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Role of K^+ Channels in Augmented Relaxations to Sodium Nitroprusside Induced by Mexiletine in Rat Aortas

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Background: **A class Ib antiarrhythmic drug, mexiletine, augments relaxations produced by adenosine triphosphate (ATP)–sensitive K^+ channel openers in isolated rat aortas, suggesting that it produces changes in the vasodilation mediated by ATP-sensitive K^+ channels. Nitric oxide can induce its vasodilator effect *via* K^+ channels, including ATP-sensitive K^+ channels, in smooth muscle cells. Effects of mexiletine on arterial relaxations to nitric oxide donors, have not been studied. Therefore, the current study in isolated rat aortas was designed to (1) evaluate whether mexiletine augments relaxation in response to nitric oxide donors, including sodium nitroprusside, and (2) determine the role of K^+ channels in mediating effects of mexiletine on such nitric oxide–mediated relaxation.**

Methods: **Rings of rat aortas without endothelia were suspended for isometric force recording. Concentration–response curves of sodium nitroprusside (10^{-10} to 10^{-5} M) and 1-hydroxy-2-oxo-3-(*N*-methyl-3-aminopropyl)-3-methyl-1-triazene (NOC-7; 10^{-9} to 10^{-5} M) were obtained in the absence and in the presence of mexiletine, in combination with a soluble guanylate cyclase inhibitor, 1H-[1,2,4]oxadiazolo [4,3,-a]quinoxaline-1-one (ODQ), or inhibitors for ATP-sensitive K^+ channels (glibenclamide), inward rectifier K^+ channels ($BaCl_2$), delayed rectifier K^+ channels (4-aminopyridine), large conductance Ca^{2+}-dependent K^+ channels (iberiotoxin), or small conductance Ca^{2+}-dependent K^+ channels (apamin).**

Results: **Mexiletine (10^{-5} or 3×10^{-5} M) augmented relaxations to sodium nitroprusside and NOC-7. In arteries treated with glibenclamide (10^{-5} M), mexiletine (3×10^{-5} M) did not affect relaxations to nitric oxide donors, whereas mexiletine augmented relaxations to sodium nitroprusside despite the presence of $BaCl_2$ (10^{-5} M), 4-aminopyridine (10^{-3} M), iberiotoxin (5×10^{-8} M) and apamin (5×10^{-8} M). Relaxations to sodium nitroprusside were abolished by ODQ (5×10^{-6} M), whereas these relaxations were augmented by mexiletine (3×10^{-5} M) in arteries treated with ODQ (5×10^{-6} M).**

Conclusions: **These results suggest that ATP-sensitive K^+ channels in vascular smooth muscle, contribute to the augmented vasodilator effect of a nitric oxide donor, sodium nitroprusside induced by mexiletine, and that the vasodilator effect is produced, at least in part, *via* the guanylate cyclase–independent mechanism. (Key words: Antiarrhythmic drugs; blood vessels; glibenclamide; nitric oxide donor; vasodilation.)**

MEXILETINE, which is classified as a class Ib antiarrhythmic drug, has been used to treat ventricular arrhythmias.[1] Similar to other class Ib antiarrhythmic drugs, mexiletine reduces Na^+ currents of cardiac myocytes, resulting in the inhibition of depolarization of cell membranes.[2] The inhibition of depolarization can also be attained by the activation of K^+ channels, followed by hyperpolarization of cell membranes.[3] A recent study of cardiac myocytes showed that mexiletine augments the adenosine triphosphate (ATP)–sensitive K^+ currents,[4] suggesting that this antiarrhythmic drug may affect the regulatory mechanism of membrane potential *via* the activation of ATP-sensitive K^+ channels. It has been well-established that the activation of ATP-sensitive K^+ channels by physiologic or pathophysiologic stimuli cause vasodilation in a number of preparations.[3,5,6] Our recent study in isolated rat aortas showed that mexiletine produces increased relaxations to ATP-sensitive K^+ channel openers, indicating that this antiarrhythmic drug augments vasodilator effects mediated by ATP-sensitive K^+ channels.[7]

Previous studies showed that nitric oxide can induce vasodilation mediated by K^+ channels, including ATP-sensitive K^+ channels, in vascular smooth muscle *via* cyclic guanosine monophosphate (GMP)–dependent or –independent mechanisms.[8–11] Effects of mexiletine on arterial relaxations induced by nitric oxide donors have

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not been studied. Therefore, the current study in isolated rat aortas was designed to (1) evaluate whether mexiletine may augment relaxation in response to nitric oxide donors, including sodium nitroprusside, and (2) determine the role of K^+ channels in mediating effects of mexiletine on such nitric oxide–mediated relaxation.

