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Involvement of K^+ channel in procainamide-induced relaxation of bovine tracheal smooth muscle

Tsutomu Nakahara [a,*], Hiroshi Moriuchi [a], Motonari Yunoki [a], Yuko Kubota [a], Yoshio Tanaka [b], Kenji Sakamato [a], Koki Shigenobu [b], Kunio Ishii [a]

[a] *Department of Molecular Pharmacology, Kitasato University School of Pharmaceutical Sciences, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[b] *Department of Pharmacology, Toho University School of Pharmaceutical Sciences, 2-2-1 Miyama, Funabashi City, Chiba 274-8510, Japan*

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Abstract

The relaxant effect of procainamide, a class Ia antiarrhythmic agent, was examined in bovine tracheal smooth muscle. Procainamide produced concentration-dependent decreases in tension and full relaxation in the preparations contracted with methacholine (0.3 μM). By comparison, in preparations contracted with 40 mM K^+, procainamide had only slight relaxant effects. The relaxant effects of cromakalim and salbutamol on 40 mM K^+-contracted preparations were significantly ($P < 0.01$) smaller than those on 0.3 μM methacholine-contracted ones. On the other hand, the concentration–response relationships for quinidine, lidocaine, mexiletine and propafenone were not so dramatically different between 0.3 μM methacholine- and 40 mM K^+-contracted preparations. Tetraethylammonium (300 μM), iberiotoxin (30 nM) and Ba^{2+} (1 mM) significantly ($P < 0.05$) attenuated the relaxant effects of procainamide on methacholine-induced contractions, whereas apamin (100 nM), 4-aminopyridine (300 μM), and glibenclamide (10 μM) did not affect them. The inhibitory effect of a combination of iberiotoxin and Ba^{2+} was greater than that of iberiotoxin or Ba^{2+} alone ($P < 0.01$). These results suggest that the activation of at least two types of K^+ (maxi-K^+ and inward rectifier K^+) channels contributes to the procainamide-induced relaxation of bovine tracheal smooth muscle.

Keywords: (Bovine); Antiarrhythmic drug; Inward rectifier K^+ channel; Maxi-K^+ channel; Smooth muscle

1. Introduction

Class I antiarrhythmic drugs include those agents which block cardiac Na^+ channels, leading to inhibition of depolarization of cardiac cells. On the basis of the rate of binding dissociation from Na^+ channels, class I antiarrhythmic drugs are further classified into three subgroups: Ia, Ib and Ic (Vaughan Williams, 1984). In addition to the blockade of Na^+ channels, most class I (a, b, c) antiarrhythmics have been shown to block other ion channels such as Ca^{2+} and K^+ channels (Ono et al., 1986; Sakuta et al., 1992; Delgado et al., 1993; Slawsky and Castle, 1994). Consistent with these findings, class I antiarrhythmic drugs could affect Ca^{2+} mobilization, resulting in the relaxation of vascular smooth muscles (Dohi et al., 1994; Fernández del Pozo et al., 1997).

The effects of class I antiarrhythmic drugs in airway smooth muscle, except those of lidocaine in class Ib category, have not been extensively investigated (Weiss et al., 1975; Downes and Loehning, 1977; Okumura and Denborough, 1980; Kai et al., 1993). Clinically, lidocaine is used for prevention of the bronchospasm associated with airway instrumentation for general anesthesia or bronchoscopy. Furthermore, recent studies demonstrated that another class Ib antiarrhythmic drug, mexiletine, can prevent the irritant-induced bronchoconstriction (Brown et al., 1995; Groeben et al., 1996). Thus, although the clinical usefulness of class Ib antiarrhythmic drugs has been established regarding the improvement in airflow limitation in addition to the treatment of arrhythmias, the effects of classes Ia and Ic drugs on the airway smooth muscles remain unknown.

The present study was thus undertaken to investigate the effects of Ia (procainamide and quinidine) and class Ic (propafenone) antiarrhythmic drugs on isolated bovine tracheal smooth muscle in comparison with those of class Ib

* Corresponding author. Tel.: +81-3-3444-6205; fax: +81-3-3444-6205.
E-mail address: nakaharat@pharm.kitasato-u.ac.jp (T. Nakahara).

