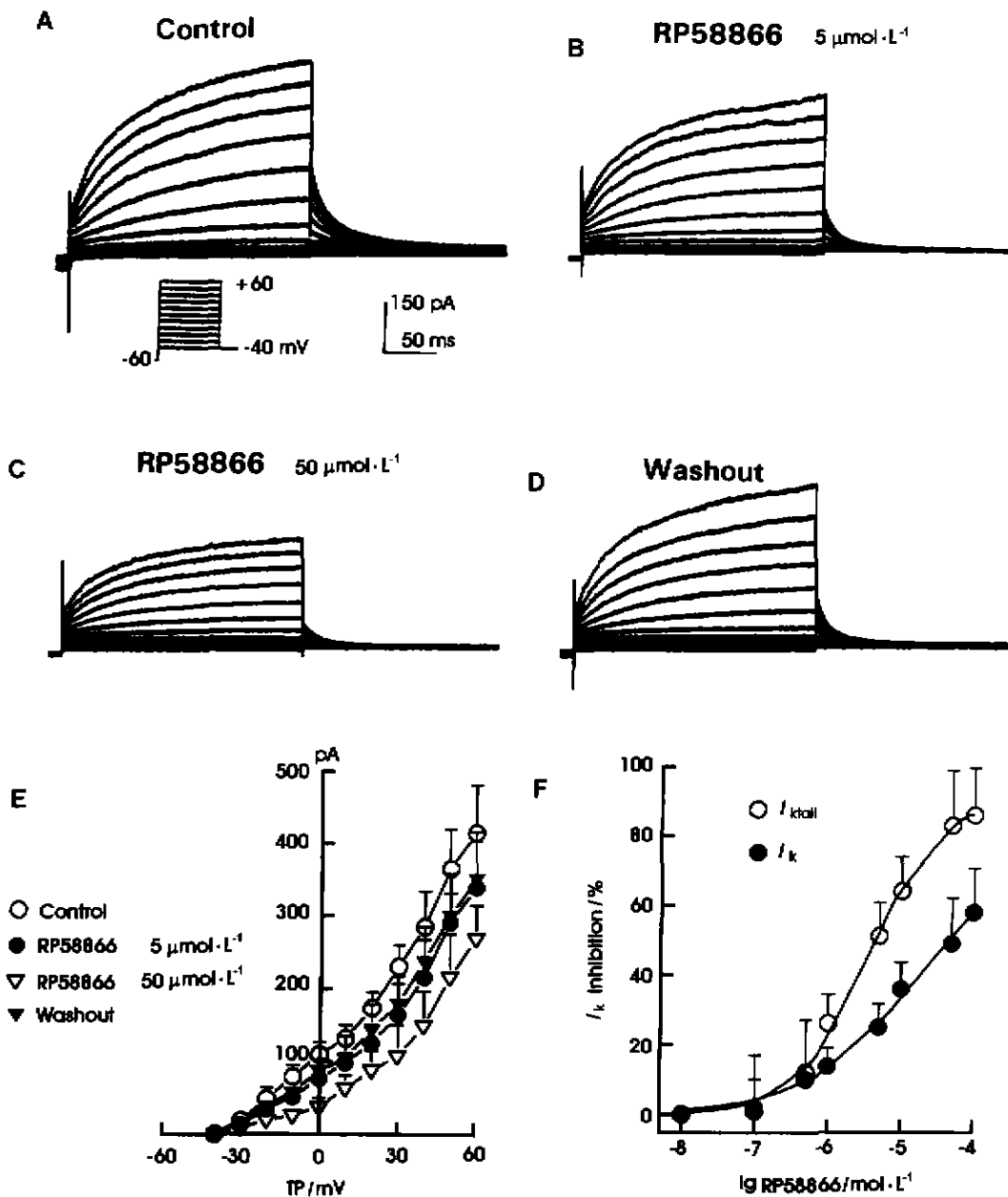


Fig 3. Effects of RP58866 on I_K in guinea pig ventricular cells. A) Current under control condition. B) Currents recorded after a perfusion of RP58866 $5 \mu\text{mol}\cdot\text{L}^{-1}$. C) Currents recorded after a perfusion of RP58866 $50 \mu\text{mol}\cdot\text{L}^{-1}$. D) After washout. E) Examples 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 $100 \mu\text{mol}\cdot\text{L}^{-1}$.

