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Pretreatment with rimalkalim changes the adrenergic responsiveness of isolated guinea pig papillary muscle

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Abstract

It has been proposed that the positive inotropic action of different drugs is influenced by the activation of ATP-sensitive K^+ channels (K_{ATP}). This hypothesis was tested by investigating the effects of rimalkalim ((3*S*,4*R*)-3-hydroxy-2,2-dimethyl-4-(oxo-1 pyrrolidinyl)-6-phenyl-sulfonylchroman hemihydrate (formerly HOE-234)) as activator of K_{ATP} channels on the positive inotropic action of forskolin, L-phenylephrine hydrochloride and dibutyryl cyclic AMP (N^6,2′-*O*-dibutyryladenosine 3′:5′-cyclic monophosphate). Experiments were performed with the isolated guinea-pig heart papillary muscle. The force of contraction (F_c), velocity of contraction ($+dF/dt$) and relaxation ($-dF/dt$), time to peak contraction (t_{tp}) and duration of contractions at the level of 10% or more of their total amplitude ($t_{t_{10}}$) were measured. Pretreatment with 1 μM rimalkalim had no significant influence on the positive inotropic effects of dibutyryl cyclic AMP and L-phenylephrine in the presence of 1 μM metoprolol. However, the positive inotropic effects of L-phenylephrine in the absence of metoprolol were significantly attenuated after pretreatment with rimalkalim. The increase in force and velocity of contraction induced by forskolin was strongly enhanced under these conditions. Addition of 1 μM glibenclamide, an inhibitor of K_{ATP} channels, to rimalkalim, prevented the above-mentioned changes in the positive inotropic effects of phenylephrine and forskolin obtained after pretreatment with rimalkalim. What is more, addition of 0.2 μM thapsigargin, a selective blocker of Ca^{2+}-adenosinetriphosphatase of sarcoplasmic reticulum (Ca^{2+} ATP-ase), abolished the potentiation of the positive inotropic action of forskolin induced by pretreatment with rimalkalim. These results demonstrate that activation of K_{ATP} channels by rimalkalim alters β-adrenoceptors, but has no effect on α-adrenoceptor signalling pathways and enhances forskolin inotropic effects by a mechanism which probably involves Ca^{2+} ATP-ase.

Keywords: α-Adrenoceptors; β-Adrenoceptors; Myocardium; K^+ channels ATP-sensitive; Forskolin

1. Introduction

Activation of K_{ATP} channels appearing during hypoxia in the heart muscle (Noma, 1983) is one of the most important events which can influence the contractile responsiveness of the myocardium. Recently published data obtained in our laboratory demonstrated that activation of K_{ATP} channels by rimalkalim in the guinea-pig papillary muscle significantly attenuates the positive inotropic effects of isoprenaline, has no effect on the action of amrinone and pimobendan, and significantly enhances the effects of digoxin and milrinone (Kocić, 1996). It has been postulated that activation of K_{ATP} channels probably disturbs β-adrenoceptor coupling to G_s protein and facilitates the release of Ca^{2+} from the sarcoplasmic reticulum store by digoxin and milrinone. In the failing human heart and during ischaemia in some animal experiments, not the β-adrenoceptor but rather the α-adrenoceptor signalling pathway is preferred in the myocardium (Sharma et al., 1983; Bristow et al., 1988; Homcy, 1991; Brodde, 1993; Billman, 1994; Harding et al., 1994). It is not clear what the reason is for such a change. Activation of K_{ATP} channels could be involved in this process.

The aim of this study was to test the influence of activation of these channels on the adrenergic responsiveness of the isolated guinea-pig heart papillary muscle. In order to carry this out, the influence of pretreatment with rimalkalim, an activator of K_{ATP} channels in the guinea-pig papillary muscle, given either alone (Kocić, 1994) or in the presence of glibenclamide (selective blocking agent of K_{ATP} channels) or thapsigargin (selective inhibitor of sarcoplasmic Ca^{2+} ATP-ase), on the positive inotropic effects of L-phenylephrine, L-phenylephrine plus metoprolol, dibutyryl cyclic AMP and forskolin was investigated.

