

Differential Effects of Lidocaine and Mexiletine on Relaxations to ATP-sensitive K^+ Channel Openers in Rat Aortas

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Background: In cardiac myocytes, lidocaine reduces but mexiletine increases adenosine triphosphate (ATP)-sensitive K^+ currents, suggesting that these class Ib antiarrhythmic drugs may differentially modify the activity of ATP-sensitive K^+ channels. The effects of lidocaine and mexiletine on arterial relaxations induced by K^+ channel openers have not been studied. Therefore, the current study was designed to evaluate whether lidocaine and mexiletine may produce changes in relaxations to the ATP-sensitive K^+ channel openers cromakalim and pinacidil in isolated rat thoracic aortas.

Methods: Rings of rat thoracic aortas without endothelia were suspended for isometric force recording. Concentration-response curves were obtained in a cumulative fashion. During submaximal contractions to phenylephrine (3×10^{-7} M), relaxations to cromakalim (10^{-7} to 3×10^{-5} M), pinacidil (10^{-7} to 3×10^{-5} M), or diltiazem (10^{-7} to 3×10^{-4} M) were obtained. Lidocaine (10^{-5} to 3×10^{-4} M), mexiletine (10^{-5} to 10^{-4} M) or glibenclamide (5×10^{-6} M) was applied 15 min before addition of phenylephrine.

Results: During contractions to phenylephrine, cromakalim and pinacidil induced concentration-dependent relaxations. A selective ATP-sensitive K^+ channel antagonist, glibenclamide (5×10^{-6} M), abolished these relaxations, whereas it did not alter relaxations to a voltage-dependent Ca^{2+} channel inhibitor, diltiazem (10^{-7} to 3×10^{-4} M). Lidocaine (more than 10^{-5} M) significantly reduced relaxations to cromakalim or pinacidil in a concentration-dependent fashion, whereas lidocaine (3×10^{-4} M) did not affect relaxations to diltiazem. In contrast, mexiletine (more than 10^{-5} M) significantly augmented relaxations to cromakalim or pinacidil. Glibenclamide (5×10^{-6} M)

abolished relaxations to cromakalim or pinacidil in arteries treated with mexiletine (10^{-4} M).

Conclusions: These results suggest that lidocaine impairs but mexiletine augments vasodilation mediated by ATP-sensitive K^+ channels in smooth muscle cells. (Key words: Antiarrhythmic drugs; glibenclamide; ion channels; local anesthetics; vasodilation.)

IN A number of vascular beds, adenosine triphosphate (ATP)-sensitive K^+ channels play an important role in mediation of vasodilator responses induced by physiologic and pathophysiologic stimuli.¹ ATP-sensitive K^+ channel openers are available vasodilators for the treatment of cardiovascular disorders, such as hypertension, angina pectoris, and congestive heart failures.² In *Xenopus* oocytes, class Ib antiarrhythmic drugs, lidocaine and mexiletine, can suppress ATP-sensitive K^+ currents.³ Studies of cardiac myocytes showed that lidocaine impairs the ATP-sensitive K^+ currents, whereas mexiletine augments these currents.^{4,5} These results suggest the complexity of the modulator role of these antiarrhythmic drugs in the activity of ATP-sensitive K^+ channels. The effects of lidocaine and mexiletine on arterial relaxations mediated by K^+ channels have not been studied. Therefore, the current study was designed to evaluate whether lidocaine and mexiletine may produce changes in relaxations to the ATP-sensitive K^+ channel openers cromakalim and pinacidil in isolated rat thoracic aortas.

Materials and Methods

The experiments were performed on 3-mm thoracic aortic rings obtained from male Wistar-Kyoto rats (300–350 g) anesthetized with 50 mg/kg intraperitoneal pentobarbital sodium. The study was approved by the institutional animal care and use committee. Rings were studied in modified Krebs-Ringer bicarbonate solution (control solution) of the following composition: NaCl: 118.3 mM; KCl: 4.7 mM; $CaCl_2$: 2.5 mM; $MgSO_4$: 1.2 mM; KH_2PO_4 : 1.2 mM; $NaHCO_3$: 25.0 mM; calcium EDTA:

