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Inhibitory Effects of Lidocaine and Mexiletine on Vasorelaxation Mediated by Adenosine Triphosphate–sensitive K^+ Channels and the Role of Kinases in the Porcine Coronary Artery

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Background: **Effects of antiarrhythmic drugs on coronary vasodilation mediated by K^+ channels have not been studied. Modulator roles of protein kinase C and tyrosine kinase in the activity of K^+ channels have also been unclear in the coronary artery. The current study examined whether lidocaine and mexiletine in the porcine coronary artery modify the vasorelaxation mediated by adenosine triphosphate–sensitive K^+ channels *via* activation of protein kinase C and tyrosine kinase.**

Methods: **Porcine coronary arteries without endothelium were suspended for isometric force recording, and vasorelaxation to levcromakalim (10^{-8} to 10^{-5} M) was obtained. Changes in membrane potentials produced by levcromakalim (10^{-5} M) were also recorded.**

Results: **Glibenclamide completely abolished vasorelaxation as well as hyperpolarization in response to levcromakalim. Lidocaine and mexiletine significantly reduced these responses. Calphostin C, Gö 6976, genistein, and erbstatin A partly restored vasorelaxation or hyperpolarization in response to levcromakalim in arteries treated with mexiletine but not in those with lidocaine, whereas these inhibitors did not alter the vasorelaxation to levcromakalim. Phorbol 12-myristate 13-acetate produced reduction of vasorelaxation in response to levcromakalim, which is recovered by calphostin C or Gö 6976.**

Conclusions: **Therefore, lidocaine and mexiletine inhibit vasorelaxation mediated by the activation of adenosine triphosphate–sensitive K^+ channels in the coronary artery. Protein kinase C and tyrosine kinase seem to have roles in the inhibitory effect of mexiletine but not in that of lidocaine. Class Ib antiarrhythmic drugs may reduce coronary vasodilation mediated by adenosine triphosphate–sensitive K^+ channels *via* the differential modulator effects on these kinases.**

INCREASING evidence suggests that adenosine triphosphate–sensitive K^+ (K_{ATP}) channels have important roles in physiologic and pathophysiologic vasodilation.[1] Importantly, these channels contribute to the regulation of coronary blood flow as well as cardiac preconditioning effects toward myocardial ischemia.[2,3] Recent studies on blood vessels have documented that intracellular second messengers protein kinase C and tyrosine kinase in smooth muscle cells modulate the activity of K_{ATP} channels.[4–6] However, whether these kinases modify the vasodilation mediated by K_{ATP} channels in the coronary circulation has not been studied.

Class Ib antiarrhythmic drugs lidocaine and mexiletine are frequently administered to ameliorate cardiac ventricular arrhythmias in clinical settings. Although our recent study in the rat aorta has documented that these drugs modify vasorelaxation mediated by K_{ATP} channels,[7] the effects of antiarrhythmic drugs on coronary vasodilation mediated by K^+ channels have not been determined. It is also unclear whether these antiarrhythmic drugs modulate membrane potential of vascular smooth muscle cells produced by the activation of K^+ channels. In addition, the mechanisms of modulator effects of these compounds on vasorelaxation mediated by K_{ATP} channels are still unknown.

Therefore, the current study was designed to examine whether lidocaine and mexiletine in the porcine coronary artery modulate the vasorelaxation *via* hyperpolarization mediated by ATP-sensitive K^+ channels and whether the modulation of these compounds is due to the activation of protein kinase C as well as tyrosine kinase.

Materials and Methods

The institutional animal care and use committee (Wakayama University, Wakayama, Japan) approved this study. Adult pig hearts were obtained from a slaughterhouse immediately after death and put in ice-cold modified Krebs-Ringer's bicarbonate solution (control solution, pH 7.4) of the following composition: 119 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.17 mM $MgSO_4$, 1.18 mM KH_2PO_4, 25 mM $NaHCO_3$, and 11 mM glucose. The left descending coronary artery was dissected and cut into 2-mm-length rings. Endothelial cells were removed mechanically to avoid the modification mediated by endothelium-derived nitric oxide as well as endothelium-derived hyperpolarizing factor.