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2. Materials and methods

2.1. Animals and preparation

Experiments were performed on mixed breed guinea pigs of both sexes, weighing 300–500 g. The animals were killed by cervical dislocation and papillary muscle (length >3 mm, diam. <1 mm) was dissected out from the right ventricle, mounted in 2 ml organ baths (Steiert Organ bath, type 813 with DC temperature controller type 319, HSE, Germany) and attached to an isometric force transducer (F-30, HSE, Germany). The papillary muscle was superfused with modified Krebs-Henseleit solution which contained (mM): NaCl 119.0; KCl 4.8; $MgSO_4$ 1.2; $CaCl_2$ 2.5; $NaHCO_3$ 24.8; KH_2PO_4 1.2 and glucose 10.0. The rate of perfusion of the solution was 7–8 ml/min (peristaltic pump, type 371, Unipan, Poland); the solution was aerated with 95% O_2 + 5% CO_2. Tissues were maintained at 0.4 g resting tension and electrically paced by two silver electrodes in contact with the muscles, with square waves (1 Hz, 1–3 ms duration, threshold voltage +20%) generated by an electronic stimulator (DISA-Multistim, Disa Elektronik, Harlev, Denmark), at 35 ± 0.1°C. The developed tension (F_c), rate of rise ($+dF/dt$) and rate of fall ($-dF/dt$) of force of contraction were measured by an isometric force-displacement transducer F-30 and bridge amplifier with a differentiator type 336 (HSE, Germany). The signals were displayed on a digital storage oscilloscope VC-6525 and personal computer (PC 486) with the HIMES software (Hitachi, Japan), which allows measurement of the time to peak contraction (t_{tp}) and the duration of contraction at an amplitude of 10% or more ($t_{t_{10}}$).

2.2. Experimental design and statistical evaluation

In the first phase of the investigation, the concentration–response curves for forskolin, dibutyryl cAMP, phenylephrine, thapsigargin and rimalkalim were made 60 min after the preparation procedure. Baseline measurements were taken before drug administration. In the second phase, the concentration–response curves for forskolin in the presence of 0.2 μM of thapsigargin or phenylephrine in the presence of 1 μM of metoprolol were made. The tissue was then allowed to recover (about 120 min). If the contractile parameters oscillated no more than 10% from the control values, the same protocol was repeated 7 min after the start of the perfusion with rimalkalim alone. A separate series of experiments was performed with phenylephrine, phenylephrine in the presence of metoprolol and forskolin after pretreatment with glibenclamide (1 μM) plus rimalkalim (1 μM). The changes in the force of contraction and rate of rise or fall of force are expressed in mN and mN/s, respectively (average control values were: $F_c = 0.975 \pm 0.128$ mN/mm^2; $+dF/dt = 6.21 \pm 0.932$ mN/s; $-dF/dt = 3.97 \pm 0.675$ mN/s; $n = 20$).

Mean values are presented with standard errors of the mean (±S.E.M.). Concentration–response curves were made by using a computer program according to Tallarida and Murray (1987). The difference between means was assessed for significance by Student's *t*-test or Newman-Keuls test when it was appropriate. The correlation coefficient (r) and the slope of the linear regression plot were also measured and compared. Values of $P < 0.05$ were taken as statistically significant.

2.3. Drugs

The following drugs were used: L-phenylephrine hydrochloride, thapsigargin, dibutyryl cyclic AMP (Sigma, USA); metoprolol–tartrate salt and glibenclamide (kindly donated by Polpharma, Poland); forskolin (Research Biochemicals International, USA) and rimalkalim ((3*S*,4*R*)-3-hydroxy-2,2-dimethyl-4-(oxo-1 pyrrolidinyl)-6-phenylsulfonylchroman hemihydrate (formerly HOE-234)), kindly donated by Hoechst, Germany. All drugs were dissolved in distilled water, except thapsigargin and forskolin. Dimethylsulphoxide (DMSO) was added to the control solution in a concentration less then 1%, which had no significant effect on the contractility of papillary muscle.

3. Results

3.1. Effects of dibutyryl cAMP on the contractility of guinea-pig papillary muscle

Dibutyryl cAMP caused concentration-dependent effects in the tissues tested (Fig. 1). The maximum increase in velocity of contraction and relaxation above the control values was 3.4 ± 1.23 and 2.5 ± 0.88 mN/s, respectively (Table 1). The pD_2 value ($-\log EC_{50}$) was 3.68 ± 0.25, $r = 0.89$, slope $= 0.095 \pm 0.024$. Pretreatment with 1 and 3 μM rimalkalim for 7 min did not change the effects of dibutyryl cAMP significantly (pD_2 value $= 3.74 \pm 0.25$, $r = 0.89$, slope $= 0.073 \pm 0.019$, after 1 μM of rimalkalim; and $pD_2 = 3.78 \pm 0.16$, $r = 0.87$, slope $= 0.086 \pm 0.012$, after 3 μM of rimalkalim).