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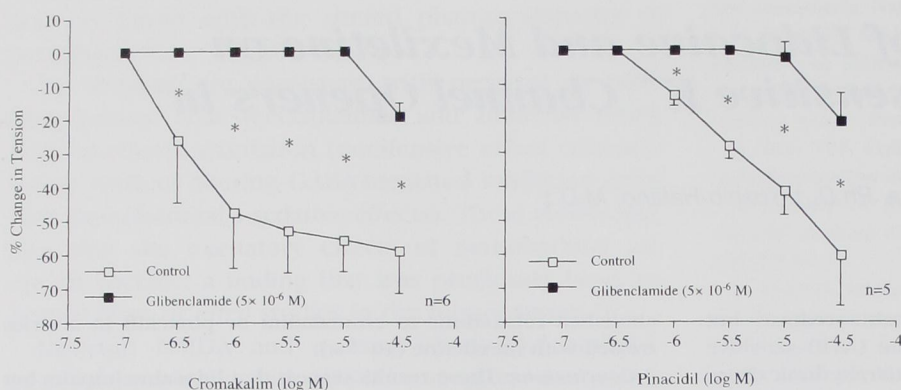


Fig. 1. Concentration-response curves to cromakalim (10^{-7} to 3×10^{-5} M) and pinacidil (10^{-7} to 3×10^{-5} M) in the absence and the presence of glibenclamide (5×10^{-6} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean \pm SD and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 753 ± 169 mg [$n = 6$] and 887 ± 114 mg [$n = 6$] for control rings of cromakalim and rings treated with glibenclamide; 100% = 840 ± 215 mg [$n = 5$] and 800 ± 198 mg [$n = 5$] for control rings of pinacidil and rings treated with glibenclamide, respectively). *Difference between control rings and rings treated with glibenclamide is statistically significant ($P < 0.05$).

0.026 mM; and glucose: 11.1 mM. In all rings, the endothelium was removed mechanically and the endothelial removal was confirmed by the absence of relaxation to acetylcholine (10^{-5} M). Several rings cut from same artery were studied in parallel. Each ring was connected to an isometric force transducer and suspended in an organ chamber filled with 25 ml control solution (37°C , pH 7.4) bubbled with 94% oxygen-6% carbon dioxide gas mixture. The artery was gradually stretched to the optimal point of its length-tension curve as determined by the contraction to phenylephrine (3×10^{-7} M). In most of the studied arteries, optimal tension was achieved approximately at 1.5 g. Preparations were equilibrated for 90 min. During submaximal contractions to phenylephrine (3×10^{-7} M), concentration-response curves to cromakalim (10^{-7} to 3×10^{-5} M), pinacidil (10^{-7} to 3×10^{-5} M), or diltiazem (10^{-7} to 3×10^{-4} M) were obtained in the absence or the presence of lidocaine, mexiletine, or glibenclamide. Concentration-response curves were obtained in a cumulative fashion. Only one concentration-response curve was made from each ring. Lidocaine, mexiletine, or glibenclamide was given 15 min before addition of phenylephrine (3×10^{-7} M). The relaxations were expressed as a percentage of the maximal relaxations to papaverine (3×10^{-4} M), which was added at the end of experiments to produce maximal relaxation (100%) of the arteries.

Drugs

The following pharmacologic agents were used: cromakalim, diltiazem hydrochloride, dimethyl sulfoxide, glibenclamide, lidocaine hydrochloride, phenylephrine (Sigma, St. Louis, MO), pinacidil (ICN Biomedicals, Inc., Aurora, OH). Mexiletine hydrochloride was a generous gift from Boehringer Ingelheim pharmaceutical Com-

pany (Ingelheim, Germany). Drugs were dissolved in distilled water such that volumes less than 0.15 ml were added to the organ chambers. Stock solutions of cromakalim (3×10^{-5} M), pinacidil (3×10^{-5} M), and glibenclamide (5×10^{-6} M) were prepared in dimethyl sulfoxide (0.5×10^{-4} to 1.6×10^{-4} M).⁶ The concentrations of drugs are expressed as final molar (M) concentration.

Statistical Analysis

The data are expressed as the mean \pm SD; n refers to the number of rats from which the aorta was taken. Statistical analysis was performed using one-way analysis of variance, followed by the Fisher test. Differences were considered to be statistically significant when $P < 0.05$.