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Organ Chamber Experiments

Each ring was connected to an isometric force transducer and suspended in an organ chamber filled with 10 ml control solution (37°C) bubbled with a 95% O_2–5% CO_2 gas mixture. The artery was gradually stretched to the optimal point of its length–tension curve as determined by the contraction to a prostaglandin H_2/thromboxane receptor agonist, U46619 (10^{-7} M). Optimal tension was achieved at approximately 3.0 g. Several rings cut from same artery were studied in parallel. The endothelial removal was evaluated by the absence of relaxation induced by bradykinin (10^{-6} M). During submaximal contraction in response to U46619 (10^{-7} M), concentration–response curves to levcromakalim (10^{-8} to 10^{-5} M) were obtained in the absence or in the presence of glibenclamide, lidocaine, mexiletine, phorbol 12-myristate 13-acetate (PMA), calphostin C, Gö 6976, genistein and/or erbstatin A, which were added 15 min before the contraction to U46619. In some experiments, these compounds for pretreatment were used as combination. The vasorelaxation was expressed as a percentage of the maximal relaxation in response to papaverine (3×10^{-4} M), which was added at the end of the experiments to produce the maximal relaxation (100%) of arteries.[7]

Electrophysiologic Experiments

Arterial rings were longitudinally cut and fixed on the bottom of an experimental chamber. The arteries were continuously perfused with control solution (37°C) bubbled with a 95% O_2–5% CO_2 gas mixture. A glass microelectrode (tip resistance 40–80 MΩ) filled with 3 M KCl and held by a micromanipulator (Narishige, Tokyo, Japan), was inserted into a smooth muscle cell from the intimal side of the vessel.[8,9] The electrical signal was amplified using a recording amplifier (Electro 705; World Precision Instruments Inc., Sarasota, FL). The membrane potential was continuously monitored and recorded on a chart recorder (SS-250F-1; SENKONIC Inc., Tokyo, Japan). The validity of a successful impalement was assessed by a sudden negative shift followed by a stable negative voltage for more than 2 min.[8,9] As previous studies demonstrated, resting membrane potential of vascular smooth muscle cells obtained using this technique was approximately −40 mV.[10] Changes in membrane potentials produced by levcromakalim (10^{-5} M) were continuously recorded. Glibenclamide, lidocaine, mexiletine, calphostin C, or erbstatin A was applied 15 min before membrane potential recordings.

Drugs

Levcromakalim was a generous gift from GlaxoSmithKline plc (Greenford, United Kingdom), and calphostin C, dimethyl sulfoxide, erbstatin A, genistein, glibenclamide, Gö 6976, lidocaine, mexiletine, papaverine, PMA, and U46619 were purchased from Sigma (St. Louis, MO). Stock solutions of levcromakalim, glibenclamide, PMA, calphostin C, Gö 6976, genistein, and erbstatin A were prepared in dimethyl sulfoxide (3×10^{-4} M), and other drugs were dissolved in distilled water.

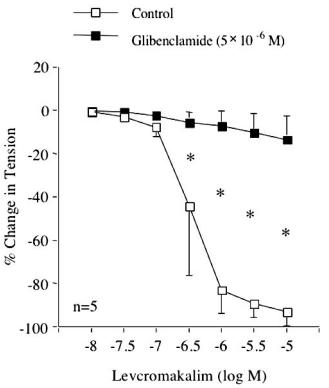

Fig. 1. Concentration–response curves to levcromakalim (10^{-8} to 10^{-5} M) in the absence or in the presence of glibenclamide (5×10^{-6} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with glibenclamide is statistically significant ($P < 0.05$).

Statistical Analysis

Data are expressed as mean ± SD. Statistical analysis was performed using repeated-measures analysis of variance followed by Scheffé F test for multiple comparison. Differences were considered to be statistically significant when P was less than 0.05.

Results

Organ Chamber Experiments

During submaximal contraction to U46619 (10^{-7} M), a selective K_{ATP} channel opener, levcromakalim (10^{-8} to 10^{-5} M) induced concentration-dependent relaxation in the porcine coronary artery without endothelium (fig. 1). A selective K_{ATP} channel antagonist, glibenclamide, completely abolished this vasorelaxation (fig. 1), whereas it did not affect the basal tone of the coronary artery. Maximal vasorelaxation induced by papaverine (3×10^{-4} M) in each group in figure 1 was 100% = 4.89 ± 1.28 or 4.24 ± 2.73 g for control rings and rings treated with glibenclamide, respectively (statistically insignificant).