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 of Wakayama Medical College. Rings were studied in modified Krebs-Ringer's 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: 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 the 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), which was bubbled with a 94% O_2–6% CO_2 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 sodium nitroprusside (10^{-10} to 10^{-5} M) or 1-hydroxy-2-oxo-3-(*N*-methyl-3-aminopropyl)-3-methyl-1-triazene (NOC-7; 10^{-9} to 10^{-5} M) were obtained in the absence or in the presence of 4-aminopyridine (10^{-3} M), apamin (5×10^{-8} M), $BaCl_2$ (10^{-5} M), glibenclamide (10^{-5} M), iberiotoxin (5×10^{-8} M), mexiletine hydrochloride (3×10^{-6}, 10^{-5}, 3×10^{-5} M), or 1H-[1,2,4]oxadiazolo [4,3,-a]quinoxaline-1-one (ODQ; 5×10^{-6} M). Concentration–response curves were obtained in a cumulative fashion. Only one concentration–response curve was made from each ring. 4-Aminopyridine, apamin, $BaCl_2$, glibenclamide, iberiotoxin, mexiletine hydrochloride, and ODQ were 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 relaxations (100%) of the arteries.

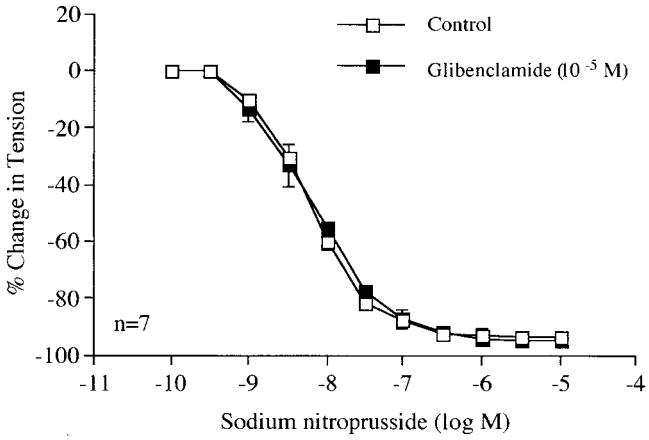

Fig. 1. Concentration–response curves to sodium nitroprusside (10^{-10} to 10^{-5} M) in the absence and in the presence glibenclamide (10^{-5} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 783 ± 80 mg [n = 7] and 703 ± 67 mg [n = 7] for control rings and rings treated with glibenclamide, respectively).

Drugs

The following pharmacologic agents were used: 4-aminopyridine, apamin, $BaCl_2$, glibenclamide, iberiotoxin, phenylephrine (Sigma, St. Louis, MO), ODQ (ICN pharmaceuticals Inc., Costa Mesa, CA), and NOC-7 (Dojindo Lab., Kumamoto, Japan). Mexiletine hydrochloride was a generous gift from Boehringer Ingelheim Pharmaceutical Company (Ingelheim, Germany). Drugs were dissolved in distilled water, such that volumes of less than 0.15 ml were added to the organ chambers. Stock solutions of ODQ (5×10^{-6} M) and glibenclamide (10^{-5} M) were prepared in dimethyl sulfoxide (DMSO; 1.6×10^{-4} M). Solutions of NOC-7 (10^{-5} M) were prepared in 0.01 N NaOH. The concentrations of drugs are expressed as final molar (M) concentration.

Statistical Analysis

The data are expressed as the mean ± SEM; n is the number of rats from which the aorta was taken. Statistical analysis was performed using repeated-measures analysis of variance, followed by the Scheffé F test for multiple comparison. Differences were considered to be statistically significant when $P < 0.05$.