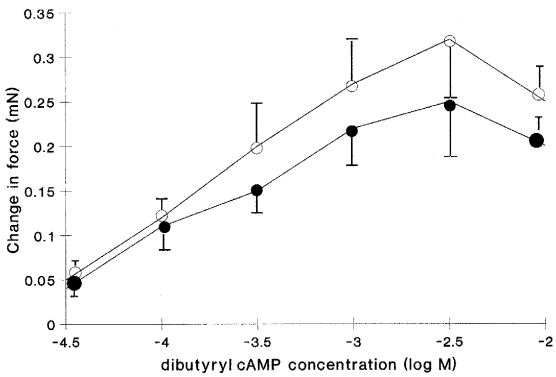

Fig. 1. Effects of dibutyryl cAMP (cAMP) on electrically stimulated contractions of papillary muscle of guinea-pig heart before (○) and after (●) pretreatment with rimalkalim (1 μM). Each point represents mean ± S.E.M. from five experiments.

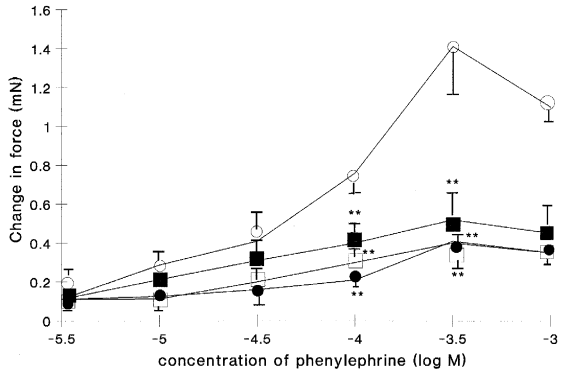

Fig. 2. Myocardial contractile response of isolated guinea-pig papillary muscle to phenylephrine alone and phenylephrine in the presence of 1 μM metoprolol before and after pretreatment with rimalkalim (1 μM) – ∘ – phenylephrine; – • – phenylephrine + metoprolol; – □ – phenylephrine after pretreatment with rimalkalim; – ■ – phenylephrine after pretreatment with rimalkalim + metoprolol. ** $P < 0.01$; significantly different from effects produced by phenylephrine alone (Newman–Keuls test). Each point represent mean ± S.E.M. from 5–6 experiments.

3.2. Effects of phenylephrine on the contractility of guinea-pig papillary muscle. Influence of pretreatment with rimalkalim

Fig. 2 shows the effects of phenylephrine and phenylephrine in the presence of 1 μM metoprolol (selective blocker of β_1 adrenoceptors) on the force of contraction of guinea-pig papillary muscle before and after pretreatment with rimalkalim, an activator of ATP-sensitive K^+ channels. Phenylephrine produced concentration-dependent effects, with a maximum increase in force equal to 1.412 mN, $pD_2 = 4.19 \pm 0.18$, $r = 0.92$, slope $= 0.49 \pm 0.1$. In the presence of metoprolol, the effects of phenylephrine on the force ($pD_2 = 4.43 \pm 0.21$, $r = 0.9$, slope $= 0.12 \pm 0.03$, $P < 0.01$) and velocity of contraction (Table 1) were significantly attenuated. Pretreatment with rimalkalim affected significantly the contractile response of the guinea-pig papillary muscle to phenylephrine ($pD_2 = 4.61 \pm 0.17$, $r = 0.94$, slope $= 0.12 \pm 0.02$, $P < 0.01$) but not to phenylephrine plus metoprolol (Fig. 2). Only the maximum increase in velocity of contraction, but not relaxation, induced by phenylephrine was significantly attenuated after pretreatment with rimalkalim (Table 1).