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_{K_r} , and a slowly activating one, I_{K_s} . If RP58866 completely blocked the fast activating component of I_K , the envelop-of-tail tests should be satisfied after exposure to RP58866, ie,

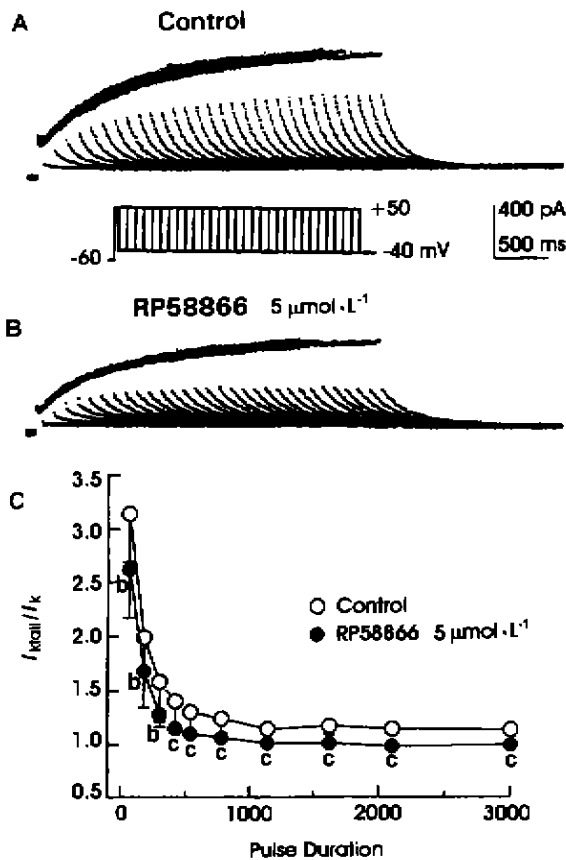


Fig 4. Envelope of tails test for the delayed rectifier (I_K) in the absence A) and presence B) of RP58866 $5 \mu\text{mol}\cdot\text{L}^{-1}$. Protocol in C (in inset) was used to elicit current with depolarizing pulse durations ranging from 60 to 3540 ms. Step and tail currents were defined as time-dependent currents during depolarization and upon repolarization, respectively. Ratio of tail current to step current (I_{Ktail}/I_{Kstep} ; $\bar{x} \pm s$, $n = 6$, ^b $P < 0.05$, ^c $P < 0.01$ 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 $200 \mu\text{mol}\cdot\text{L}^{-1}$, barium $200 \mu\text{mol}\cdot\text{L}^{-1}$ under the control condition. The envelop of tails test showed that I_k consisted of more than one component, whereas after exposure to

RP58866 $5 \mu\text{mol}\cdot\text{L}^{-1}$ (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 specific blockade of I_{K1} in guinea pig myocytes¹⁰. At concentration upto $50 \mu\text{mol}\cdot\text{L}^{-1}$, RP58866 did not markedly affect the delayed rectifier K^+ current elicited by 10 s depolarizing pulses to $+40$ mV¹⁰. This is different from our results, which proved that RP58866 inhibited markedly I_{step} and I_{Ktail} . Escande found that RP58866 ($< 30 \mu\text{mol}\cdot\text{L}^{-1}$) did not block markedly I_{tol} in rat. We proved that this drug inhibited markedly I_{tol} 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 selectivity³¹. 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 actions¹³. Our experiments proved that RP58866 was less selective for I_{Kr} . I_{tol} has been shown to play important roles in repolarization. Therefore, blockade of I_{tol} 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_{tol} in a dose-dependent and reversible manner. This agent

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_{tot} , I_{K1} , and I_K are its major mechanisms of anti-arrhythmic actions.