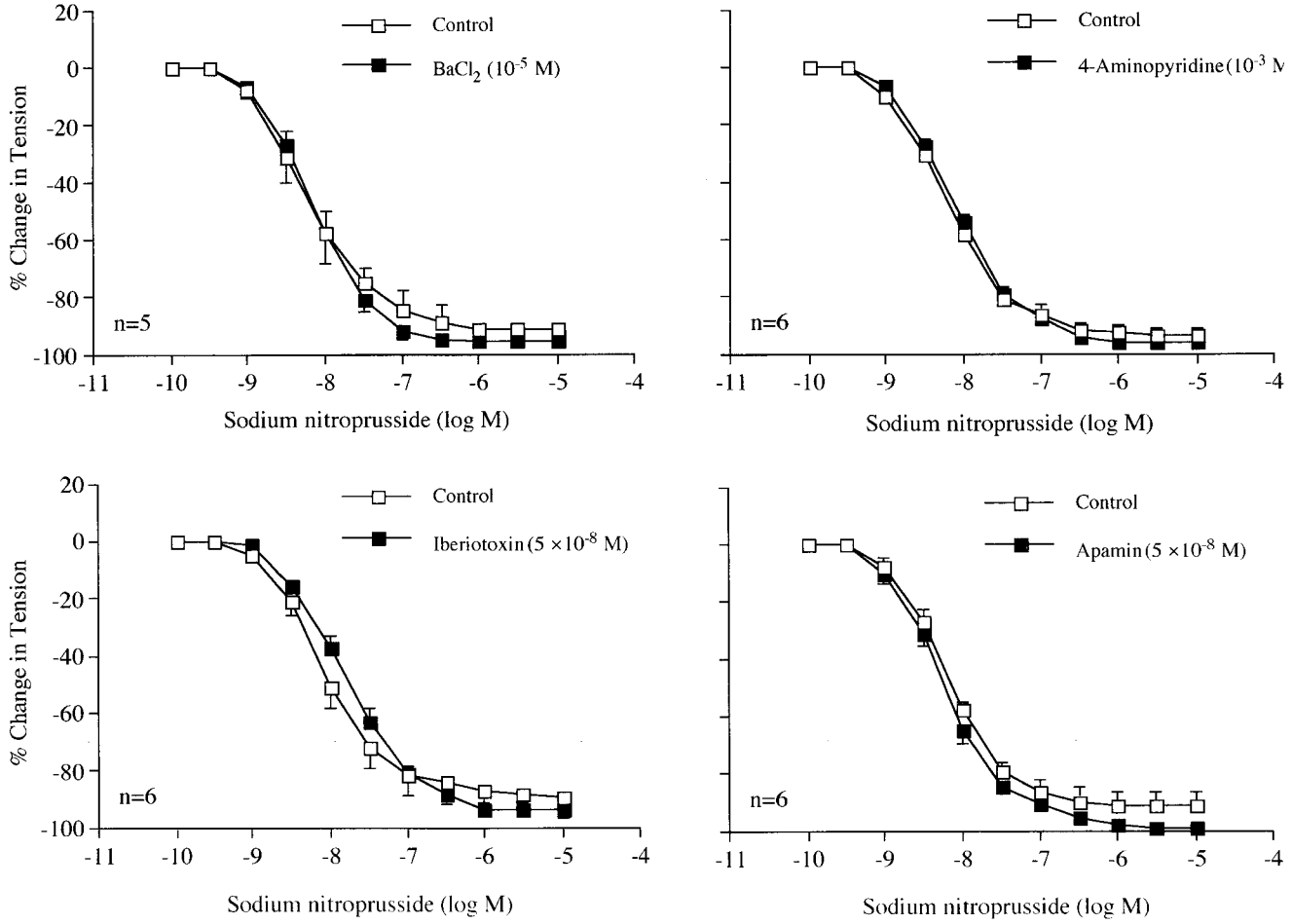

Fig. 2. Concentration–response curves to sodium nitroprusside in the absence and in the presence of $BaCl_2$ (10^{-5} M), 4-aminopyridine (10^{-3} M), iberiotoxin (5×10^{-8} M), or apamin (5×10^{-8} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 824 ± 85 mg [n = 5] and 968 ± 62 mg [n = 5] for control rings and rings treated with $BaCl_2$ [10^{-5} M]; 100% = 800 ± 77 mg [n = 6] and 800 ± 77 mg [n = 6] for control rings and rings treated with 4-aminopyridine; 100% = 893 ± 75 mg [n = 6] and 840 ± 70 mg [n = 6] for control rings and rings treated with iberiotoxin; 100% = 780 ± 106 mg [n = 6] and 633 ± 75 mg [n = 6] for control rings and rings treated with apamin, respectively).