Lidocaine and mexiletine (10^{-5} to 10^{-4} M) significantly reduced vasorelaxation in response to levcromakalim in a concentration-dependent fashion (fig. 2). Maximal vasorelaxation induced by papaverine (3×10^{-4} M) in each group in figure 2 (left) was 100% = 5.00 ± 1.05, 5.15 ± 2.17, 5.40 ± 2.17, or 4.85 ± 1.25 g for control rings and rings treated with 10^{-5} M, 3×10^{-5} M, or 10^{-4} M lidocaine, respectively (statistically insignificant), and that in each group in figure 2 (right) was 100% = 4.75 ± 1.50, 5.64 ± 1.77, 4.65 ± 1.16, or 4.58 ± 1.07 g for control

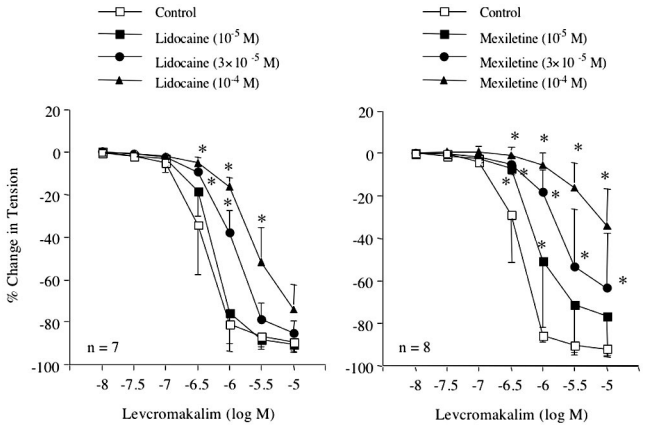

Fig. 2. Concentration–response curves to levcromakalim in the absence or in the presence of lidocaine or mexiletine (10^{-5}, 3×10^{-5}, 10^{-4} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with lidocaine or mexiletine is statistically significant ($P < 0.05$).

rings and rings treated with 10^{-5} M, 3×10^{-5} M, or 10^{-4} M mexiletine, respectively (statistically insignificant).

Protein kinase C inhibitors calphostin C (3×10^{-7} M) and Gö 6976 (3×10^{-7} M) partly restored vasorelaxation in response to levcromakalim in the coronary arteries treated with mexiletine (10^{-4} M) (figs. 3 and 4). In contrast, in arteries treated with lidocaine (10^{-4} M), these protein kinase C inhibitors did not produce any statistically significant effects on vasorelaxation, although we noticed a tendency for Gö 6976 to recover vasorelaxation to levcromakalim (figs. 3 and 4). These inhibitors themselves did not alter the vasorelaxation produced by levcromakalim (figs. 3 and 4). A phorbol ester, PMA (3×10^{-6} M), impaired vasorelaxation in response to levcromakalim, which is completely recovered by calphostin C (3×10^{-7} M) or Gö

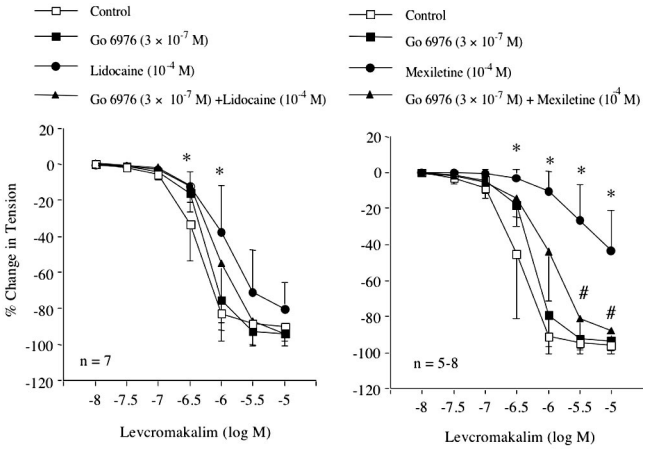

Fig. 3. Concentration–response curves to levcromakalim in the absence or in the presence of lidocaine or mexiletine (10^{-4} M) in combination with Gö 6976 (3×10^{-7} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with lidocaine or mexiletine is statistically significant ($P < 0.05$). Only in the arteries treated with mexiletine, Gö 6976 significantly restored vasorelaxation induced by levcromakalim (# $P < 0.05$).