Results

During submaximal contractions to phenylephrine (3×10^{-7} M), cromakalim (10^{-7} to 3×10^{-5} M), and pinacidil (10^{-7} to 3×10^{-5} M) induced concentration-dependent relaxations (fig. 1). A selective ATP-sensitive K^{+} channel inhibitor, glibenclamide (5×10^{-6} M), abolished these relaxations (fig. 1), whereas it did not affect relaxations to a voltage-dependent Ca^{2+} channel inhibitor, diltiazem (10^{-7} to 3×10^{-4} M) (table 1). Lidocaine (more than 10^{-5} M) significantly reduced relaxations to cromakalim or pinacidil in a concentration-dependent fashion (fig. 2), whereas it did not alter relaxations to diltiazem (fig. 3). In contrast, mexiletine (more than 10^{-5} M) significantly augmented relaxations to cromakalim or pinacidil (fig. 4). Glibenclamide (5×10^{-6} M) abolished these relaxations in arteries treated with mexiletine (10^{-4} M) (fig. 5). Lidocaine and mexiletine did not

LIDOCAINE, MEXILETINE, AND K^+ CHANNELS**Table 1. Effect of Glibenclamide (5×10^{-6} M) on Relaxations to Diltiazem in Rat Thoracic Aortas without Endothelium**

	-Log EC_{50}	% of Maximal Relaxation
Control (n = 5)	4.4 ± 0.4	-84.4 ± 10.7
Glibenclamide (5×10^{-6} M)(n = 5)	4.8 ± 0.1	-86.9 ± 9.0

Data are shown as the mean \pm SD.

produce any effects on contractions to phenylephrine (legends for figs. 2 and 4).

Discussion

This is the first study that shows the effects of the class Ib antiarrhythmic drugs lidocaine and mexiletine on vasorelaxations mediated by ATP-sensitive K^+ channels. In the current study, lidocaine reduced relaxations to the ATP-sensitive K^+ channel openers cromakalim and pinacidil. In contrast, mexiletine produced augmentation of these relaxations, which are abolished by a selective ATP-sensitive K^+ channel inhibitor, glibenclamide. These results suggest that lidocaine and mexiletine differently modify vasodilation *via* ATP-sensitive K^+ channels.

It has been shown that cromakalim and pinacidil are selective ATP-sensitive K^+ channel openers,⁷⁻¹⁰ and they cause the efflux of K^+ and subsequent hyperpolarization of vascular smooth muscle cells.¹¹ Glibenclamide has been shown to be a selective antagonist of ATP-sensitive K^+ channels, and it does not affect the activity

Fig. 2. Concentration-response curves to cromakalim and pinacidil in the absence or the presence of lidocaine (10^{-5} , 3×10^{-5} , 10^{-4} , 3×10^{-4} M) obtained in rat thoracic aortas without endothelia. Data are shown as the mean \pm SD and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 864 ± 159 mg [n = 5], 820 ± 219 mg [n = 6], 816 ± 201 mg [n = 5], 744 ± 104 mg [n = 5], and 744 ± 149 mg [n = 5] for control rings of cromakalim and rings treated with lidocaine [10^{-5} M], lidocaine [3×10^{-5} M], lidocaine [10^{-4} M], or lidocaine [3×10^{-4} M]; 100% = 840 ± 215 mg [n = 5], 832 ± 216 mg [n = 5], 872 ± 232 mg [n = 5], 856 ± 189 mg [n = 5], and 800 ± 110 mg [n = 5] for control rings of pinacidil and rings treated with lidocaine [10^{-5} M], lidocaine [3×10^{-5} M], lidocaine [10^{-4} M], or lidocaine [3×10^{-4} M], respectively). *Difference between control rings and rings treated with lidocaine is statistically significant ($P < 0.05$).