Results

During submaximal contractions to phenylephrine (3×10^{-7} M), a nitric oxide donor, sodium nitroprusside (10^{-10} to 10^{-5} M) induced concentration-dependent relaxations (fig. 1). A selective ATP-sensitive K^+ channel inhibitor (glibenclamide, 10^{-5} M), an inward rectifier K^+ channel inhibitor ($BaCl_2$, 10^{-5} M), a delayed rectifier K^+ channel inhibitor (4-aminopyridine, 10^{-3} M), a selective large-conductance Ca^{2+}-dependent K^+ channel inhibitor (iberiotoxin, 5×10^{-8} M), and a selective small-conductance Ca^{2+}-dependent K^+ channel inhibitor (apamin, 5×10^{-8} M) did not affect these relaxations (figs. 1 and 2). A nitric oxide donor, NOC-7 (10^{-9} to 10^{-5} M) induced concentration-dependent relaxations, which were not altered by glibenclamide (10^{-5} M; data not shown).

Mexiletine (10^{-5} or 3×10^{-5} M) significantly augmented relaxations to sodium nitroprusside (fig. 3) and NOC-7 (fig. 4). In arteries treated with glibenclamide (10^{-5} M), mexiletine (3×10^{-5} M) did not affect relaxations to sodium nitroprusside and NOC-7 (fig. 5), whereas mexiletine augmented relaxations to sodium nitroprusside despite the presence of $BaCl_2$ (10^{-5} M), 4-aminopyridine (10^{-3} M), iberiotoxin (5×10^{-8} M), and apamin (5×10^{-8} M; fig. 6). Mexiletine did not produce effects on baseline tension and contractions to phenylephrine (data not shown).

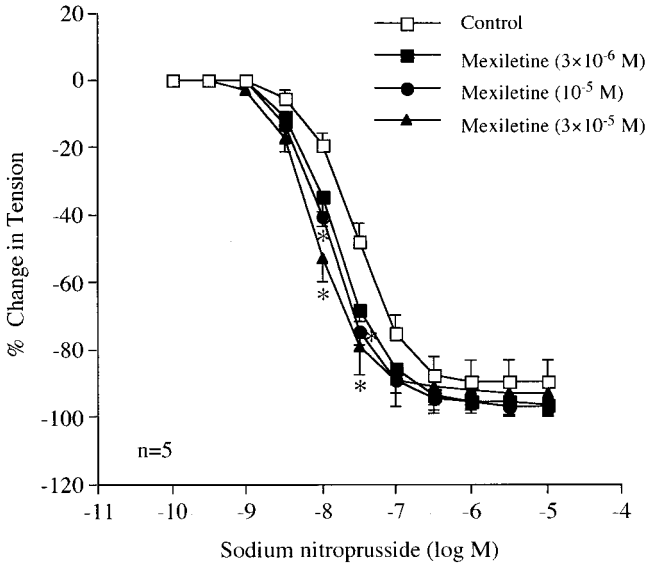

Fig. 3. Concentration–response curves to sodium nitroprusside in the absence or in the presence of mexiletine (3×10^{-6}, 10^{-5}, 3×10^{-5} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 920 ± 40 mg [n = 5], 816 ± 64 mg [n = 5], 844 ± 64 mg [n = 5], and 824 ± 37 mg [n = 5] for control rings and rings treated with mexiletine [3×10^{-6} M], mexiletine [10^{-5} M], or mexiletine [3×10^{-5} M], respectively). *Difference between control rings and rings treated with mexiletine is statistically significant ($P < 0.05$).

Relaxations to sodium nitroprusside were abolished by a selective soluble guanylate cyclase inhibitor, ODQ (5×10^{-6} M), whereas in arteries treated with ODQ (5×10^{-6} M), these relaxations were augmented by mexiletine (3×10^{-5} M; fig. 7).

Discussion

The current study showed several new findings. First, mexiletine augmented relaxations to sodium nitroprusside and NOC-7. Second, mexiletine did not affect relaxations to sodium nitroprusside and NOC-7 in arteries treated with glibenclamide; however, it augmented relaxations to sodium nitroprusside in arteries treated with iberiotoxin, apamin, 4-aminopyridine, $BaCl_2$, or ODQ. These results suggest that ATP-sensitive K^+ channels in vascular smooth muscle contribute to the augmented vasodilator effect of a nitric oxide donor, sodium nitroprusside induced by mexiletine, and that the vasodilator effect is produced, at least partly, *via* the guanylate cyclase–independent mechanism.

