CARDIOPROTECTIVE ACTIONS OF ATP-SENSITIVE K^+ CHANNEL OPENERS (CROMAKALIM, PINACIDIL AND NICORANDIL) IN CARDIAC PURKINJE FIBERS

HIROYASU SATOH, TOSHIAKI NAKATANI and
TOSHIKATSU NAKASHIMA
Department of Pharmacology, Nara Medical University
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Summary: Effects of ATP-dependent K^+ channel openers on the action potentials and the contractile force in canine cardiac Purkinje fibers were examined. Cromakalim and pinacidil (0.3 to 10 μM), and nicorandil (0.3 to 1 mM) shortened both the 50% and 90% action potential durations (APD), and decreased the contractile force, in a concentration- and frequency-dependent manner. These responses were reversible. The APD shortening and the negative inotropic effect induced by a switch of stimulation frequency (from 0.5 to 3 Hz) were potentiated by application of the openers. Other action potential parameters were unaffected, but the resting potential of relatively less negative voltage was hyperpolarized. These effects were potently antagonized by glibenclamide (a selective blocker of ATP-sensitive K^+ channel). Under the calcium overload condition, the K^+ channel openers abolished a delayed afterdepolarization and recovered the contractile force. These results suggest that the ATP-sensitive K^+ channel openers increase the K^+ conductance and simultaneously may possess cardioprotective actions to reduce the cellular Ca^{2+} level in calcium overloaded cells.

Index Terms

ATP-sensitive K^+ channel openers, nicorandil, pinacidil, cromakalim, action potential, contractile force, electrophysiology

INTRODUCTION

As a new class drug, K^+ channel openers have recently been developed, which produce vasodilating and antihypertensive effects due to the activation of K^+ channel in a variety of smooth muscles[1)~4)]. An increase in K^+ conductance hyperpolarizes the smooth muscle cell membrane, resulting in decrease in Ca^{2+} entry through voltage-dependent Ca^{2+} channels. The resulting decrease in intracellular Ca^{2+} concentration ($[Ca]_i$) could produce vascular relaxation. In heart muscle, these openers shorten the action potential duration (APD) due to enhancement of the delayed rectifier K^+ current[5)~8)]. However, the drugs neither hyperpolarize the resting potential (RP), nor affect the maximum rate of depolarization ($\dot{V}_{max}$)[9),10)].

It has recently been found that cromakalim (a benzopyran derivative), pinacidil (a cyanoguanidine derivative) and nicorandil (a nicotinamide ester) open an ATP-sensitive K^+ (K_{ATP}) channel[5),11~16)]. Nicorandil also acts through the cGMP-dependent mechanism as well as through the K_{ATP} channel opening[17),18)]. In addition, it has been reported that these K_{ATP}

channel openers act the Ca^{2+}-dependent K^+ channel in smooth muscle[19].

In the present study, we sought to examine the effects of the K_{ATP} channel openers on the action potentials and the contractile force in canine Purkinje fibers. We wanted to investigate the modulation by different frequencies (0.5 to 3 Hz) of stimulation to elevate $[Ca]_i$, and also examine whether or not the K_{ATP} channel openers reduce the $[Ca]_i$ under calcium overload condition.

METHODS

Eighteen mongrel dogs, weighing 10-20 kg, were anesthetized with pentobarbital sodium (30 mg/kg, i. v.). The heart was quickly excised. The Purkinje fibers were placed in an organ bath, and superfused with Tyrode solution at a temperature of 36℃, as described previously[16),20)]. The preparation was usually driven at 1 Hz using a stimulator (Nihon Koden SEN-7103). The stimulation voltage was about 50% above the threshold, and the duration was 1 - 2 ms. Recording of the action potential was obtained by the conventional microelectrode technique. The contractile force was recorded using a force displacement transducer (Nihon Koden SB-1T). Values are given as mean ± SEM.