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drugs (lidocaine and mexiletine). We also examined the possibility of a contribution of K^+ channels to the relaxation of tracheal smooth muscle by these antiarrhythmic drugs.

2. Materials and methods

2.1. Tissue preparation

We obtained freshly excised bovine tracheas from the local abattoir and transported these to the laboratory immersed in cold Krebs–Ringer bicarbonate buffer of the following composition (in millimolar): 118.5 NaCl, 4.47 KCl, 1.18 $MgSO_4$, 1.18 KH_2PO_4, 2.54 $CaCl_2$, 24.9 $NaHCO_3$, 10.0 glucose, and 1.0 pyruvic acid (pH 7.4). We carefully separated smooth muscle from cartilage, mucosa, and connective tissues, with the muscle kept immersed in ice-cold Krebs–Ringer bicarbonate buffer gassed with 95% O_2–5% CO_2 as described previously (Katsuki and Murad, 1977; Ishii and Murad, 1989).

2.2. Measurement of mechanical activity

We used segments of smooth muscle ($1–2 \times 10$ mm) for measurement of mechanical responses. Muscle tension was recorded isometrically. One end of each muscle was attached with cotton thread to a force-displacement transducer (model TB-611T, Nihon Kohden, Tokyo, Japan), and the other end was tied to a stainless steel holder. We mounted muscle segments on 20-ml jacketed organ baths containing Krebs–Ringer bicarbonate buffer gassed with 95% O_2–5% CO_2 at 37°C. Muscle segments were placed under an initial tension of 0.75 g, and the buffer was changed every 15 min during equilibration for 60 min. During incubation, the muscle relaxed gradually, therefore, we adjusted the resting tension to 0.5 g at 10 min before the start of each experiment.

2.3. Experimental procedure

In the first series of experiments, we examined the effects of procainamide, quinidine, lidocaine, mexiletine and propafenone on the contraction produced by 0.3 μM methacholine or 40 mM K^+. After the contractile responses had reached a stable plateau, we cumulatively added procainamide (0.003–10 mM), quinidine (0.003–0.3 mM), lidocaine (0.003–10 mM), mexiletine (0.01–10 mM) or propafenone (0.001–0.3 mM) to the tissue bath. Concentrations of the drugs were increased when steady responses to the preceding concentration were obtained. In experiments with high K^+ solution, Na^+ in the bathing medium was replaced by an equimolar concentration of K^+.

In the second series of experiments, we examined the effects of cromakalim (0.1–10 μM) and salbutamol (0.1–100 nM) on the contraction produced by 0.3 μM methacholine or 40 mM K^+.

In the third series of experiments, we examined the effects of K^+ channel blockers on the procainamide-induced relaxations. When plateau tone was reached 20–30 min after the addition of methacholine (0.3 μM), the tissues were exposed to vehicle, tetraethylammonium (300 μM), iberiotoxin (30 nM), Ba^{2+} (1 mM), iberiotoxin (30 nM) plus Ba^{2+} (1 mM), apamin (100 nM), 4-aminopyridine (300 μM), or glibenclamide (10 μM). After an additional 15-min incubation period, we added procainamide cumulatively to the tissue baths. In separate experiments, we examined the effects of iberiotoxin and Ba^{2+} on the diltiazem (0.3–300 μM)-induced relaxation. Only one concentration–response curve was made for each preparation.

2.4. Data analysis and statistics

The data were expressed as the means ± SEM. Relaxant responses were expressed as percentages of the methacholine-induced tension obtained just before the cumulative addition of drugs. IC_{50} values (the concentration required to decrease the methacholine-induced tension by 50%) were calculated by linear regression analysis using the two data points that bracketed the 50% relaxant concentration. The data were analyzed using either Student's *t*-test or Scheff's multiple comparison test after one-way analysis of variance (one-way ANOVA). A P value smaller than 0.05 was considered statistically significant.