In rat aortas, glibenclamide did not affect relaxations to sodium nitroprusside and NOC-7. Because it is well-known that glibenclamide is a selective inhibitor of ATP-sensitive K^+ channels,[3,12] these results suggest that ATP-sensitive K^+ channels do not play a role in relaxations to nitric oxide donors. This conclusion is in agreement with a recent study, which showed that, in isolated rat aortic segments, sodium nitroprusside does not produce membrane hyperpolarization mediated by the activation of glibenclamide-sensitive K^+ channels.[13] The low concentration of $BaCl_2$ (10^{-5} M) is a selective inward rectifier K^+ channel inhibitor.[3,14] 4-Aminopyridine, at the concentration in the current study, is a selective inhibitor of delayed rectifier K^+ channels.[3,15] Large-conductance or small-conductance Ca^{2+}-dependent K^+ channels are selectively inhibited by the scorpion venom iberiotoxin and the honey bee venom apamin, respectively.[3,16,17] Therefore, inability of $BaCl_2$, 4-aminopyridine, iberiotoxin, and apamin to alter relaxations to sodium nitroprusside, suggests that inward rectifier K^+ channels, delayed rectifier K^+ channels, and large-conductance or small-conductance Ca^{2+}-dependent K^+ channels do not mediate these relaxations in rat aortas.

It has been shown that ODQ is a potent inhibitor of soluble guanylate cyclase, which abolishes increased levels of cyclic GMP induced by conversion of guanosine triphosphate (GTP) to cyclic GMP *via* the activation of the enzyme.[18] Indeed, the inhibitory effect of ODQ on increased levels of cyclic GMP induced by sodium nitro-

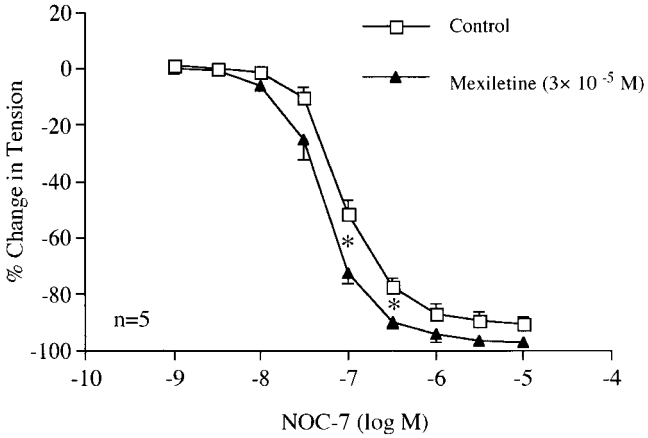

Fig. 4. Concentration–response curves to NOC-7 in the absence or in the presence of mexiletine (3×10^{-5} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 1,168 ± 73 mg [n = 5] and 1,084 ± 96 mg[n = 5] for control rings and rings treated with mexiletine [3×10^{-5} M], respectively). *Difference between control rings and rings treated with mexiletine is statistically significant ($P < 0.05$).