The composition of modified Tyrode solution (mM) was as follows : NaCl 137, KCl 4 , $MgCl_2$ 1 , $CaCl_2$ 1.8, NaH_2PO_4 0.4, $NaHCO_3$ 12, and glucose 5 . The solution was oxygenated with 95% O_2 and 5%CO_2. The pH was adjusted to 7.4 with NaOH. The drugs were cromakalim (Beecham Research Lab., Ltd.), pinacidil (Shionogi Pharmaceutical Co., Ltd.) and nicorandil (Chugai Pharmaceutical Co., Ltd.). Glibenclamide (Sigma Chemical Co.) was also used.

RESULTS

Effects on the action potentials at different stimulation frequencies

In canine Purkinje fibers, the electrophysiological effects of the K_{ATP} channel openers were examined. Figure 1 shows typical changes in the action potentials induced by cromakalim (10 μM), pinacidil (10 μm) and nicorandil (1 mM). The preparations were stimulated at 1 Hz. These openers pronouncedly shortened the APD. Addition of glibenclamide (1 μM), a selective ATP-sensitive K^+ channel blocker[1),21)], almost fully recovered the shortened APD induced by openers to control value.

The shortenings of APD_{50} and APD_{90} (50% and 90% repolarizations) by the openers are summarized in Figs. 2 and 3. At 1 Hz, cromakalim (10 μM) shortened APD_{50} by 77.2±4.1% (n=8, $P<0.05$), and APD_{90} by 54.3±4.8% (n=8, $P<0.01$). Pinacidil (10 μM) and nicorandil (1 mM) decreased APD_{50} by 77.2±5.0% (n=5, $P<0.05$) and by 43.6±5.1% (n=5, $P<0.01$), and APD_{90} by 62.1±4.8% (n=5, $P<0.05$) and by 27.4±4.5% (n=5, $P<0.05$), respectively. The openers did not affect the resting potential (RP), the action potential amplitude (APA), or $\dot{V}_{max}$ to any significant extent. The incidence of arrest in the spontaneous beating Purkinje fibers was in 5 out of 6 preparations in cromakalim (10 μM), in 3 of 5 preparations in pinacidil (10 μM), and in 3 of 5 preparations in nicorandil (100 μM). The averaged RP was −60.4±1.1 mV (n=10). At the lower concentrations, no arrest occurred.

At 0.5, 2 and 3 Hz of stimulation, the changes in APDs are also summarized in Figs. 2 and

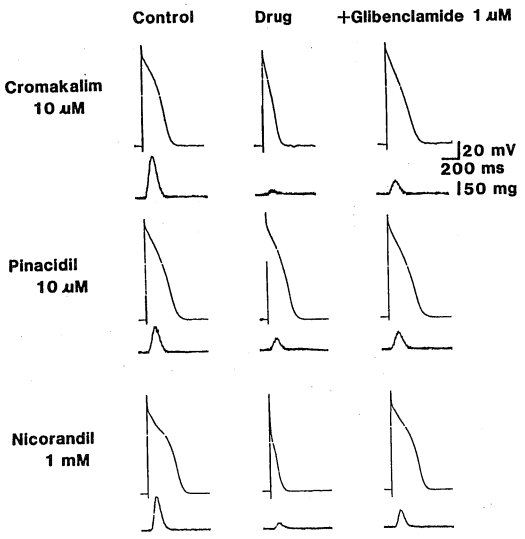

Fig. 1. Effects of the K^+ channel openers on the action potentials and the contractile force in canine Purkinje fibers. Glibenclamide (1 μM) antagonized the shortened action potential duration and the negative inotropic effect.

3. Usually, a switch to higher frequencies of stimulation (from 0.5 to 3 Hz) shortened the APDs frequency-dependently. Both the shortened APDs were potentiated with an increase in concentration of the K_{ATP} channel openers. The concentration-response curves at different frequencies were decreased more steeply at 0.5 Hz than at 3 Hz. Nicorandil tended to prolong the APD at 1 Hz and at low concentrations.