REFERENCES

- 1 Spelli W, Hoffman BF. Mechanisms of termination of reentrant atrial arrhythmias by class I and class III anti-arrhythmic agents. *Circ Res* 1989; 65: 1665 - 79.
- 2 Wang ZG, Feng JL, Nattel S. Class III anti-arrhythmic drug action in experimental atrial fibrillation; differences in reverse use dependence and effectiveness between *d*-sotalol and the new anti-arrhythmic drug ambassilide. *Circulation* 1994; 90: 2032 - 40.
- 3 Colatsky TJ, Follmer CH, Starmer CF. Channel specificity in anti-arrhythmic drug action; mechanism of potassium channel block and its role in suppressing and aggravating cardiac arrhythmias. *Circulation* 1990; 82: 2235 - 42.
- 4 Balsler JR, Bennett PB, Roden DM. Time-dependent outward current in guinea pig ventricular myocytes; gating kinetics of the delayed rectifier. *J Gen Physiol* 1990; 96: 835 - 63.
- 5 Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K^+ current; differential sensitivity to block by class III anti-arrhythmic agents. *J Gen Physiol* 1990; 96: 195 - 215.
- 6 Sanguinetti MC, Jurkiewicz NK, Scott A, Siegel PKS. Isoproterenol antagonizes prolongation of refractory period by the class III anti-arrhythmic agent E-4031 in guinea pig myocytes. *Circ Res* 1991; 68: 77 - 84.
- 7 Jurkiewicz NK, Sanguinetti MC. Rate-dependent prolongation of cardiac action potentials by a methanesulfonanilide class III anti-arrhythmic agent. Specific block of rapidly activating delayed rectifier K^+ current by dofetilide. *Circ Res* 1993; 72: 75 - 83.
- 8 Gwilt M, Arrowsmith JE, Blackburn KJ, Burges RA, Cross PE, Dalrymple HW, et al. UK-68,798; a novel, potent and highly selective class III anti-arrhythmic agent which blocks potassium channels in cardiac cells. *J Pharmacol Exp Ther* 1991; 256: 318 - 24.
- 9 Rees SA, Curtis MJ. Specific I_{K1} blockade; a new anti-arrhythmic mechanism? Effect of RP58866 on ventricular arrhythmias in rat, rabbit, and primate. *Circulation* 1993; 87: 1979 - 89.
- 10 Escande D, Mestre M, Hardy JC, Caverio I. RP58866, a pure class III anti-arrhythmic agent, specifically blocks the inwardly rectifying K^+ current in heart cells. (abstract) *Circulation* 1989; 80 (Suppl II); II - 607.
- 11 Li GR, Yang BF, Feng JL, Bosch RF, Carrier M, Nattel S. Transmembrane I_{Ca} contributes to rate-dependent changes of action potentials in human ventricular myocytes. *Am J Physiol* 1999; 276: H98 - H106.
- 12 Hiraoka M, Kawano S. Calcium-sensitive and insensitive transient outward current in rabbit ventricular myocytes. *J Physiol (Lond)* 1989; 410: 187 - 212.
- 13 Balsler JR, Bennett PB, Hondeghem LB, Roden DM. Suppression of time-dependent outward current in guinea pig ventricular myocytes; Actions of guiridine and amiodarone. *Circ Res* 1991; 69: 519 - 29.
- 14 Josephson IR, Sanchez-Chapula J, Brown AM. Early outward current in rat single ventricular cells. *Circ Res* 1984; 54: 157 - 62.
- 15 Dukes ID, Morad M. The transient K current in rat ventricular myocytes; evaluation of its Ca^{2+} and Na^+ dependence. *J Physiol (Lond)* 1991; 435: 395 - 420.
- 16 Colatsky TJ, Follmer CH. K-channel blockers and activators in cardiac arrhythmias. *Cardiovasc Drug Dev* 1989; 7: 199 - 209.

RP58866 对哺乳动物心室肌细胞跨膜钾电流的作用

杨宝峰¹, 李贵荣², 徐长庆³, Stanley NATTEL² (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, HITIC8, 加拿大)

关键词 心肌; 培养的细胞; 膜片钳技术; 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_{K1} 的影响. 方法;采用全细胞膜片箱技术. 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_{K1} , 其 IC_{50} 为 $(3.4 \pm 0.8) \mu\text{mol} \cdot \text{L}^{-1}$ ($n = 6$). 在犬心室肌细胞, RP58866 可明显抑制 I_{to} , 其 IC_{50} 为 (2.3 ± 0.5)

$\mu\text{mol} \cdot \text{L}^{-1}$. RP58866 $100 \mu\text{mol} \cdot \text{L}^{-1}$ 阻断豚鼠的心室肌细胞 I_K , 在 $+40$ mv 时使 $I_{K\text{step}}$ 减少 $(58 \pm 13) \%$, 其 IC_{50} 为 $(7.5 \pm 0.8) \mu\text{mol} \cdot \text{L}^{-1}$, $I_{K\text{tail}}$ 减少 $(86 \pm 17) \%$, 其 IC_{50} 为 $(3.5 \pm 0.9) \mu\text{mol} \cdot \text{L}^{-1}$. 尾电流分析表明, RP58866 对 I_{K1} 和 I_{Ks} 均有阻断作用. 结论; RP58866 对心肌细胞的 I_{K1} 和 I_{to} , I_K 均有抑制作用, 而不是一种特殊的 I_{K1} 抑制剂.

(责任编辑 李颖)

书 讯

《中国药学文摘》是我国唯一的药学科技文献综合性检索类刊物(月刊, 刊号为 CN11-2529). 本刊的特点是收载我国公开发行的药学期刊、地方医药杂志、医药大中专校学报、植物、微生物、化学化工杂志、专利等近 500 种刊物中有关中西药理论、综述、药物的科研、生产技术、制剂、分析、药理、临床应用、药品评价、药品生产管理和质量管理、制药设备和工厂设计、新药介绍等文献. 并同时建有近 24 万多条的文献数据库, 其中中药文献占一半左右, 所以该库也是世界上拥有中药文献最多的数据库. 通过十几年来对外检索服务, 受到了广大医药工作者的普遍欢迎. 该库每年可为医药生产、科研、交流、教学、医院、情报研究等部门提供 2 万多条数据, 并可提供网络版和光盘版.