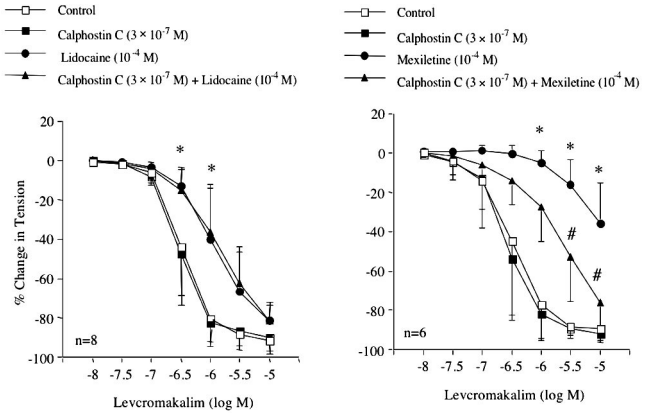

Fig. 4. Concentration–response curves to levcromakalim in the absence or in the presence of lidocaine or mexiletine (10^{-4} M) in combination with calphostin C (3×10^{-7} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with lidocaine or mexiletine is statistically significant ($P < 0.05$). Only in the arteries treated with mexiletine, calphostin C significantly restored vasorelaxation induced by levcromakalim (# $P < 0.05$).

6976 (3×10^{-7} M) (fig. 5). Maximal vasorelaxation induced by papaverine (3×10^{-4} M) in each group in figure 3 (left) was 100% = 5.04 ± 0.97, 4.47 ± 1.16, 4.59 ± 0.99, or 4.40 ± 1.08 g for control rings and rings treated with Gö 6976, lidocaine, or Gö 6976 plus lidocaine, respectively (statistically insignificant), and that in each group in figure 3 (right) was 100% = 4.63 ± 1.60, 4.6 ± 1.14, 4.25 ± 0.89, or 5.25 ± 1.39 g for control rings and rings treated with Gö 6976, mexiletine, or Gö 6976 plus mexiletine, respectively (statistically insignificant). Maximal vasorelaxation induced by papaverine in each group in figure 4 (left) was 100% = 5.23 ± 1.67, 3.97 ± 1.46, 3.74 ± 1.21, or 4.51 ± 2.19 g for control rings and rings treated with calphostin C, lidocaine, or calphostin C plus lidocaine, respectively (statistically insignificant), and that in each group in figure 4 (right) was 100% = 3.58 ± 1.52, 3.82 ± 0.92, 4.23 ± 0.53, or 3.26 ±

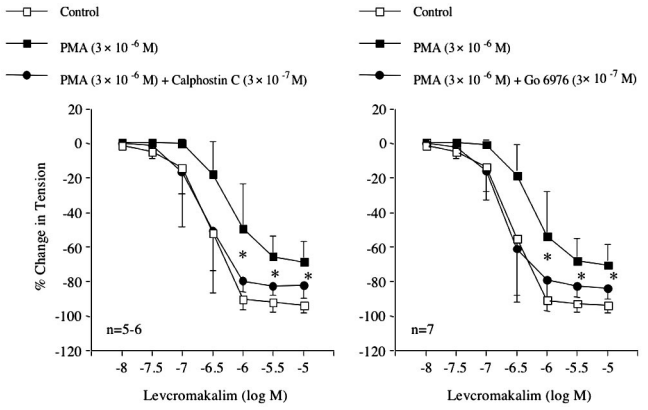

Fig. 5. Concentration–response curves to levcromakalim in the absence or in the presence of phorbol 12-myristate 13-acetate (PMA, 3×10^{-6} M) in combination with calphostin C (3×10^{-7} M) or Gö 6976 (3×10^{-7} M), obtained in the porcine coronary artery without endothelium. * Differences between rings treated with PMA and control rings or rings treated with PMA in combination with calphostin C or Gö 6976 are statistically significant ($P < 0.05$).