The changes in the membrane potentials after a rest of stimulation and in the contractile force after re-started stimulation were examined in the absence and presence of the K_{ATP} channel openers (Fig. 4). The stimulation frequency was 2 Hz. No effect occurred in normal Tyrode solution ($[Ca]_o$=1.8 mM), but in 10.8 mM, a delayed afterdepolarization (DAD) was elicited (Fig. 4, left arrow). Pinacidil at 3 μM inhibited the DAD, and at 10 μM abolished it completely.

Effects of the K_{ATP} openers on the RP in the quiescent preparation were examined (Fig. 5). Pinacidil (3 to 10 μM) hyperpolarized the RP (from -43 to -61 mV). Glibenclamide (1 μM) depolarized the RP by approximately 15 mV, but never recovered the spontaneous activity (n=8). After a wash out, the spontaneous activity was resumed. Other two drugs also caused similar responses in 6 to 8 preparations.

Effects on contractile force at different stimulation frequencies

As shown in Fig. 6, cromakalim (0.1 to 3 μM) decreased the contractile force in a concentration-dependent manner. The preparation was stimulated at 1 Hz. Nicorandil (10 μM to 1 mM) also induced similar effects. The changes are summarized in Fig. 7. Cromakalim (10 μM) decreased the contractile force by 81.6±3.4% (n=8, $P<0.01$), and the percentage decreases of other drugs were 74.8±4.5% (n=5, $P<0.01$) in pinacidil (10 μM) and 41.8±6.9% (n=5, $P<0.01$) in nicorandil (1 mM). The concentration-response curves were decreased more steeply by the stimulations at 0.5 Hz than at 3 Hz. In some preparations, pinacidil and nicorandil tended to increase the contractile force at low concentrations (0.3 to

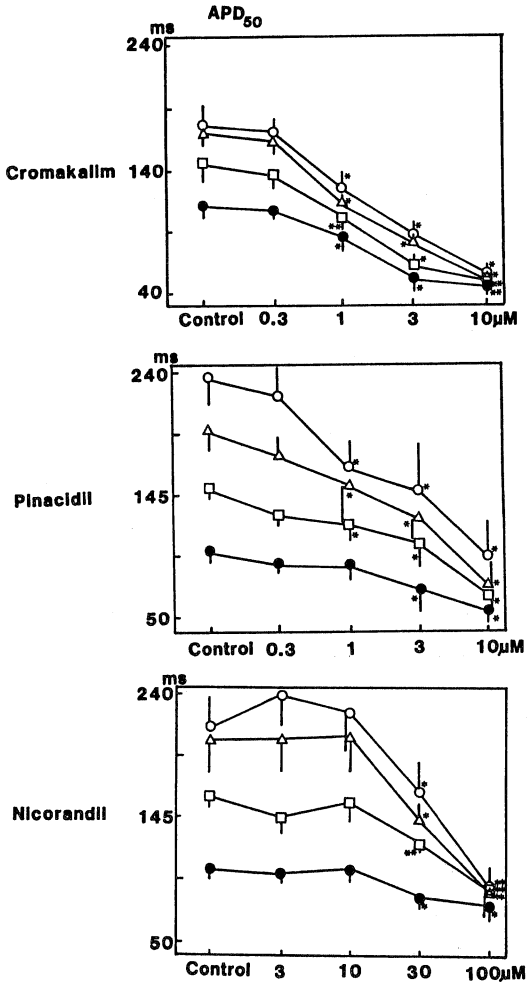

Fig. 2. Effects on the action potential duration at 50 % repolarization with different frequencies of stimulation. These K_{ATP} openers shortened APD_{50} in a concentration- and frequency-dependent fashion. Symbols used are 0.5 Hz (open circles). 1 Hz (triangles), 2 Hz (squares), and 3 Hz (filled circles). Values represent mean ± SEM. * : P<0.05, ** : P<0.01, *** : P<0.001, with respect to control value.