3.3. Effects of forskolin on the contractility of guinea-pig papillary muscle. Interaction with rimalkalim and thapsigargin

As shown in Fig. 3 and Table 1 forskolin caused concentration-dependent effects on the guinea-pig papillary muscle ($pD_2 = 6.06 \pm 0.16$, $r = 0.95$, slope $= 0.74 \pm$

Table 1
Influence of activation of ATP-sensitive K^+ channels by 1 μM rimalkalim on the increase in velocity of contraction ($+dF/dt$) and relaxation ($-dF/dt$) induced by dibutyryl cAMP (cAMP), phenylephrine, phenylephrine in the presence of 1 μM metoprolol and forskolin in the guinea-pig papillary muscle

Drugs	Control		After pretreatment with rimalkalim	
	$+dF/dt$ (mN/s)	$-dF/dt$ (mN/s)	$+dF/dt$ (mN/s)	$-dF/dt$ (mN/s)
cAMP				
Control	5.25 ± 0.94	3 ± 1.35	3.25 ± 1.42	2.62 ± 1.14
100 μM	0.94 ± 0.42	0.52 ± 0.18	0.8 ± 0.122	0.5 ± 0.17
300 μM	2.15 ± 1.11	1.5 ± 0.67	1.5 ± 0.63	1.1 ± 0.47
1000 μM	2.9 ± 1.21	2.5 ± 0.88	2.27 ± 0.93	1.4 ± 0.54
3000 μM	3.4 ± 1.23	1.92 ± 0.8	2.25 ± 1.05	1.17 ± 0.31
Phenylephrine				
Control	3 ± 0.21	1.85 ± 0.28	1.05 ± 0.15	0.57 ± 0.1
10 μM	0.675 ± 0.12	0.85 ± 0.18	0.7 ± 0.12	0.42 ± 0.085
30 μM	1.15 ± 0.45	0.97 ± 0.23	1.27 ± 0.047	0.9 ± 0.17
100 μM	2.47 ± 0.78	1.2 ± 0.29	1.67 ± 0.31	1.15 ± 0.23
300 μM	3.55 ± 0.67	0.8 ± 0.24	2.05 ± 0.26 [a]	1.25 ± 0.18
Phenylephrine plus metoprolol				
Control	3.4 ± 0.82	2.4 ± 0.48	1.75 ± 0.62	1 ± 0.34
10 μM	0.5 ± 0.057	0.45 ± 0.095	0.67 ± 0.22	0.6 ± 0.16
30 μM	0.7 ± 0.17	0.5 ± 0.12	1.05 ± 0.2	0.87 ± 0.12
100 μM	0.9 ± 0.31	0.65 ± 0.21	1.3 ± 0.17	1.27 ± 0.27
300 μM	1.65 ± 0.17	1.15 ± 0.18	1.65 ± 0.29	1.5 ± 0.34
Forskolin				
Control	9.75 ± 2.28	6.37 ± 2.01	3.75 ± 0.47	2.12 ± 0.31
0.1 μM	0.55 ± 0.26	0.55 ± 0.26	2.05 ± 0.36 [b]	1.82 ± 0.36
0.3 μM	2.05 ± 0.36	2.9 ± 0.8	3.8 ± 1.06	3.2 ± 0.89
1 μM	5.9 ± 0.98	5.42 ± 1.78	12.5 ± 2.95 [a]	9.2 ± 2.79
3 μM	8.35 ± 0.94	5.4 ± 1.82	15.9 ± 3.0 [a]	9.5 ± 3.12

Note that the control values are absolute values (mN/s) and experimental values are the changes from the control values.
[a] $P < 0.05$; [b] $P < 0.01$; significant differences between corresponding values. Mean ± S.E.M. from 5 to 6 experiments.

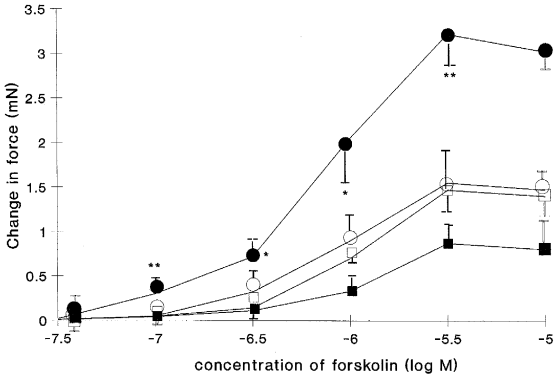

Fig. 3. Effects of forskolin on contractile force of isolated electrically paced guinea-pig papillary muscle alone (○), after pretreatment with 1 μM rimalkalim (●), after pretreatment with 0.2 μM thapsigargin (□) and after pretreatment with rimalkalim plus thapsigargin (■). * $P < 0.05$; ** $P < 0.01$; significant differences to the effects of forskolin alone (*t*-test and Newman–Keuls test). Each point represents mean ± S.E.M. from 5–6 experiments.