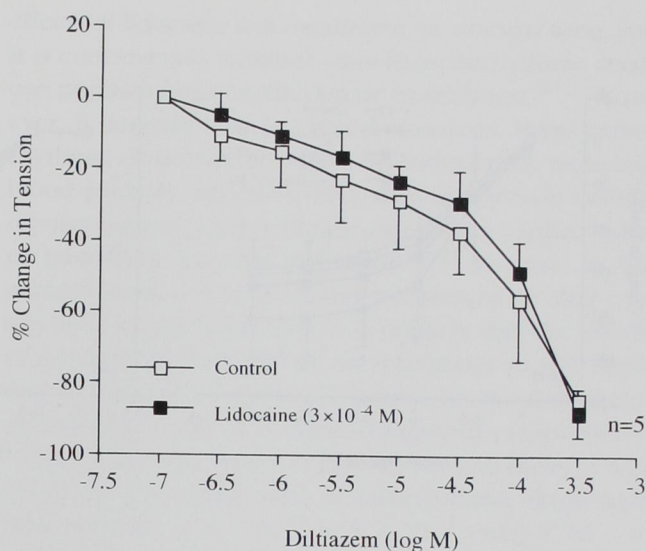
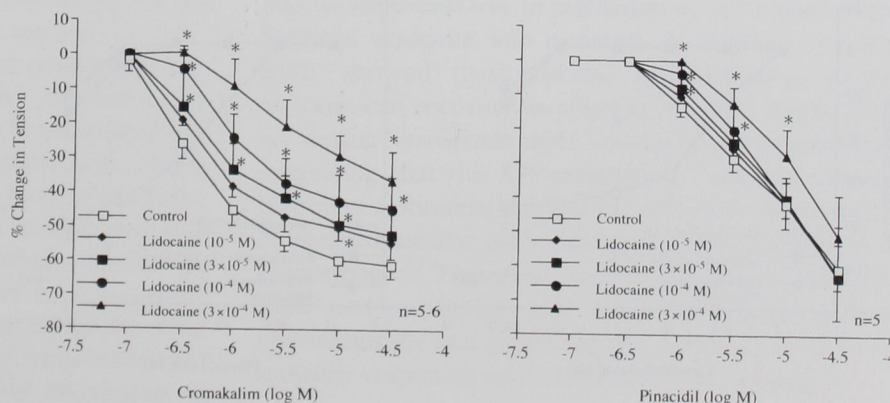
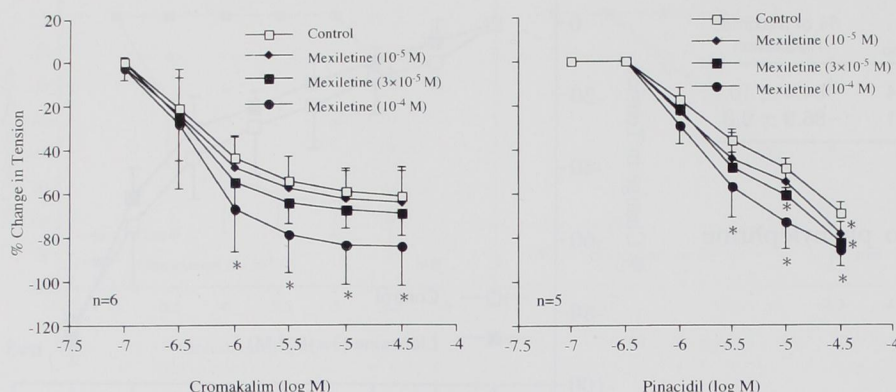


Fig. 3. Concentration-response curves to diltiazem (10^{-7} to 3×10^{-4} M) in the absence and the presence of lidocaine (3×10^{-4} M) obtained in rat thoracic aortas without endothelia. Data are shown as the mean \pm SD and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 736 ± 104 mg [n = 5], 712 ± 156 mg [n = 5] for control rings and rings treated with lidocaine).

of Ca^{2+} channels, inward rectifier, delayed rectifier, and Ca^{2+} -dependent K^+ channels.^{7,12} Our findings that, in rat thoracic aortas without endothelia, glibenclamide abolished relaxations to cromakalim and pinacidil, whereas it did not alter relaxations to a voltage-dependent Ca^{2+} channel inhibitor, diltiazem, reinforce these previous studies regarding the selectivity of glibenclamide on ATP-sensitive K^+ channels.^{7,12}