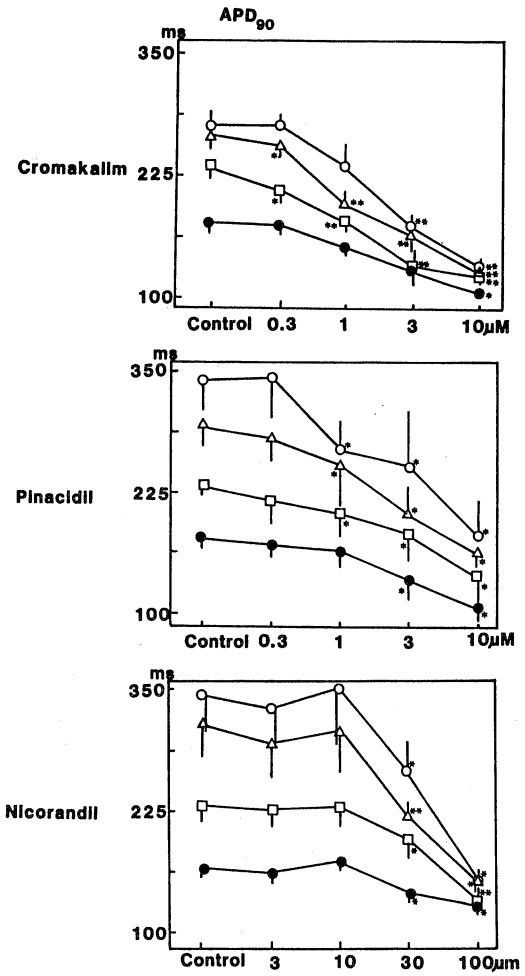

Fig. 3. Effects on the action potential duration at 90 % repolarization with different frequencies of stimulation. These K_{ATP} openers shortened APD_{90} in a concentration- and frequency-dependent fashion. Symbols used are 0.5 Hz (open circles), 1 Hz (triangles), 2 Hz (squares), and 3 Hz (filled circles). Values represent mean ± SEM. * : P<0.05, ** : P<0.01, *** : P<0.001, with respect to control value.

1 μM) or at low stimulation frequencies (0.5 Hz).

With pretreatment of glibenclamide (1 μM), the negative inotropic effects induced by the K_{ATP} openers were antagonized significantly (Fig. 6). As shown in Fig. 1, however, the contractile force was not completely resumed by addition of glibenclamide (1 μM) ; by 67% recovery in cromakalim, by 78% in pinacidil, and by 55% in nicorandil. The percentage recovery by glibenclamide (1 μM) was 65.0±9.1% (n=5, P<0.01) in cromakalim (1 μM), 52.1±4.9% (n=6, P<0.001) in pinacidil (1 μM), and 65.2±3.9% (n=4, P<0.001) in