0.1) with a maximum increase in $F_c = 1.55 \pm 0.53$ mN and caused a maximum increase in $+dF/dt = 8.35 \pm 0.94$ mN/s and $-dF/dt = 5.4 \pm 1.82$ mN/s, above the control values. Pretreatment with rimalkalim significantly enhanced the effectiveness and potency ($pD_2 = 6.68 \pm 0.18$, $r = 0.95$, slope $= 1.58 \pm 0.29$, $P < 0.05$) of forskolin (Fig. 3 and Table 1). Addition of 0.2 μM of thapsigargin, a selective blocker of the Ca^{2+}-ATP-ase of cardiac sarcoplasmic reticulum, 10 min before forskolin, reversed the influence of rimalkalim on the effects of forskolin ($pD_2 = 6.05 \pm 0.18$, $r = 0.92$, slope $= 0.44 \pm 0.1$, $P < 0.05$, compared with the effects of forskolin after pretreatment with rimalkalim alone). Under such a condition, instead of potentiation, rimalkalim pretreatment induced slight but statistically insignificant attenuation of the forskolin-positive inotropic effects. Also, thapsigargin itself did not have a significant effect on the contractile response of guinea-pig papillary muscle to forskolin (Fig. 3 and Table 1). Additionally, the time to peak contraction (t_{tp}) and duration of contraction at 10% or more of the total amplitude ($t_{t_{10}}$) were measured. Forskolin induced a shortening of the t_{tp} and $t_{t_{10}}$ from 60.01 ± 4.57 to 47.51 ± 3.23 ms, $P < 0.05$ and from 129.4 ± 7.38 to 91.315 ± 6.31 ms, $P < 0.05$, respectively, $n = 5$. Pretreatment with rimalkalim (which itself had no significant effect on the t_{tp} and $t_{t_{10}}$ duration) prevented the shortening of the t_{tp} by forskolin but the duration of contraction at 10% or more of total amplitude was decreased (from 102.5 ± 7.5 to 81.26 ± 8.06 ms, $P < 0.05$, $n = 5$). In the presence of thapsigargin the effects of forskolin alone and after pretreatment with rimalkalim on the t_{tp} and $t_{t_{10}}$ were abolished.

Thapsigargin itself decreased the F_c (from 0.27 ± 0.025 to 0.17 ± 0.01 mN, $P < 0.05$) $+dF/dt$ (from 1.27 ± 0.33 to 0.6 ± 0.2 mN/s, $P < 0.05$) and $-dF/dt$ (from 0.7 ± 0.19 to 0.35 ± 0.15 mN/s, $P < 0.05$) and prolonged the t_{tp} from 73 ± 5.38 to 89.39 ± 6.11 ms, $P < 0.01$ without having a significant effect on $t_{t_{10}}$. Rimalkalim induced concentration-dependent negative inotropic effects which were competitively attenuated by glibenclamide, as it has been shown previously in our laboratory (Kocić, 1994; Kocić and Siluta, 1995). In the presence of higher concentrations of rimalkalim (up to 10 μM), the changes in contractility induced by dibutyryl cAMP, phenylephrine and forskolin were not significantly different compared to those obtained after pretreatment with 1 μM rimalkalim. Glibenclamide (1 μM), a well-known blocker of K_{ATP} channels, added with rimalkalim prevented the influence of rimalkalim on the effects of phenylephrine and forskolin (data not shown because they were almost identical to the data obtained without rimalkalim).