《国内医药信息总览》是专门收集国内 300 多种报纸、内刊及资料的医药类信息资料;是集政策法规、科研、生产、市场信息的大全书, 也是查找医药经济类、科技类医药信息的唯一途径. 每月一期, 每期为您提供近千条信息. 同时可提供数据库、光盘服务.

《全国医药信息》由国家药品监督管理局主管. 是沟通全国药品监督管理信息及医药信息的载体, 是为国家及地方药品监督管理局或医药、药政管理部门和企事业单位及有关单位提供信息的重要媒介. 重点内容为: 政策、法规(包括局长令等)、各种管理办法. 具体为中西药品、医疗器械的政策、法规、认证、注册、仿制、进出口、行政保护品种、中药保护品种及其管理监督、抽验查处; 批准的新药及新药临床; 非处方药(OTC)制度、审定、目录; 医药工商统计数据; 市场、价格、流通、分析预测; 合资、改革情况等最新信息. 它是当前最具权威性的快、准、新综合体的信息资料.

《国外药讯》专为全国医药系统及有关单位提供国外信息资料. 主要内容为国外发展医药的方针、政策、措施、规划和药品管理及有关的法律、法规; 中西药品的生产、销售、价格、市场; 新产品上市; 新药(包括诊断试剂)的发现、临床研究; 重要新技术、新工艺、新材料, 新剂型的开发与应用; 药物安全性监察和相互作用; 治疗指南; 药物经济学; 企业动态; 市场情况等方面的最新信息. 用户只需最少的时间即可获得大量国外医药信息. 同时可为您提供以光盘和数据库的形式提供各类专题服务.

《全国医药商情》由国家药品监督管理局信息中心和国家经贸委医药司共同主办, 是全国性、综合性、医药经济贸易市场性资料. 本资料的特点是专门报道全国经济运行、市场分析与预测、国内外医药市场动态、物价动态、行情、新药上市、医药用药、药品行政保护、产品供求信息、医药包装以及 60 余个热点品种在全国 24 个省市、自治区大中城市每月 15 日的批发价、实价、生产厂家行情. 还包括全国药品交易会及全国医药原料药中间体市场交易会情况, 以及原料药、制剂、中药(中成药及中药材)、新特药、卫生材料、医疗器械、制药装备、化肥、化工原料和中间体及其它方面信息.

《中国药品检验文摘》是从事药检人员的必备工具书. 它汇集所有医药方面期刊(包括公开刊和内刊)、报纸上所载的药品检验方面的文献资料. 以药检所、药厂质检科及化验室、研究院(所)药物分析室、大中专校药物分析及中药鉴定教研室、医院药剂科及药政管理等工作人员为服务对象. 开辟栏目有: 药政管理(药品检验与监督)、中药材鉴定与鉴别、中、西药及其制剂的分析与检验、药物的血药浓度测定、生物利用度与生物等效性、药品质量标准与质量控制、药品卫生学检验、分析方法介绍与综述、药检新书介绍. 同时可提供数据库和光盘服务.

《中国医药情报》报道以医药战略情报研究为主的一次文献科技信息. 内容包括: 国内外医药行业的发展趋势, 政策法规, 先进技术, 药品与医疗器械的科研、生产、临床应用、合理用药, 药物不良反应, 新药的临床评价, 国内外医药贸易与市场动态; 出国考察与对外交流等. 通过本资料您可掌握国内外医药最新动态及经过专家分析、综合的报道及评论.

《中国药品专利》为了配合药品专利的实施, 增强专利意识, 保护知识产权, 卓有成效地指导医药新产品的研究开发、生产、销售及进出口贸易等. 国家药品监督管理局信息中心与中国专利局专利文献出版社共同编辑出版《中国药品专利》及《中国药品专利说明书光盘》. 它是集法律、经济、技术情报于一体的重要信息源. 它对于掌握世界上科研发展的最新动态, 跟踪某一专业领域、借鉴国外先进技术, 避免重复研究, 确定企业发展决策等方面提供了重要的情报依据.

联系地址: 北京西城区北礼士路甲 38 号国家药品监督管理局信息中心期刊信息处. 邮编: 100610. 联系电话: 010-6835-0889 或 6835-2546 转编辑部.