Cromakalim produced better relaxations in lower concentration ranges, compared to pinacidil, whereas relaxations to these ATP-sensitive K^+ channel openers are similar in higher concentration ranges. These results are consistent with previous observations in other vascular beds that cromakalim is a more potent vasodilator than pinacidil.^{7,9} It appears that differences of chemical structures between benzopyran and pyridine compounds are responsible for differential vasodilator effects of these ATP-sensitive K^+ channel openers.² A recent finding suggested that, in vascular smooth muscle cells, pinacidil may act as a nonselective K^+ channel opener.¹³ How-

ever, in the current study, a selective ATP-sensitive K^+ channel inhibitor, glibenclamide, abolished relaxations to pinacidil, showing that these relaxations are mediated by ATP-sensitive K^+ channels. Therefore, it is unlikely in our experimental condition that pinacidil can produce relaxations *via* channels other than ATP-sensitive K^+ channels.

In rat aortas without endothelia, lidocaine significantly reduced relaxations to cromakalim and pinacidil, whereas it did not affect relaxations to a voltage-dependent Ca^{2+} channel inhibitor, diltiazem. These results suggest that lidocaine may selectively impair relaxations

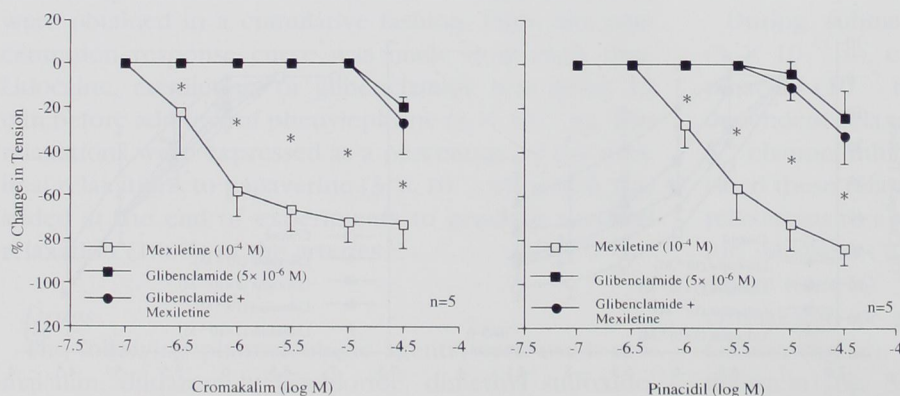


Fig. 5. Concentration-response curves to cromakalim and pinacidil in the presence of mexiletine (10^{-4} M) or glibenclamide (5×10^{-6} M), or both, obtained in rat thoracic aortas without endothelia. Data are shown as the mean \pm SD and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 813 ± 222 mg [n = 6], 860 ± 87 mg [n = 6], 787 ± 126 mg [n = 6], and 773 ± 213 mg [n = 6] for control rings of cromakalim and rings treated with mexiletine [10^{-5} M], mexiletine [3×10^{-5} M], or mexiletine [10^{-4} M]; 100% = 832 ± 209 mg [n = 5], 776 ± 96 mg [n = 5], 784 ± 173 mg [n = 5], and 808 ± 151 mg [n = 5] for control rings of pinacidil and rings treated with mexiletine [10^{-5} M], mexiletine [3×10^{-5} M], or mexiletine [10^{-4} M], respectively). *Difference between control rings and rings treated with mexiletine is statistically significant ($P < 0.05$).

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mediated by ATP-sensitive K⁺ channels in smooth muscle cells. This conclusion, supported by previous studies of *Xenopus* oocytes and cardiac myocytes, showed the inhibitory effect of lidocaine on the activity of ATP-sensitive K⁺ channels.^{3,4} In addition, in cardiac myocytes and myelinated nerve, lidocaine suppressed inward rectifier and flicker K⁺ currents, indicating that, in these preparations, this class Ib antiarrhythmic drug is capable of reducing activity of K⁺ channels other than ATP-sensitive K⁺ currents.^{14,15} The precise mechanisms of inhibitory effects of lidocaine on K⁺ channels remain to be determined.