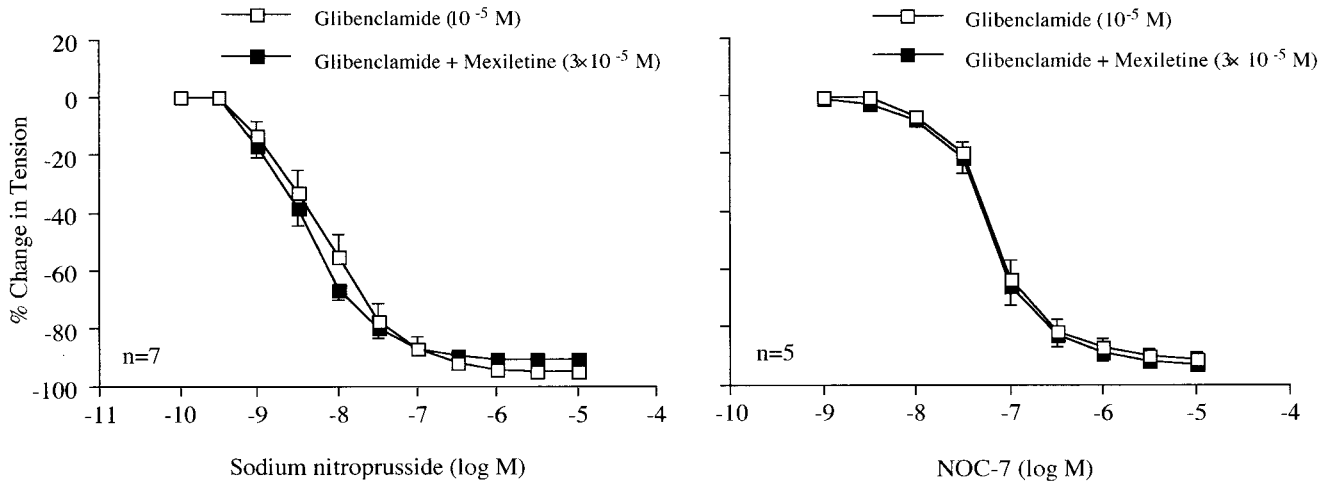

Fig. 5. Concentration–response curves to sodium nitroprusside and NOC-7 in the presence of glibenclamide (10^{-5} M) or in the presence of glibenclamide (10^{-5} M) plus mexiletine (3×10^{-5} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 703 ± 80 mg [n = 7] and 669 ± 63 mg[n = 7] for rings of sodium nitroprusside treated with glibenclamide, or glibenclamide plus mexiletine; 100% = 1,224 ± 74 mg [n = 5] and 1,076 ± 85 mg[n = 5] for rings of NOC-7 treated with glibenclamide, or glibenclamide plus mexiletine, respectively).

prusside have been reported by many studies, including those of blood vessels, and the concentration of ODQ used in our study has been proved to be effective to abolish the increased production of cyclic GMP induced by this nitric oxide donor.[18,19] Recent studies of rat aortas also showed that ODQ can inhibit the activity of soluble guanylate cyclase in vascular smooth muscle cells, with neither effect on nitric oxide synthase activity nor interaction with nitric oxide, supporting the selectivity of this compound to soluble guanylate cyclase.[20,21] Because, in the current study, ODQ abolished relaxations to sodium nitroprusside, it appears that, in rat aortas, sodium nitroprusside can induce relaxations *via* augmented activity of soluble guanylate cyclase, probably concurrently with increased levels of cytosolic cyclic GMP.

Mexiletine significantly augmented relaxations to sodium nitroprusside and NOC-7, which are the conventional and the newly developed nitric oxide donors, respectively.[22] A previous study of rat mesenteric arteries suggested that mexiletine, in concentrations higher than in the current study, can induce relaxations *via* inhibition of transmembrane Ca^{2+} movement.[23] However, in the current study, mexiletine did not produce changes in baseline tensions and in contractions to phenylephrine, indicating that, in our experimental condition, augmentation of vasodilator effects of nitric oxide donors induced by mexiletine are not caused by the vasodilator effect of mexiletine itself.

In arteries treated with glibenclamide, mexiletine did not affect relaxations to sodium nitroprusside or NOC-7; however, it augmented relaxations to sodium nitroprusside despite the presence of $BaCl_2$, 4-aminopyridine, iberiotoxin, and apamin. These results suggest that ATP-sensitive K^+ channels,[12] but not inward rectifier,[14] delayed rectifier,[15] large-conductance Ca^{2+}-dependent[17] or small-conductance Ca^{2+}-dependent K^+ channels,[16] mediate augmented vasodilator effect of sodium nitroprusside or NOC-7 induced by mexiletine. These results are also in agreement with our recent study of isolated rat aortas that mexiletine augmented relaxations to ATP-sensitive K^+ channel openers.[7] Because mexiletine reportedly has a higher lipid solubility,[24] the likely explanation for the effects of mexiletine on relaxations to nitric oxide donors is the higher lipophilicity of this compound, which can easily bind to the channel compartment. Indeed, a recent study of rat skeletal muscles showed that mexiletine can bind the nucleotide site of ATP-sensitive K^+ channels, suggesting that this antiarrhythmic drug may alter the activity of ATP-sensitive K^+ channels *via* direct action on the channels.[25]

Adenosine triphosphate–sensitive K^+ channels can mediate vasodilator effects of nitric oxide donors only in the presence of mexiletine. Although potentiation of ATP-sensitive K^+ channels by nitric oxide has been reported,[26] in our experimental condition, nitric oxide may not activate these K^+ channels in the absence of mexiletine. Mexiletine probably produces changes in