2.5. Drugs

The following drugs were used: acetyl-β-methylcholine chloride (methacholine), 4-aminopyridine, atropine sulfate, barium chloride, cromakalim, diltiazem hydrochloride, lidocaine hydrochloride, mexiletine hydrochloride, nifedipine, procainamide hydrochloride, propafenone hydrochloride, quinidine hydrochloride monohydrate, tetraethylammonium chloride, tetrodotoxin, salbutamol hemisulfate (Sigma, St. Louis, MO, USA); ethylenedioxybis(ethylamine)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) (Kanto Chemical, Tokyo, Japan); glibenclamide (Nacalai Tesque, Kyoto, Japan); apamin, iberiotoxin (Peptide Institute, Osaka, Japan). Glibenclamide and cromakalim were dissolved in dimethyl sulfoxide. Other drugs were dissolved in distilled water and diluted further with Krebs–Ringer bicarbonate buffer.

3. Results

3.1. Contractile responses to methacholine and high K^+

Methacholine (0.3 μM) and high K^+ (40 mM) caused sustained contractile responses. Tensions developed with

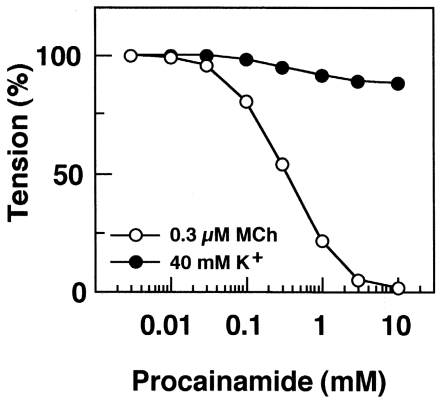

Fig. 1. Effect of procainamide on the tension of bovine tracheal smooth muscle contracted with 0.3 μM methacholine (MCh) or 40 mM K^+. Each point represents the mean ± SEM from six separate preparations. All SEM values were so small that they are hidden behind the symbols.

0.3 μM methacholine and 40 mM K^+ were 10.3 ± 0.5 g ($n = 36$) and 10.2 ± 0.6 g ($n = 37$), respectively. The tensions developed were not significantly different and were approximately 50% of the maximum tension of each bovine tracheal smooth muscle preparation on its own (data not shown). The contractile responses to 0.3 μM methacholine and 40 mM K^+ were abolished by atropine (1 μM) and nifedipine (0.3 μM), respectively. In contrast, tetrodotoxin (1 μM), a Na^+ channel blocker, did not affect the contractions induced by methacholine and by 40 mM K^+. In Ca^{2+}-free Krebs–Ringer bicarbonate buffer containing 0.3 mM EGTA, 40 mM K^+ failed to produce tension.

3.2. Effects of procainamide, quinidine, lidocaine, mexiletine and propafenone on preparations contracted with methacholine and high K^+

Fig. 1 and Table 1 show the effects of procainamide, quinidine, lidocaine, mexiletine and propafenone on preparations contracted with 0.3 μM methacholine and 40 mM K^+. Procainamide caused concentration-dependent decreases in tension, and full relaxation was obtained at 10 mM in the preparations contracted with 0.3 μM methacholine. In contrast, in preparations contracted with 40 mM K^+, even 10 mM procainamide exhibited only a small relaxant effect (12.1 ± 2.7% relaxation, $n = 6$) (Fig. 1). Concentration-dependent relaxations were also observed with other antiarrhythmic agents (quinidine, lidocaine, mexiletine and propafenone) in preparations contracted with both 0.3 μM methacholine and 40 mM K^+. At the highest concentrations examined, these drugs almost abolished the enhanced tones whether the muscle was stimulated with 0.3 μM methacholine or with 40 mM K^+. Therefore, the concentration–response relationships for these agents were not so strikingly different between 0.3 μM methacholine- and 40 mM K^+-contracted preparations. The IC_{50} values and maximal relaxant responses are summarized in Table 1. Quinidine and lidocaine were equipotent to attenuate the precontractions induced by both 0.3 μM methacholine and 40 mM K^+. Mexiletine and propafenone were more potent to inhibit 40 mM K^+-induced contractions.