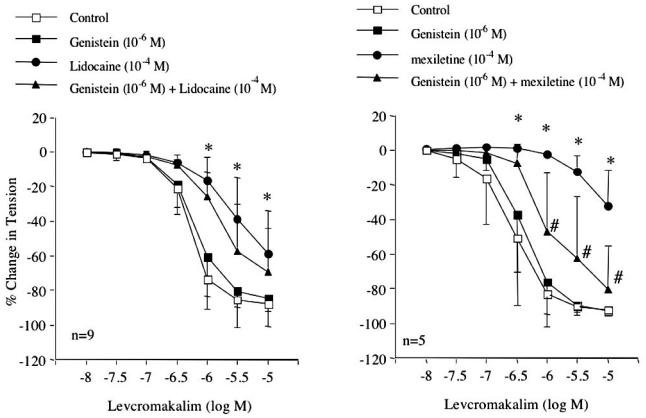

Fig. 6. Concentration–response curves to levcromakalim in the absence or in the presence of lidocaine or mexiletine (10^{-4} M) in combination with genistein (10^{-6} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with lidocaine or mexiletine is statistically significant ($P < 0.05$). Only in the arteries treated with mexiletine, genistein significantly restored vasorelaxation induced by levcromakalim (# $P < 0.05$).

1.18 g for control rings and rings treated with calphostin C, mexiletine, or calphostin C plus mexiletine, respectively (statistically insignificant). Maximal vasorelaxation in each group in figure 5 (left) was 100% = 5.67 ± 0.82, 4.67 ± 0.82, or 5.00 ± 0.71 g for control rings and rings treated with PMA or PMA plus calphostin C, respectively (statistically insignificant), and that in each group in figure 5 (right) was 100% = 5.57 ± 0.79, 4.71 ± 0.76, or 4.43 ± 1.27 g for control rings and rings treated with PMA or PMA plus Gö 6976, respectively (statistically insignificant).

Genistein (10^{-6} M) and erbstatin A (3×10^{-6} M) partly restored vasorelaxation in response to levcromakalim in the coronary arteries treated with mexiletine (10^{-4} M) but not in those treated with lidocaine (10^{-4} M), whereas these inhibitors did not alter vasorelaxation (figs. 6 and 7). Maximal vasorelaxation induced by papaverine (3×10^{-4} M) in each group in figure 6 (left) was 100% = 4.47 ± 1.25, 3.91 ± 1.38, 3.71 ± 0.99, or 4.27 ± 1.31 g for control rings and rings treated with genistein, lidocaine, or genistein plus lidocaine, respectively (statistically insignificant), and that in each group of figure 6 (right) was 100% = 4.00 ± 1.26, 3.59 ± 1.62, 4.21 ± 0.59, or 4.93 ± 1.08 g for control rings and rings treated with genistein, mexiletine, or genistein plus mexiletine, respectively (statistically insignificant). Maximal vasorelaxation in each group in figure 7 (left) was 100% = 5.58 ± 1.57, 5.01 ± 1.17, 4.55 ± 1.10, or 4.78 ± 1.91 g for control rings and rings treated with erbstatin A, lidocaine, or erbstatin A plus lidocaine, respectively (statistically insignificant), and that in each group in figure 7 (right) was 100% = 3.91 ± 0.84, 4.38 ± 1.31, 4.11 ± 0.58, or 3.70 ± 1.25 g for control rings and rings treated with erbstatin A, mexiletine, or erbstatin A plus mexiletine, respectively (statistically insignificant).

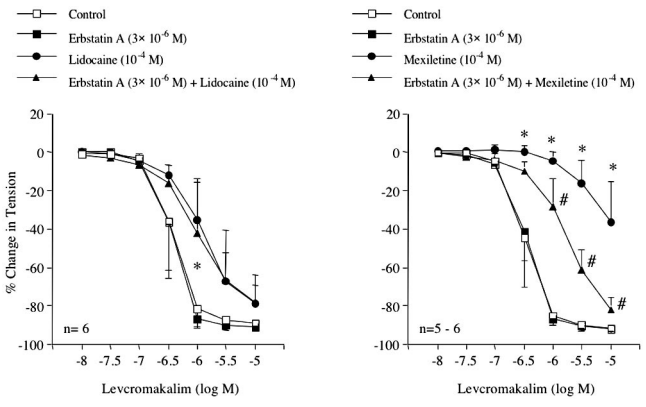

Fig. 7. Concentration–response curves to levcromakalim in the absence or in the presence of lidocaine or mexiletine (10^{-4} M) in combination with erbstatin A (3×10^{-6} M), obtained in the porcine coronary artery without endothelium. * Difference between control rings and rings treated with lidocaine or mexiletine is statistically significant ($P < 0.05$). Only in the arteries treated with mexiletine, erbstatin A significantly restored vasorelaxation induced by levcromakalim (# $P < 0.05$).