In rat aortas without endothelia, mexiletine produced augmentation of relaxations to ATP-sensitive K⁺ channel openers, which is abolished by glibenclamide, suggesting that mexiletine favors an increase in relaxations mediated by ATP-sensitive K⁺ channels in smooth muscle cells. A previous observation of cardiac myocytes showed that mexiletine induces shortening of the action potential duration by the activation of ATP-sensitive K⁺ channels, indicating that mexiletine can augment the activity of these channels.⁵ In contrast to these findings, studies of *Xenopus* oocytes and isolated guinea pig perfused heart showed that mexiletine, in similar concentrations to the current study, reduces glibenclamide-sensitive K⁺ currents and that it induces prolongation of QRS duration in electrocardiography, which is inhibited by pinacidil.^{3,16} These results suggest that mexiletine is capable of producing inhibition of the activity of ATP-sensitive K⁺ channels in oocytes and cardiac myocytes. In addition, it was reported that, in cardiac myocytes, mexiletine can inhibit delayed rectifier K⁺ currents.¹⁷ Therefore, this evidence suggests that, in preparations other than blood vessels, mexiletine may reduce the activity of K⁺ channels. The reasons responsible for the discrepancies among preparations are unclear.

In rat aortas, lidocaine impaired but mexiletine augmented relaxations to ATP-sensitive K⁺ channel openers. Lidocaine and mexiletine are class Ib antiarrhythmic drugs, which have very similar electrophysiologic effects on cardiac myocytes caused by Na⁺ channel blockade, and they can produce shortening of action potential duration.¹⁸ In contrast to these similarities, mexiletine has a higher lipid solubility than that of lidocaine.¹⁹ Although the differential lipophilicity between lidocaine and mexiletine may be, at least in part, responsible for the differential effect of these drugs on relaxations to ATP-sensitive K⁺ channel openers, the precise mechanism of differences remains to be determined.

There have been a number of animal studies regarding

effects of lidocaine and mexiletine on vascular tone, and it is controversial whether class Ib antiarrhythmic drugs can produce vasoconstriction or vasodilation.²⁰⁻²² However, it appears that, in clinical situations, these antiarrhythmic drugs may not affect hemodynamics, including blood pressure and heart rate, although several clinical reports suggest that mexiletine can reduce cardiac index or peripheral vascular resistance.²³⁻²⁵ Because, in the current study, neither lidocaine nor mexiletine alter contractions to phenylephrine, it is unlikely that the effects of lidocaine and mexiletine on relaxations to ATP-sensitive K⁺ channel openers are caused by vasoconstrictor or vasodilator effects of these compounds, respectively.

The therapeutic ranges of plasma concentrations of lidocaine and mexiletine used as antiarrhythmic drugs have been reported as 8×10^{-6} to 5×10^{-5} and 8×10^{-7} to 10^{-5} M for lidocaine or mexiletine, respectively.^{26,27} In addition, after administration of an initial dose of epidural anesthesia, the plasma concentrations of lidocaine can reach 4×10^{-5} M.²⁸ Because lidocaine and mexiletine are bound to plasma proteins (approximately 50%), concentrations of lidocaine or mexiletine used in the current study are within and beyond the free plasma concentrations in the clinical situations, respectively.²⁹ Therefore, the current results regarding the effects of antiarrhythmic drugs on relaxations to ATP-sensitive K⁺ channel openers suggest that, in the clinical situations, lidocaine impairs vasodilation mediated by ATP-sensitive K⁺ channels, whereas mexiletine may not affect these vasodilator results.

During hypoxia, acidosis, and ischemia, ATP-sensitive K⁺ channels are activated, resulting in arterial dilation or increased tolerance of tissues to ischemia, or both.^{6,30,31} These findings suggest that ATP-sensitive K⁺ channels play an important role in regulation of circulation during hypoxia, acidemia, and ischemia. In addition, a recent study showed that systemic administration of cromakalim can recover vasodilation of rabbit basilar arteries during vasospasm after subarachnoid hemorrhage, suggesting that the ATP-sensitive K⁺ channel openers represent a potential therapeutic effect for the treatment of cerebrovascular pathophysiology after subarachnoid hemorrhage.³² Therefore, our results indicate that lidocaine and mexiletine may differently modulate these physiologically and pathologically induced beneficial vasodilator responses *via* ATP-sensitive K⁺ channels.

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