3.3. Effects of cromakalim and salbutamol on preparations contracted with methacholine and high K^+

Cromakalim (0.1–10 μM) and salbutamol (0.1–100 nM) caused concentration-dependent decreases in the tension developed with methacholine (0.3 μM) (Fig. 2). The maximal relaxant responses caused by 10 μM cromakalim and 100 nM salbutamol in the preparations contracted with methacholine were 82.0 ± 3.1% and 99.5 ± 0.3%, respectively ($n = 5$ in each case). These maximal relaxant responses to cromakalim and salbutamol were significantly ($P < 0.01$) smaller in the preparations contracted with 40 mM K^+ (cromakalim, 6.5 ± 3.0%; salbutamol, 57.2 ± 5.0%) ($n = 5$ in each case).

3.4. Effects of K^+ channel blockers on relaxant responses to procainamide

The markedly reduced potency of procainamide to relax the preparations contracted with 40 mM K^+ indicates the

Table 1
IC_{50} values and maximal responses of class I antiarrhytmic drugs to relax 0.3 μM methacholine- or 40 mM K^+-induced contraction of bovine tracheal smooth muscle preparations

	0.3-μM Methacholine		40-mM K^+	
	IC_{50} (mM)	Maximal response (%)	IC_{50} (mM)	Maximal response (%)
Procainamide	0.40 ± 0.04	98.7 ± 0.6	ND	12.1 ± 2.7
Quinidine	0.057 ± 0.005	98.4 ± 0.8	0.067 ± 0.002	92.6 ± 1.3
Lidocaine	0.26 ± 0.04	100 ± 0.0	0.25 ± 0.01	100 ± 0.0
Mexiletine	0.78 ± 0.05	99.9 ± 0.1	0.40 ± 0.04[a]	99.2 ± 0.4
Propafenone	0.038 ± 0.004	99.9 ± 0.1	0.012 ± 0.002[a]	99.6 ± 0.3

The values represent the mean ± SEM from 4–6 separate preparations.
ND indicates not determinable.
[a] $P < 0.01$ vs. corresponding values obtained with 0.3 μM methacholine.

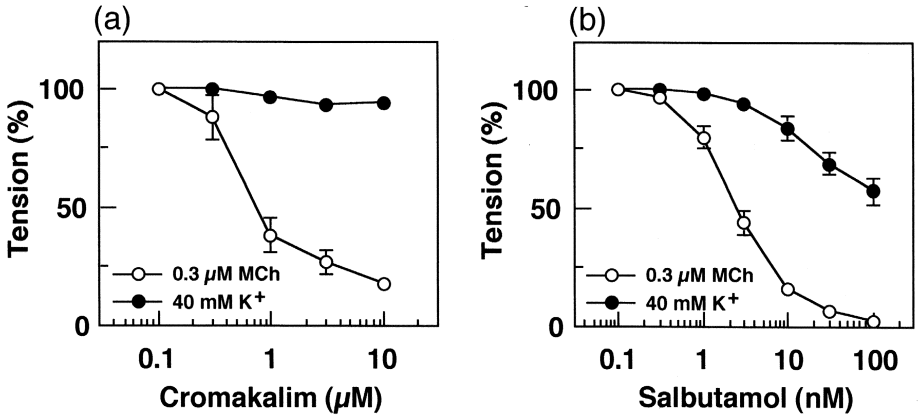

Fig. 2. Effects of cromakalim (a) and salbutamol (b) on the tension of bovine tracheal smooth muscle contracted with 0.3 μM methacholine (MCh) or 40 mM K^+. Each point represents the mean ± SEM from five separate preparations. SEM values are within the symbols for some points.

involvement of K^+ channels in the response. Therefore, we examined the effects of various K^+ channel blockers on the procainamide-induced relaxation of tracheal smooth muscles contracted with methacholine to determine the types of K^+ channels involved in the response.