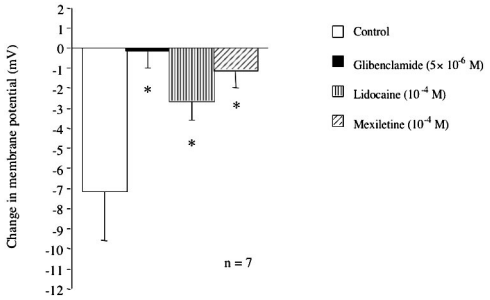

Fig. 8. Changes in membrane potential of smooth muscle cells in the porcine coronary artery induced by levcromakalim (10^{-5} M). Levcromakalim-induced hyperpolarization is significantly reduced by glibenclamide (5×10^{-6} M), lidocaine (10^{-4} M), or mexiletine (10^{-4} M), respectively (* $P < 0.05$).

Electrophysiologic Experiments

Levcromakalim (10^{-5} M) produced hyperpolarization of smooth muscle cells of the coronary artery, which is abolished by glibenclamide (5×10^{-6} M) and reduced by lidocaine (10^{-4} M) as well as mexiletine (10^{-4} M) (fig. 8). In the arteries treated with mexiletine (10^{-4} M) but not lidocaine (10^{-4} M), levcromakalim-induced hyperpolarization is significantly restored by calphostin C (3×10^{-7} M) as well as by erbstatin A (3×10^{-6} M) (fig. 9). Resting membrane potentials did not differ among the groups shown in figures 8 and 9 (for fig. 8: control, −40.1 ± 6.4 mV; glibenclamide [5×10^{-6} M], −45.7 ± 4.1 mV; lidocaine [10^{-4} M], −40.7 ± 6.8 mV; mexiletine [10^{-4} M], −43.1 ± 6.4 mV; for fig. 9: lidocaine [10^{-4} M], −37.2 ± 6.1 mV; calphostin C [3×10^{-7} M] plus lidocaine [10^{-4} M], −35.2 ± 4.2 mV; erbstatin A [3×10^{-6} M] plus lidocaine [10^{-4} M], −32.8 ± 2.2 mV; mexiletine [10^{-4} M], −40.6 ± 6.8 mV; calphostin C [3×10^{-7} M] plus mexiletine [10^{-4} M], −36.2 ± 1.1 mV; erbstatin A [3×10^{-6} M] plus lidocaine [10^{-4} M], −37.0 ± 1.9 mV).

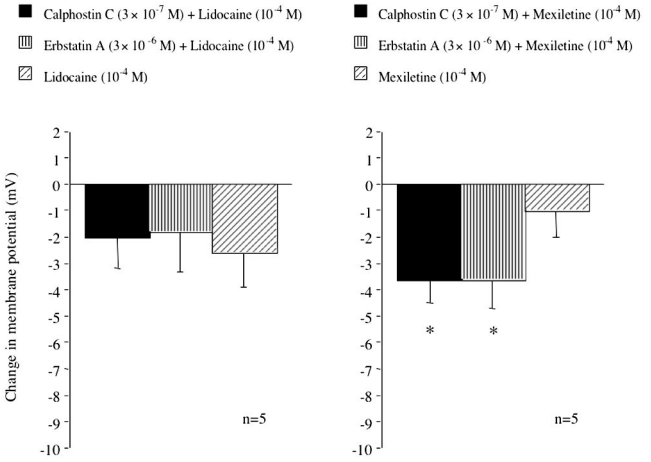

Fig. 9. Changes in membrane potential of smooth muscle cells in the porcine coronary artery induced by levcromakalim (10^{-5} M). In the arteries treated with mexiletine (10^{-4} M) but not lidocaine (10^{-4} M), levcromakalim-induced hyperpolarization is significantly restored by calphostin C (3×10^{-7} M) as well as erbstatin A (3×10^{-6} M) (* $P < 0.05$).