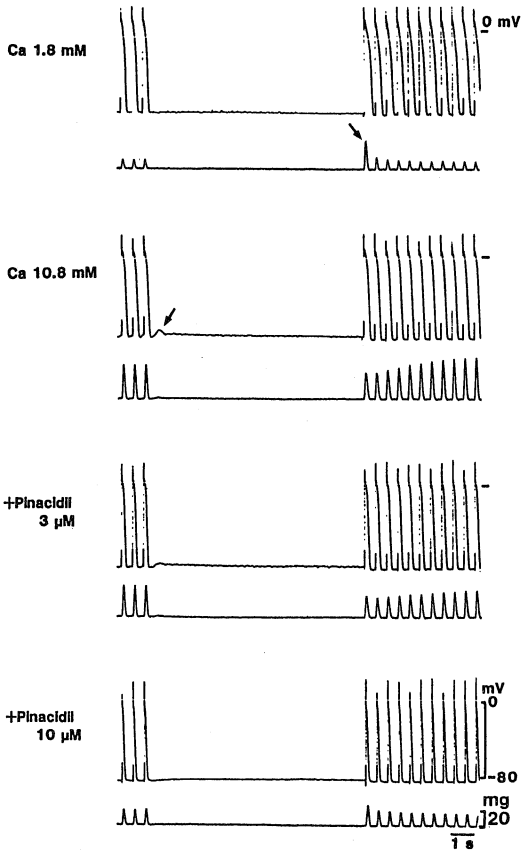

Fig. 4. Abolishment of delayed afterdepolarization and recovery of post-rest potentiation in the presence of pinacidil. Action potentials and contractile forces were represented. The preparation was stimulated at 2 Hz, and a arrest was for 10 sec. Increasing extracellular Ca^{2+} concentration to 10.8 mM elicited a delayed afterdepolarization (DAD, left arrow), and depression in a post-rest potentiation (right arrow). Addition of pinacidil at 3 μM inhibited, and at 10 μM abolished the DAD. The post-rest potentiation was recovered by pinacidil (10 μM). Short line represent zero mV.

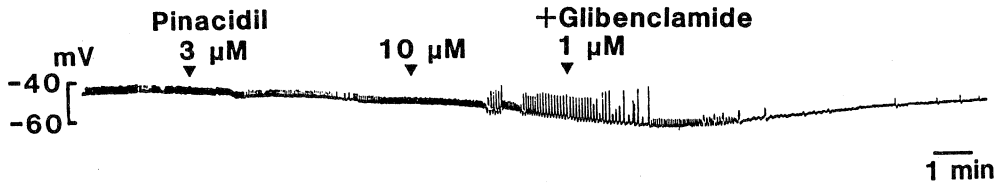

Fig. 5. Effects of K^+ channel openers on a quiescent Purkinje fiber. Resting potential (RP) was -45 mV. Pinacidil (3 to 10 μM) hyperpolarized the RP, and glibenclamide (1 μM) depolarized it.

nicorandil (100 μM).

When the stimulation is re-started, the first response at the first stimulation are potentiated strongly by 270±8% (n=11) in normal solution ; that is a post-rest potentiation (Fig. 4, right arrow). The post-rest potentiation after 10 sec-pause was inhibited by 26±3% (n=11) under high Ca^{2+} condition. The values are the ratio between the amplitude of last force development before a pause and that of the first one at re-started stimulation after 10 sec-pause. Pinacidil (10 μM) enhanced the depressed post-rest potentiation to 310±6% (n=5, $P<0.001$) under the Ca^{2+} overload condition. Similar results were also observed at 10 μM cromakalim (by 518±

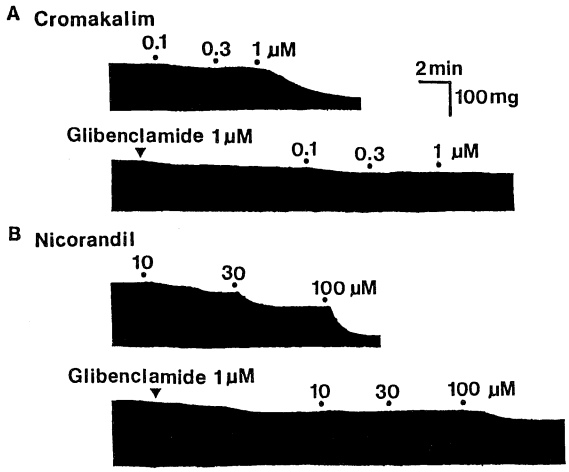

Fig. 6. Negative inotropic effect induced by cromakalim and nicorandil. The same concentrations of cromakalim (0.1 to 30 μM) and nicorandil (10 μM to 1 mM) were applied in the absence and presence of glibenclamide (1 μM). The effects were concentration-dependent. The preparations were stimulated at 1 Hz.