Table 2 shows the effects of K^+ channel blockers on tension developed on addition of 0.3 μM methacholine. Tetraethylammonium (300 μM) decreased the methacholine-induced tension, whereas iberiotoxin (30 nM), Ba^{2+} (1 mM) and 4-aminopyridine (300 μM) increased it. In airway smooth muscle, 4-aminopyridine has been shown to stimulate muscarinic receptors (Drukarch et al., 1989; Li et al., 1998). Therefore, when we evaluated the effect of 4-aminopyridine on procainamide-induced relaxation, we compared the concentration–response relationships for responses to procainamide after addition of 4-aminopyridine during precontraction with 0.3 μM methacholine with those on 0.6 μM methacholine-contracted preparations. The plateau levels of methacholine (0.6 μM)-induced contraction were similar to those for methacholine (0.3 μM) plus 4-aminopyridine (12.8 ± 0.8 vs. 12.9 ± 1.3 g, $n = 5$). In contrast, apamin (100 nM) and glibenclamide (10 μM) did not affect the methacholine-induced contractions ($n = 5–6$).

Table 2
Comparison of tensions (g) before and after treatment with tetraethylammonium (300 μM), iberiotoxin (30 nM), Ba^{2+} (1 mM), the combination of iberiotoxin (30 nM) and Ba^{2+} (1 mM), apamin (100 nM), 4-aminopyridine (300 μM) or glibenclamide (10 μM) in bovine tracheal smooth muscle preparations precontracted with 0.3 μM methacholine

Treatment	Before	After
Tetraethylammonium	11.8 ± 1.9	7.2 ± 1.3[a]
Iberiotoxin	11.5 ± 1.0	13.1 ± 1.1[b]
Ba^{2+}	10.7 ± 0.4	13.1 ± 0.6[a]
Iberiotoxin + Ba^{2+}	9.6 ± 0.8	13.8 ± 1.4[a]
Apamin	12.2 ± 2.5	12.1 ± 2.4
4-Aminopyridine	10.5 ± 1.1	12.9 ± 1.3[b]
Glibenclamide	12.7 ± 0.9	12.7 ± 1.0

The values represent the mean ± SEM from 5–6 separate preparations.
[a] $P < 0.01$ vs. corresponding values obtained before drug treatment.
[b] $P < 0.05$.

Fig. 3 shows that tetraethylammonium (300 μM), iberiotoxin (30 nM), Ba^{2+} (1 mM) and a combination of iberiotoxin (30 nM) and Ba^{2+} (1 mM) attenuated the relaxant responses to procainamide. The IC_{50} values for procainamide-induced relaxation in the absence and presence of tetraethylammonium were 0.30 ± 0.03 and 1.08 ± 0.21 mM, respectively ($n = 5$). This difference was statistically significant ($P < 0.01$) (panel A). Furthermore, iberiotoxin and Ba^{2+} significantly ($P < 0.05$) increased the IC_{50} values for responses to procainamide (control, 0.44 ± 0.04 mM vs. iberiotoxin, 1.91 ± 0.17 mM; control, 0.50 ± 0.08 mM vs. Ba^{2+}, 1.53 ± 0.40 mM)($n = 5$ in each case) (panels B and C), whereas they did not increase the IC_{50} values for responses to diltiazem (control, 15.4 ± 1.1 μM vs. iberiotoxin, 16.6 ± 1.4 μM; control, 15.7 ± 5.5 μM vs. Ba^{2+}, 9.1 ± 1.4 μM)($P > 0.05$)($n = 3$ in each case). Panel D illustrates the marked attenuation of the relaxant response to procainamide by the combination treatment with 30 nM iberiotoxin plus 1 mM Ba^{2+}.

Fig. 4 shows the inhibitory effects of iberiotoxin (30 nM), Ba^{2+} (1 mM), and a combination of both agents on the relaxation by procainamide at the maximal concentration examined (10 mM). Any of these treatments significantly ($P < 0.01$) attenuated the procainamide-induced relaxation. The inhibition by the combination treatment with iberiotoxin plus Ba^{2+} was more potent than the inhibition by iberiotoxin or Ba^{2+} alone.