Discussion

Role of K_{ATP} Channels in the Coronary Circulation

In the coronary artery, glibenclamide (5×10^{-6} M) abolished vasorelaxation as well as hyperpolarization in response to levcromakalim (10^{-5} M), indicating that both compounds probably act on K_{ATP} channels.[11,12] In the current study, we used this concentrations of glibenclamide because, in some specific blood vessel preparations, including rabbit portal veins and cultured aortic smooth muscle cells from neonatal rats, glibenclamide usually above 10^{-5} M may produce somewhat nonselective effects on ion channels other than K_{ATP} channels,[13,14] and previous studies have demonstrated that higher concentration of glibenclamide ($> 10^{-5}$ M) is needed to completely block K_{ATP} channels in the vascular smooth muscle cell.[15] However, it is important to note that 10^{-5} M glibenclamide or levcromakalim has been used as the selective antagonist and the opener of K_{ATP} channels in electrophysiologic studies on vascular smooth muscle cells, including those from the porcine coronary artery.[16,17] In the current study, glibenclamide did not produce any effects on the basal tension and contraction in response to a prostaglandin H_2/thromboxane receptor agonist, indicating that at least in the pig, K_{ATP} channels may contribute to neither the resting tone nor vasocontraction to an agonist acting *via* receptors in the coronary circulation. In contrast to this finding, a recent human study has documented that direct administration of glibenclamide to the large coronary artery during percutaneous coronary intervention provokes reduction of resting vessel diameter, suggesting that in humans, these channels may modulate resting tone of the large coronary artery.[5] We cannot rule out the possible involvement of species differences in the differential role of K_{ATP} channels in the coronary circulation.

Involvement of Protein Kinase C in the Regulation of Coronary Vasodilation Mediated by K_{ATP} Channels and the Effects of Class Ib Antiarrhythmic Drugs

In the current study, a phorbol ester, PMA, impaired vasorelaxation in response to levcromakalim, which is completely recovered by selective inhibitors of protein kinase C, calphostin C, and Gö 6976. Calphostin C or Gö 6976 reportedly acts on regulatory and catalytic domains of protein kinase C, respectively, and the former has wide-range effects on protein kinase C isozymes, whereas the latter shows rather limited effects, especially on α and β_1 isozymes.[18,19] Therefore, our results indicate that the activation of α and β_1 isozymes of protein kinase C may have a role in the inhibitory effects of PMA in the vasorelaxation mediated by K_{ATP} channels in the porcine coronary artery. Previous studies have documented the expression of these subtypes of protein kinase C in arterial smooth muscle cells of the porcine coronary.[20] In the current study, inhibitors of protein kinase C themselves did not affect vasorelaxation produced by levcromakalim, also supporting the conclusion that the nonselective inhibitory effects of kinase inhibitors in our experimental condition are negligible. Our results are in accord with those of previous studies on the cerebral arteries, portal veins, and mesenteric arteries showing that the activation of protein kinase C inhibits vasorelaxation as well as currents *via* K_{ATP} channels.[4,21–26]

Class Ib antiarrhythmic drugs lidocaine and mexiletine attenuated vasorelaxation as well as hyperpolarization in response to levcromakalim in a concentration-dependent fashion, suggesting that these compounds may impair coronary vasodilation mediated by the activation of K_{ATP} channels. Our previous studies on the rat aorta demonstrated the inhibitory effect of lidocaine as well as augmenting effects of mexiletine on the vasorelaxation induced by K_{ATP} channel openers.[7] We do not have a clear explanation of these differential effects of lidocaine and mexiletine on the vasorelaxation mediated by K_{ATP} channels between the coronary and the aorta. However, it is most likely that species as well as regional differences contribute to the differential affects of antiarrhythmic drugs.

In the porcine coronary artery, selective protein kinase C inhibitors calphostin C and Gö 6976 similarly restored vasorelaxation or hyperpolarization in response to levcromakalim in the coronary arteries treated with mexiletine but not in those treated with lidocaine. Mutual targets of the protein kinase C isozyme for calphostin C and Gö 6976 are reportedly α and β_1 isozymes, and a protein kinase C activator similarly impaired vasorelaxation in response to levcromakalim, which is completely recovered by these inhibitors.[18,19] Therefore, it is natural to speculate that protein kinase C α and β_1 isozymes may contribute to the inhibitory effect of mexiletine but not

that of lidocaine on the activity of K_{ATP} channels in the coronary artery.