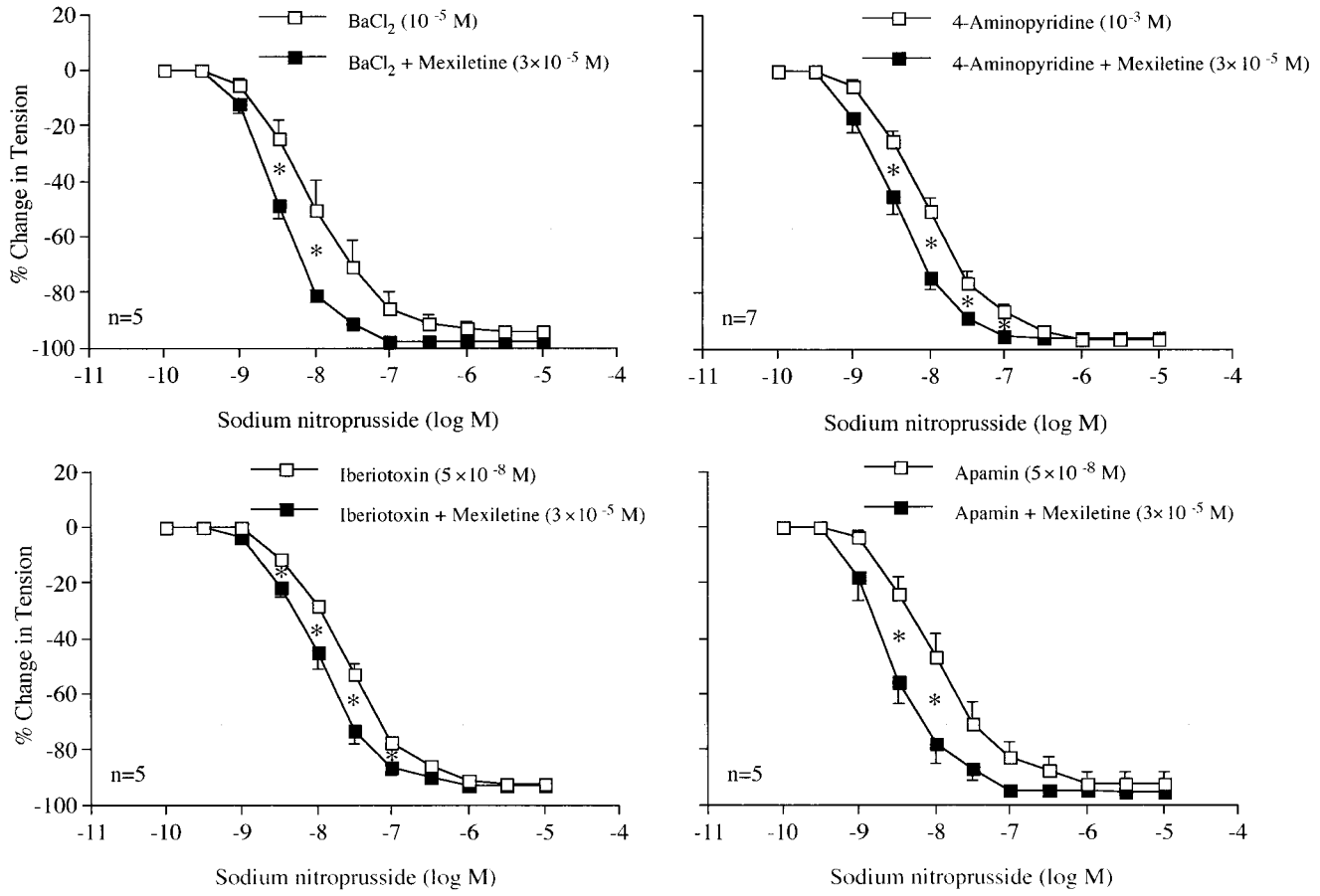

Fig. 6. Concentration–response curves to sodium nitroprusside in the presence of $BaCl_2$ (10^{-5} M), 4-aminopyridine (10^{-3} M), iberiotoxin (5×10^{-8} M), or apamin (5×10^{-8} M), and in the presence of the K^+ channel inhibitor plus mexiletine (3×10^{-5} M), obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 856 ± 39 mg [n = 5] and 760 ± 36 mg [n = 5] for rings treated with $BaCl_2$ or $BaCl_2$ plus mexiletine; 100% = 789 ± 66 mg [n = 7] and 789 ± 56 mg [n = 7] for rings treated with 4-aminopyridine, or 4-aminopyridine plus mexiletine; 100% = 896 ± 81 mg [n = 5] and 800 ± 89 mg [n = 5] for rings treated with iberiotoxin, or iberiotoxin plus mexiletine; 100% = 792 ± 95 mg [n = 5] and 760 ± 70 mg [n = 5] for rings treated with apamin, or apamin plus mexiletine, respectively). *Difference between rings treated with $BaCl_2$, 4-aminopyridine, iberiotoxin, or apamin and rings treated with the K^+ channel inhibitor plus mexiletine is statistically significant ($P < 0.05$).

the sensitivity of ATP-sensitive K^+ channels to nitric oxide, resulting in augmentation of relaxations to nitric oxide donors. However, the mechanisms of interaction between ATP-sensitive K^+ channels and nitric oxide remains unclear. Relaxations to sodium nitroprusside were augmented by mexiletine, even in arteries treated with a selective, soluble guanylate cyclase inhibitor: ODQ.[18,20,21] Therefore, in our experimental condition, mexiletine may produce changes in relaxations to sodium nitroprusside *via* ATP-sensitive K^+ channels in a guanylate cyclase–independent fashion. However, the molecular mechanism regarding the effects of mexiletine remains to be determined.