Neither apamin (100 nM), 4-aminopyridine (300 μM) nor glibenclamide (10 μM) caused significant changes in IC_{50} values for the procainamide-induced relaxations (control, 0.44 ± 0.05 mM vs. apamin, 0.46 ± 0.08 mM; control, 0.69 ± 0.11 mM vs. 4-aminopyridine, 0.89 ± 0.07 mM; control, 0.40 ± 0.06 mM vs. glibenclamide, 0.44 ± 0.04 mM)($n = 5–6$). Furthermore, the maximal relaxant responses to procainamide were not affected by these K^+ channel blockers (control, 99.7 ± 0.2% vs. apamin, 99.3 ± 0.3%; control, 98.8 ± 0.5% vs. 4-aminopyridine, 99.4 ±

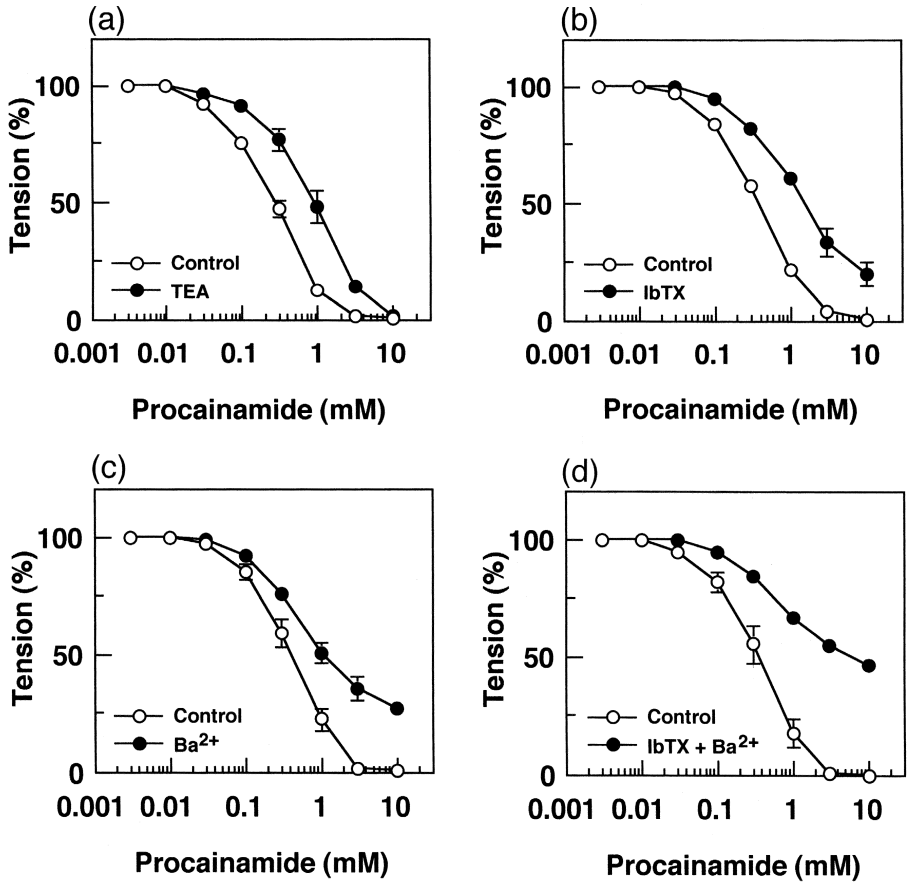

Fig. 3. Effects of tetraethylammonium (TEA, 300 μM) (a), iberiotoxin (IbTX, 30 nM) (b), Ba^{2+} (1 mM) (c) and a combination of iberiotoxin and Ba^{2+} (IbTX + Ba^{2+}) (d) on the procainamide-induced relaxation in bovine tracheal smooth muscle contracted with 0.3 μM methacholine. Each point with a vertical bar represents the mean ± SEM from five separate preparations. SEM values are within the symbols for some points.

0.3%; control, 99.7 ± 0.2% vs. glibenclamide, 99.7 ± 0.2%) ($n = 5–6$). The concentration of glibenclamide used in the present study (10 μM) abolished the relaxant responses of the tracheal preparations to cromakalim (10 μM), an opener of the ATP-sensitive K^+ channels (data not shown).