The K_{ATP} channel is a complex of two proteins: the sulfonylurea receptor (SUR) and the pore forming subunit, which belongs to the inward rectifier K^+ channel (Kir) family.[27] Because recent direct functional and biochemical studies have revealed that the SUR of K_{ATP} channel is a primary target of the channel openers, the action of lidocaine and mexiletine on some components of SUR may have a role in these inhibitory effects.[28] In addition to this assumption, recent electrophysiologic studies have documented that activation of protein kinase C is capable of modulating the limited subtype of K_{ATP} channel expressed in vascular smooth muscle cells (SUR 2B + Kir6.1).[29,30] More importantly, the activity of the channel subtypes produced by SUR 2B and Kir6.2 was not altered by the kinase, suggesting the crucial role of the Kir6.1 compartment of K_{ATP} channels in the modulator effect of protein kinase C.[25] Therefore, mexiletine but not lidocaine may modulate Kir6.1 compartment of K_{ATP} channels, leading to the inhibition of vasorelaxation mediated by these channels in the coronary artery. However, further electrophysiologic studies using mutation for each compartment in these channels are needed to clarify the exact mechanisms of class Ib antiarrhythmic drugs on K_{ATP} channels.

Involvement of Tyrosine Kinase in the Effects of Class Ib Antiarrhythmic Drugs in Coronary Vasodilation Mediated by K_{ATP} Channels

Genistein and erbstatin A restored vasorelaxation or hyperpolarization in response to levcromakalim in the coronary arteries treated with mexiletine but not in those treated with lidocaine. Because previous studies demonstrated that these inhibitors, in the concentrations used in the current study, can be administered as inhibitors of tyrosine kinase, our results indicate that activation of tyrosine kinase may also contribute to the inhibitory effect of mexiletine but not that of lidocaine.[31–33] Previous studies on cerebral arteries and the portal vein demonstrated that protein tyrosine phosphorylation modulates the activity of K_{ATP} channels.[6,34,35] The evidence that neither inhibitors of tyrosine kinase solely alter vasorelaxation produced by levcromakalim seems to neglect the nonselective inhibitory effects of kinase inhibitors in our experimental condition. These results support our conclusion that in the coronary artery, activity of tyrosine kinase may also have a role in the regulation of vasodilation mediated by K_{ATP} channels and that lidocaine and mexiletine differentially modulate this vasorelaxation. In addition, it is important to note that in the coronary artery treated with mexiletine, erbstatin A as well as calphostin C restored changes in membrane potential by approximately 3.5 mV and that in the control artery, levcromakalim produces hyperpolarization by approximately −7.0 mV. Therefore, these results may also indicate that recovery of hyperpolarization obtained by two types of kinase inhibitors in the artery treated with mexiletine is additive.

Clinical Relevancy of the Inhibitory Effects of Lidocaine and Mexiletine on Coronary Vasodilation Mediated by K_{ATP} Channels

The therapeutic ranges of plasma concentrations of lidocaine and mexiletine used as antiarrhythmic drugs were reported up to 5×10^{-5} M and 10^{-5} M for lidocaine or mexiletine, respectively.[36,37] When one considers the protein binding of these compounds, protein-unbound concentrations of these antiarrhythmic compounds should be lower than those examined in the current study. Therefore, our results may be clinically important from a toxicologic point of view. However, lidocaine and mexiletine may impair coronary vasodilation mediated by K_{ATP} channels under some specific conditions in the clinical setting, because higher free plasma concentrations of drugs, which have the capability of protein binding, were reported in diseased infants with a low α-1 acid glycoprotein.[38]

Class Ib antiarrhythmic drugs are frequently administered to treat ventricular arrhythmias, which can be seen in patients with ischemic heart disease or those receiving cardiopulmonary resuscitation.[39,40] It is well known that during hypoxia, acidosis, and ischemia, K_{ATP} channels are activated, resulting in coronary arterial dilation, increased tolerance of cardiac myocytes toward ischemia, or both.[2,3,41] In addition, these antiarrhythmic drugs can be coadministered with clinically available K_{ATP} channel openers to treat these patients.[42,43] Therefore, it may be speculated that lidocaine and mexiletine reduce these beneficial vasodilator effects *via* K_{ATP} channels, which have important roles in the regulation of coronary circulation during diverse pathophysiologic situations.

Perspectives

This is the first study examining the roles of kinases and the effects of class Ib antiarrhythmic drugs in vasodilation mediated by K_{ATP} channels in the coronary circulation. Our results have clearly shown that lidocaine and mexiletine inhibit vasorelaxation as well as hyperpolarization *via* K_{ATP} channels in the coronary artery. In addition, the activation of protein kinase C and tyrosine kinase seems to contribute to the inhibitory effect of mexiletine but not in that of lidocaine. Class Ib antiarrhythmic drugs may reduce coronary vasodilation mediated by these channels *via* the differential modulator effects on these kinases.

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