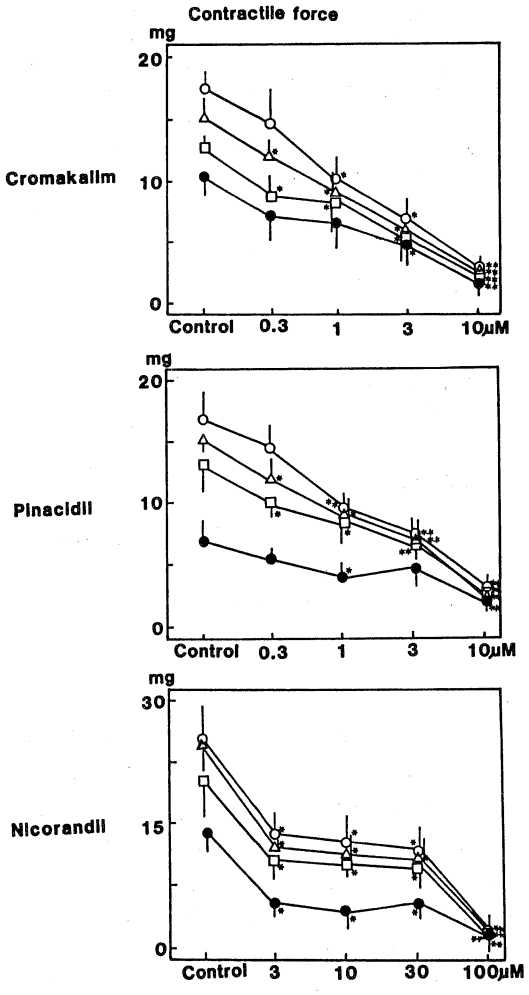

Fig. 7. Summarized changes in the negative inotropic effects of the K_{ATP} channel openers at different stimulation frequencies. The preparation was stimulated at 0.5 to 3 Hz of the frequencies. The response was frequency-dependent. Symbols are 0.5 Hz (open circles), 1 Hz (triangles), 2 Hz (squares), and 3 Hz (filled circles), Values represent mean ± SEM. * : $P<0.05$, ** : $P<0.01$, *** : $P<0.001$, with respect to control value.

4%, n=4, $P<0.001$) and at 100 μM nicorandil (by 283±6%, n=4, $P<0.001$).

DISCUSSION

K^+ channel openers, as new vasodilating drugs, have been known to increase K^+ permeability of vascular smooth muscle membrane[1),22)], resulting in the hyperpolarization of RP and the relaxation of smooth muscles[4),23)]. Cromakalim and pinacidil have been reported to activate the K_{ATP} channels[12),22)], whereas nicorandil has reported to act another K^+ channel through cGMP-dependent mechanism, causing dilation of blood vessels[17),18)]. Holzmann[17)] has suggested that, since the correlation between cGMP level and relaxation by nicorandil was different from that by other nitrocompounds, nicorandil might have an additional relaxing effect. In this study, the effects of nicorandil were also antagonized by glibenclamide (an antidiabetic K_{ATP} channel drug), like cromakalim and pinacidil. The results are consistent with those of Hiraoka and Fan[24)] and Satoh[16)]. Therefore, the present results indicate that cromakalim and pinacidil affect APD and the contractile force through the K_{ATP} channels, and also that nicorandil could activate not only K^+ channels through the cGMP-dependent mechanism, but also the K_{ATP} channels.

On effects on action potential and contractile force

The K_{ATP} channel is activated by the decrease in the cellular ATP level[6),24)]. The activity of K_{ATP} channels is not evident unless cytosolic ATP concentration falls below 1 mM[13)]. The effective concentration in cardiac muscles is higher by 10-100 fold than those in vascular and other smooth muscles (0.1-1 μM)[22),25)]. In the present experiments, however, the K_{ATP} openers shortened the APD and decreased the contractile force in cardiac Purkinje fibers even in normal Tyrode solution. Thus, it appears that the effects were due to the activation of the K_{ATP} channels, because glibenclamide antagonized the shortened APD and the negative inotropic effect induced by the K_{ATP} openers. In addition, these openers hyperpolarized the RP in quiescent Purkinje fibers, and glibenclamide depolarized it. When the cellular ATP level is reduced by 2-deoxy-D-glucose (2-DG)[26)], glibenclamide produced potent APD prolongation[16)]. Therefore, these results strongly indicate that the responses induced by the K_{ATP} channel openers are mediated through K_{ATP} channels, independent of cellular ATP concentration.