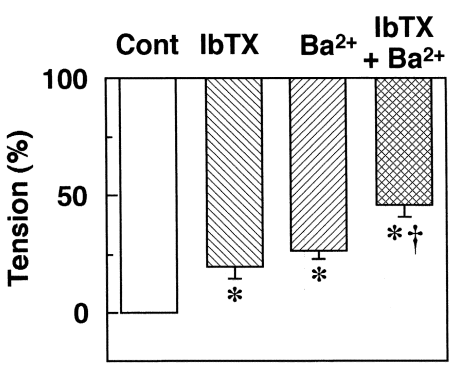

Fig. 4. Relaxations induced by procainamide at maximal concentration examined (10 mM) in the absence (Cont) and presence of iberiotoxin (IbTX), Ba^{2+}, or a combination of both agents (IbTX + Ba^{2+}) in bovine tracheal smooth muscle contracted with 0.3 μM methacholine. Each column with a vertical bar represents the mean ± SEM from 5–15 separate preparations. SEM value of Cont was so small that it is hidden behind the column. $^{*}P < 0.01$ vs. Cont; †$P < 0.01$ vs. IbTX or Ba^{2+}.

4. Discussion

We have shown for the first time that class Ia (procainamide and quinidine) and class Ic (propafenone) antiarrhythmics show relaxant actions in the bovine tracheal smooth muscle contracted with methacholine and a high concentration of K^+. Of the antiarrhythmics tested in the present study, only procainamide was shown to relax tracheal smooth muscle via activation of K^+ channels. It is likely that at least two types of K^+ channels (maxi-K^+ and inward rectifier K^+ channels) contribute to the procainamide-induced relaxant responses.

Class I antiarrhythmics have blocking actions on Na^+ channels. Blockade of Na^+ channels not only reduces the amount of intracellular Na^+ available for the Na^+–Ca^{2+} exchange mechanism but also hyperpolarizes the membrane. It is possible that both mechanisms contribute to the reduction in the concentration of intracellular Ca^{2+} and thus smooth muscle relaxation. However, our present study

showed that tetrodotoxin (1 μM) did not affect the contractile responses to methacholine and high K^+. Thus, blockade of Na^+ channels can be ruled out as the main mechanism responsible for the tracheal smooth muscle relaxations induced by class I antiarrhythmic drugs.

High K^+-induced contraction of tracheal smooth muscle was abolished by nifedipine or by removal of extracellular Ca^{2+}, indicating that it depends on Ca^{2+} entry through voltage-dependent Ca^{2+} channels. Furthermore, the class I antiarrhythmics tested in the present study, with the exception of procainamide, markedly attenuated the contractile responses to high K^+. Therefore, as previously proposed for vascular smooth muscle (Fernández del Pozo et al., 1997), the relaxant effects evoked in bovine tracheal smooth muscle by quinidine (class Ia), lidocaine, mexiletine (class Ib) and propafenone (class Ic) may be partly attributable to the inhibition of Ca^{2+} entry through voltage-dependent Ca^{2+} channels. Additionally, these drugs relaxed the preparations contracted with methacholine. In tracheal smooth muscles, acetylcholine receptor agonists act to increase both intracellular Ca^{2+} concentration and Ca^{2+} sensitivity of the contractile systems (Ozaki et al., 1990). Thus, some intracellular mechanisms decreasing the sensitivity of contractile systems to Ca^{2+} might be involved in the actions of class I antiarrhythmics. In support of this speculation, lidocaine was reported to attenuate the acetylcholine-induced contraction of airway smooth muscle by decreasing both Ca^{2+} sensitivity and Ca^{2+} entry (Kai et al., 1993). Further studies are needed to determine whether other class I antiarrhythmics affect the Ca^{2+} sensitivity of the contractile systems in tracheal smooth muscles.