4. Discussion

This study supports and extends the previous one performed in our laboratory. Namely, it has been demonstrated that activation of K_{ATP} channels in the guinea-pig papillary muscle strongly attenuates the positive inotropic effect of isoprenaline, potentiates the effects of digoxin and milrinone and has no influence on the contractile response to amrinone and pimobendan (Kocić, 1996). It was postulated that the β-adrenoceptor signalling pathway was affected as an explanation for the action of isoprenaline under such conditions. The potentiation of the effects of digoxin and milrinone was probably due to their ability to release calcium ions from the sarcoplasmic reticulum (Holmberg and Williams, 1991; McGarry and Williams, 1993). The results reported in this paper confirm our hypothesis that activation of K_{ATP} channels modulates the contractile response of guinea-pig papillary muscle. While the positive inotropic effects of dibutyryl cAMP and phenylephrine in the presence of metoprolol were not affected significantly by the pretreatment with rimalkalim, the effects of phenylephrine were strongly attenuated and the effects of forskolin strongly potentiated. Glibenclamide, a known inhibitor of K_{ATP} channels in the heart (Venkatesh et al., 1991), added with rimalkalim, prevented the above-mentioned effects of rimalkalim on the action of phenylephrine and forskolin. The analysis of the concentration–responses curves for phenylephrine and phenylephrine in the presence of metoprolol showed clearly that this compound can stimulate not only α-adrenoceptors, but also β_1-adrenoceptors. Activation of K_{ATP} channels by rimalkalim significantly attenuated only the effects of the higher concentrations of phenylephrine (β-adrenoceptor-mediated effects). Also, it is worth stressing that the effects of phenylephrine in the presence of metoprolol (α-adrenoceptor-mediated effects) on the contractility of guinea-pig papillary muscle were almost the same as the effects of phenylephrine after pretreatment with rimalkalim. However, the precise mechanism by which activation

of K_{ATP} channels disturbs the β-adrenoceptor signalling pathway is unclear. A possible explanation is interference with the β-adrenoceptors coupling to G_s protein, because in this study activation of K_{ATP} channels did not significantly affect the effects of dibutyryl cAMP or potentiated the effects of forskolin. Further, it has been shown previously that congestive heart failure affects the coupling between β-adrenoceptors and G_s proteins in the heart (Horn and Bilezikian, 1990; Brodde, 1993). The results of this study suggest that activation of K_{ATP} channels, which takes place during ischaemia in the heart (Hearse, 1995), could be responsible for this phenomenon. Also, the previously reported domination of α-adrenoceptor effects in the failing myocardium (Bristow et al., 1988; Billman, 1994) can be at least partially explained by the favourable influence of activation of K_{ATP} channels on this pathway, as shown by our results. However, the action potential shortening due to the activation of K_{ATP} channels by rimalkalim and the consequently smaller Ca^{2+} influx could also explain the attenuation of the effects of phenylephrine and isoprenaline (Kocić, 1996) after pretreatment with rimalkalim. But, this hypothesis can not explain the different influence of pretreatment with rimalkalim on the effects of isoprenaline and phenylephrine (attenuation), dibutyryl cAMP, phenylephrine + metoprolol, amrinone and pimobendan (lack of influence) and forskolin, digoxin and milrinone (potentiation). Also, one must remember that the relation between the duration of action potential and force of contraction is not simple.

Forskolin, a known activator of adenylate cyclase, had a stronger potency and efficacy than dibutyryl cAMP and phenylephrine. Additionally, the pretreatment with rimalkalim enhanced significantly the contractile response of papillary muscle to forskolin. This potentiation of the effects of forskolin after activation of K_{ATP} channels was affected by the application of thapsigargin, a known inhibitor of Ca^{2+} ATP-ase in cardiac sarcoplasmic reticulum (Kirby et al., 1992; Wrzosek et al., 1992). Thapsigargin itself had a slight negative inotropic action and significantly prolonged the time to peak contraction, which is in accordance with recent data (Lewartowski et al., 1994). What is more, thapsigargin prevented the influence of forskolin on the t_{tp} and $t_{t_{10}}$ duration without changing the force of contraction. These results suggest that only forskolin, but not isoprenaline, dibutyryl cAMP or phenylephrine, has a unique action which probably involves direct activation of Ca^{2+} ATP-ase in the cardiac sarcoplasmic reticulum. It is interesting that pretreatment with rimalkalim prevented the increase in the velocity of contraction but not the relaxation induced by phenylephrine. Further, only the shortening of the t_{tp} but not $t_{t_{10}}$ duration induced by forskolin was prevented by previous addition of rimalkalim. These results suggest that selective inhibition of Ca^{2+} release but not Ca^{2+} reuptake from the sarcoplasmic reticulum occurs during activation of K_{ATP} channels in the guinea-pig papillary muscle.

In conclusion, the activation of K_{ATP} channels in the guinea-pig papillary muscle by rimalkalim caused significant attenuation of the contractile response to higher concentrations of phenylephrine, strong potentiation of the forskolin-induced effects but had no influence on the effects of dibutyryl cAMP and phenylephrine + metoprolol. Further investigation is necessary in order to determine the precise mechanisms involved in modulation of myocardial contractility by activation of K_{ATP} channels.

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