In contrast to these findings in blood vessels, effects of mexiletine on K^+ channels are rather controversial. Although a study of cardiac myocytes showed that mexiletine induces shortening of the action potential duration by the activation of ATP-sensitive K^+ channels,[4] studies of *Xenopus* oocytes and isolated guinea pig perfused heart showed that mexiletine reduces glibenclamide-sensitive K^+ currents, and that it induces prolongation of QRS duration in electrocardiography, which is inhibited by an ATP-sensitive K^+ channel opener.[27,28] These results suggest that mexiletine may be capable of producing activation or inhibition of the activity of ATP-sensitive K^+ channels in oocytes and cardiac myocytes. In addition, mexiletine can inhibit delayed rectifier K^+ currents in cardiac myocytes.[29] Although the reasons re-

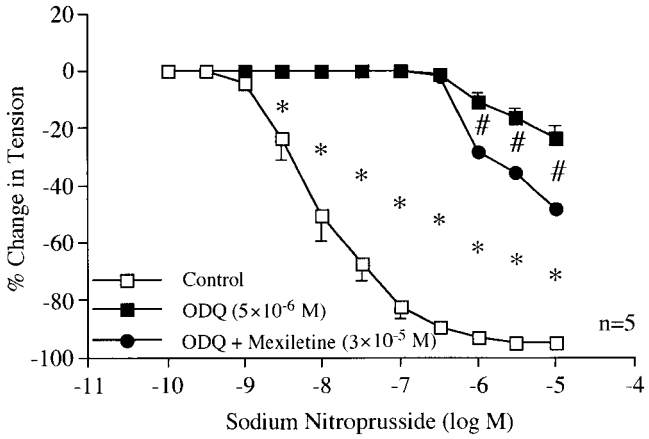

Fig. 7. Concentration–response curves to sodium nitroprusside in the absence or in the presence of ODQ (5×10^{-6} M) or mexiletine (3×10^{-5} M) obtained in rat thoracic aortas without endothelia. Data are shown as the mean ± SEM and expressed as percent of maximal relaxation induced by papaverine (3×10^{-4} M; 100% = 816 ± 102 mg [n = 5], 824 ± 61 mg [n = 5], and 760 ± 18 mg [n = 5] for control rings, rings treated with ODQ, or rings treated with ODQ plus mexiletine (3×10^{-5} M), respectively). *Difference between control rings and rings treated with ODQ and #difference between rings treated with ODQ and rings treated with ODQ plus mexiletine, are statistically significant, respectively ($P < 0.05$).

sponsible for the discrepancies of effects of mexiletine on the activity of K^+ channels among preparations are unclear, the evidence suggests that, in these preparations, mexiletine may also modulate the activity of these channels.

The therapeutic ranges of plasma concentrations of mexiletine used as an antiarrhythmic drug have been reported as 8×10^{-7} to 10^{-5} M.[30] Because mexiletine is bound to plasma proteins (approximately 50%), concentrations of mexiletine used in the current study appear to be slightly higher than the free plasma concentrations in the clinical situations (unpublished observations from Boehringer Ingelheim Pharmaceutical Co.). However, a decrease in peripheral vascular resistance by intravenous mexiletine has been reported in cardiac surgery patients.[31] Such patients are often treated with nitric oxide donors. Therefore, the current results regarding the effects of mexiletine suggest that antiarrhythmic drug may augment vasodilator effects of simultaneously administered nitric oxide–releasing agents.

Recent studies showed that relaxations to ATP-sensitive K^+ channel openers were modulated by inhibition of nitric oxide synthase or endothelial removal.[32–34] These results suggest that the activity of ATP-sensitive K^+ channels may be dependent on the presence of nitric oxide produced in endothelial cells. Nitric oxide donors are used as vasodilators to treat patients with cardiovascular disorders, including hypertension. It has been shown that, in these patients, endothelial function is impaired, resulting in decreased endothelium-dependent relaxations.[35] Therefore, our results in the preparations without endothelia indicate that mexiletine may augment the vasodilator effects of nitric oxide donors, particularly in the patients with endothelial dysfunction.

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