K^+ channels are proposed to play an important role in the regulation of airway smooth muscle excitability and tone (Kotlikoff, 1993). Indeed, cromakalim (a K^+ channel opener) and salbutamol (a β_2-adrenoceptor agonist), which activate K^+ channels (Chiu et al., 1993; Cook et al., 1993), relaxed the bovine tracheal smooth muscle contracted with methacholine. The relaxant responses to cromakalim and salbutamol were strongly diminished in the preparations contracted with 40 mM K^+. Similarly, the relaxant effect of procainamide on 40 mM K^+-contracted preparations was markedly weaker than that on methacholine-contracted muscles. These results suggest that K^+ channel activation might play an important role in the relaxant responses to procainamide. Furthermore, significant inhibition of the relaxant response to procainamide was observed in the preparations treated with iberiotoxin (30 nM), a selective blocker of maxi-K^+ (large conductance Ca^{2+}-activated K^+) channels (Galvez et al., 1990), and with Ba^{2+} (1 mM) which blocks inward rectifier K^+ channels (Nelson and Quayle, 1995). Tetraethylammonium (300 μM) also strongly inhibited procainamide-induced relaxation, which suggests a significant contribution of maxi-K^+ channels in the relaxant response (Nelson and Quayle, 1995). Thus, as the subtypes of K^+ channels that contribute to the procainamide-induced relaxation of bovine tracheal smooth muscle, at least two types of K^+ channels seem to be involved judging from the susceptibility of the response to inhibition by selective channel blockers. Since the inhibition by a combination of iberiotoxin and Ba^{2+} was greater than that by iberiotoxin or Ba^{2+} alone, procainamide might independently activate these two types of K^+ channels, thereby relaxing bovine tracheal smooth muscle. In contrast, apamin, 4-aminopyridine, and glibenclamide did not affect the procainamide-induced relaxation. Therefore, it is unlikely that small-conductance Ca^{2+}-activated K^+ channels (apamin-sensitive), delayed rectifier K^+ channels (4-aminopyridine-sensitive), and ATP-sensitive K^+ channels (glibenclamide-sensitive) play an important role in the relaxant responses to procainamide. At present, participation of K^+ channel activation cannot be ruled out as the mechanism for the relaxant actions by other class I antiarrhythmics though the concentration–response relationships for the relaxations induced by these drugs were similar in both methacholine- and high K^+-contracted preparations.

Both iberiotoxin (30 nM) and Ba^{2+} (1 mM) caused additional contractions in the preparations contracted with methacholine (0.3 μM). Because the levels of precontraction could affect the relaxant responses of smooth muscles, the procainamide-induced relaxation might be attenuated due to the additional contractions by the K^+ channel blockers. Indeed, as shown by the results with 4-aminopyridine, the IC_{50} value for procainamide-induced relaxation was increased to 0.69 mM when the concentration of methacholine to induce precontraction was changed to 0.6 μM. However, the levels of precontraction with 0.6 μM methacholine were similar to those after the addition of iberiotoxin or Ba^{2+} in preparations contracted with 0.3 μM methacholine (see Table 2). Moreover, neither iberiotoxin nor Ba^{2+} changed the relaxation produced by diltiazem, a Ca^{2+} channel blocker. These findings indicate that the attenuation of procainamide-induced relaxation by iberiotoxin and Ba^{2+} can be ascribed to their blocking actions on the K^+ channels but not to the additional contractions induced by the blockers.

The IC_{50} values of antiarrhythmics now tested for the relaxant responses on isolated bovine tracheal smooth muscle exceed the blood concentrations observed during clinical use (therapeutic ranges of plasma concentrations; procainamide, 14–29 μM; quinidine, 5–13 μM; lidocaine, 5.5–18 μM; mexiletine, 2.3–9.2 μM; propafenone, < 2.6 μM). Therefore, these compounds at concentrations reached when they are used as antiarrhythmics might fail to show potent brochodilating actions. However, when these drugs are administered locally, it is possible that the concentrations of these antiarrhythmics around the bronchial smooth muscle cells reach the concentrations used in the present study, which relax bronchial tubes.

In summary, we showed relaxant effects of class I antiarrhythmic drugs (procainamide, quinidine, lidocaine,

mexiletine and propafenone) on bovine tracheal smooth muscle contracted with methacholine. For these antiarrhythmics, only the relaxation produced by procainamide was markedly attenuated in the muscles contracted with high K^+ as compared to the responses of methacholine-contracted muscles. Our present results suggest that, not only the drugs in the class Ib category, but also the drugs in classes Ia and Ic categories may be useful in preventing airway obstruction. Since the present data were obtained using isolated tracheal smooth muscle preparations, the effects of these drugs on respiratory function must be carefully evaluated under in vivo conditions. Nevertheless, we would like to stress here that this is the first report demonstrating the relaxant effects of procainamide, quinidine, and propafenone on airway smooth muscle and the possible involvement of K^+ channel activation in the procainamide-induced relaxation.

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