In cardiac muscles, the effect of the K_{ATP} openers on the RP is controversial: RP was unaffected[6),24)], whereas RP was hyperpolarized[10),27)]. In this study, the K_{ATP} openers had no effect on the RP, even though the openers shortened the APD and decreased the contractile force, significantly. The finding that the K^+ openers had no effect on RP is supported by the patch clamp report of Keizer and Magnus[12)], in which the inward rectifier K^+ current (I_{Krec}) was unaffected by pinacidil. The I_{Krec} contributes to the RP of cardiac muscles[28),29)]. On the other hand, the openers in this study hyperpolarized the less negative RP of −40 to −60 mV. The action of the K^+ openers seems to depend on the RP level. This may be explained by whether or not RP is much closer to the K^+ reversal potential. When the RP was more negative than −80 mV, the K^+ channel openers did not cause any effect on the RP. On the contrary, in quiescent Purkinje fibers (at −40 to −50 mV of RP), the hyperpolarization was produced (see

Fig. 5). Addition of glibenclamide depolarized the hyperpolarized RP. Therefore, these results indicate that the hyperpolarization is due to the activation of the K_{ATP} channels. Furthermore, Satoh[16] has shown that, since the K_{ATP} openers-induced hyperpolarization was potentiated by high Ca^{2+} (10.8 mM), the stimulation of Ca^{2+}-activated K^+ channel may be in part contributed to the regulation of RP, although the RP in this study was not dependent on the stimulation frequencies.

There is a difference between the recoveries of the APDs and the contractile force by glibenclamide. The mechanism still remains unclear, but may be explained by some possibilities: (a) the APD is mainly dependent on the K_{ATP} channels, whereas the contractile force is less dependent; (b) the prolongation of APD is less contributed to regulation of the contractile force.

On cardioprotective actions

The K_{ATP} channel openers produce protective actions for cardiac functions. At first, in this study, the openers abolished the DAD and recovered the post-rest potentiation during Ca^{2+} overload. These results indicate that the K_{ATP} channel openers reduced $[Ca]_i$ level. The development of DAD and the depression in post-rest potentiation are elicited under Ca^{2+} overloaded cardiac muscle cells[26),30),31)]. It seems that reduction in $[Ca]_i$ may be due to inhibition of voltage-dependent Ca^{2+} channels, and to decrease in the inactivation time of the Ca^{2+} channels by the APD shortening. Secondly, the openers suppressed spontaneous automaticity in rabbit sino-atrial node[8)] and Purkinje fibers[16,32)]. Arrest occurred in some preparations. Since the spontaneous action potentials are slow Ca^{2+} current-dependent[33)], the K_{ATP} channel openers inhibited the voltage-dependent Ca^{2+} channels by the hyperpolarization. Finally, the K_{ATP} openers did not affect the RP at -80 to -90 mV. These results suggest that the openers have a stabilizing action of the membrane. The openers can maintain the diastolic potential close to the equilibrium potential for K^+ ions, resulting in prevention of abnormal depolarizations and automaticity[32),34)].

However, the K_{ATP} channel openers may also produce arrhythmogenic actions[35),36)].The APD shortening may tend to induce arrhythmias. The drugs enhanced the rate of tachycardia and shortened the time required to develop fibrillation in isolated rat hearts[35),37)]. In the present experiments, all the K_{ATP} openers had no arrhythmia even at high frequency of stimulation and at high $[Ca]_o$. But pinacidil and nicorandil, at low concentrations (0.3 to 1 μM) and at low stimulation frequency (0.5 Hz), had a slight positive inotropic effect in some preparations. Nicorandil at low concentration also tended to prolong the APD. Thus, the openers might not only shorten the refractory period, but also at low concentrations elevate $[Ca]_i$ level by an unknown mechanism. The hyperpolarization (but at less negative voltage) induced by the openers may also be one of the arrhythmogenic factors. The hyperpolarization may elicit instability of the membrane. Thus, the K_{ATP} channel openers possess many complex actions on the cardiac muscles, including inefficiencies. Clinically, we need to take care in using these drugs, and further experiments are required to obtain more informations.

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