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Effects of K^+ channel inhibitors on the basal tone and KCl- or methacholine-induced contraction of mouse trachea

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Abstract

The present study examined the effects of K^+ channel inhibitors on the basal tone and on KCl- or methacholine-induced contraction of the mouse-isolated trachea. Glibenclamide and iberiotoxin, procaine, quinine and tetraethylammonium did not induce any contraction of the indomethacin-treated mouse trachea. 4-Aminopyridine induced concentration-dependent contraction. This action of 4-aminopyridine was abolished by atropine and reduced by tetrodotoxin and nifedipine. Glibenclamide failed to modify KCl- or methacholine-induced contraction. Iberiotoxin and 4-aminopyridine potentiated KCl- and methacholine-induced contractions. Nifedipine, procaine, quinine and tetraethylammonium inhibited KCl- and methacholine-induced contractions. These data suggest that the closure of large Ca^{2+}-dependent K^+ channels can potentiate KCl- and methacholine-induced contraction. The effects of 4-aminopyridine on the mouse trachea reflect chiefly activation of muscarinic receptors. Procaine, quinine and tetraethylammonium inhibit depolarization-induced and receptor-mediated contractions of the mouse-isolated trachea. © 1998 Elsevier Science B.V.

Keywords: Trachea, mouse; Contraction; Smooth muscle, airway; K^+ channel inhibitor

1. Introduction

K^+ channels are important in regulating airway smooth muscle excitability and force generation. A diverse range of K^+ channels has been described in the plasmalemma of airway smooth muscle cells. These include the large Ca^{2+}-dependent K^+ channels (BK_{Ca}), the ATP-sensitive K^+ channels (K_{ATP}) and the 4-aminopyridine sensitive, delayed rectifier K^+ channels (K_{dr}) (Kotlikoff, 1993; Knox and Tattersfield, 1994). There have been few studies on the effects of blockade of the K_{dr}, BK_{Ca}, K_{ATP} on the sensitivity and responsiveness of airway smooth muscle to constricting agents. Boyle et al. (1988) showed that the non-selective inhibitors of K^+ channels, tetraethylammonium and procaine, failed to potentiate acetylcholine- or histamine-induced contraction of the guinea pig-isolated trachea. In contrast, tetraethylammonium has been shown to potentiate both acetylcholine- or 5-hydroxytryptamine-induced contraction of rat-isolated trachea (Chand et al., 1990). Recently, the effects of the selective K^+ channel inhibitors on carbachol-, histamine- or KCl-induced contraction of the guinea pig trachea have been reported. Glibenclamide was without effect on carbachol-, histamine- or KCl-induced contraction, but iberiotoxin potentiated the contraction. 4-Aminopyridine potentiated histamine-induced but not carbachol- or KCl-induced contraction (Issac et al., 1996).

The study of pharmacology of murine tissue is increasingly interesting and important because it is possible to prepare transgenic and knock out mice. These animals may be useful in the future to dissect out the signaling pathways of K^+ channels. However, to date little has been done concerning the K^+ channels in the mouse airway smooth muscle. Recently, we have investigated the role of K^+ channels in the relaxations induced by bradykinin, lemakalim and sodium nitroprusside in the mouse-isolated trachea by using the selective inhibitors for different K^+ channel types. Glibenclamide, but not 4-aminopyridine and iberiotoxin, inhibited relaxation to lemakalim, indicating that relaxation of the mouse trachea by lemakalim is mediated by the K_{ATP} (Li et al., 1997). The aim of the present study was to examine the role of inhibition of different K^+ channels in the basal tone and KCl- or methacholine-induced contraction in the mouse-isolated trachea.

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2. Materials and methods

2.1. Tissue preparation

BALB/c mice (8–12 weeks) of either sex were used in the studies. Following an intraperitoneal injection of 0.25 ml of pentobarbital sodium (60 mg kg^{-1}) and thoracotomy, one piece of trachea from each animal was isolated as described previously (Garssen et al., 1990). The trachea (3-mm long ring) was then mounted in organ baths filled with 8 ml of Krebs solution of the following composition (mM): NaCl: 119; $NaHCO_3$: 25; $CaCl_2 \cdot H_2O$: 1.6; KCl: 4.7; KH_2PO_4: 1.2; $MgSO_4 \cdot 7H_2O$: 1.2; glucose: 11.1. The solution was maintained at 37°C and bubbled with 96% O_2 and 4% CO_2 gas mixture. The trachea was equilibrated under an optimal resting tension of 400 mg for at least 45 min with replacement of the bath fluid every 15 min. The tone of the tracheal smooth muscle was measured with a force displacement transducer (FT03) connected to a Model 7 D polygraph (Grass Instrument, Quincy, MA, USA). The experimental procedure was approved by the Animal Experimentation Committee of the University of Helsinki, Finland.

2.2. Experimental procedures

All the experiments were performed in the presence of indomethacin (2 μM) which was added to Krebs solution. Following the equilibration period, all tissues were first exposed to methacholine (10 μM). The tissues were then washed. After 20 min, in the first group of experiments the test tissues were treated for 20 min with vehicle or different kinds of K^+ channel inhibitors, including glibenclamide (10–33 μM), iberiotoxin (10–100 nM), procaine (20–200 μM), quinine (20–200 μM) or tetraethylammonium (200 μM–2 mM). In the case of 4-aminopyridine, cumulative concentration–response curves to 4-aminopyridine (1 μM–2 mM) were obtained in the absence or in the presence of atropine (1 μM), nifedipine (1 μM) or tetrodotoxin (2 μM), preincubated for 20 min.

The effects of K^+ channel inhibitors on the action of the constricting agents were studied by constructing cumulative concentration–response curves for KCl (20–60 mM) or methacholine (0.01–100 μM). Each concentration of KCl or methacholine was allowed to act for 6–8 min to reach a stable level before the next addition was made. Glibenclamide (10–33 μM), iberiotoxin (10–100 nM), procaine (20–200 μM), quinine (20–200 μM), tetraethylammonium (200 μM–2 mM) or 4-aminopyridine (20–200 μM) was added to the bathing medium 20 min before the construction of the concentration–response curves. Time-matched control tissues were treated similarly to the test tissues but were exposed to vehicle instead of the K^+ channel inhibitor. When digitizing the data, the baseline was taken from the point the contractile agent was added after drug pretreatment up to the point the tissue returned to the resting state after washing.

2.3. Statistical analysis

Contractile responses to 4-aminopyridine, KCl and methacholine were expressed as a percentage of the maximal contraction induced by methacholine (10 μM). The experimental values are given as the mean ± S.E.M. of the indicated number of experiments. Statistical analysis of the results was performed by analysis of variance (ANOVA) followed by Duncan's multiple range test. Differences were considered significant when $P < 0.05$.

2.4. Drugs

Drugs from the following sources were used: 4-aminopyridine, atropine sulfate, iberiotoxin, indomethacin, methacholine, tetrodotoxin and tetraethylammonium acetate (Sigma Chemical, St. Louis, MO, USA), glibenclamide (Leiras, Turku, Finland), procaine hydrochloride, nifedipine (Orion Pharmaceutical, Espoo, Finland) and pentobarbital sodium, (Grinsted Products, Grinsted, Denmark), quinine sulfate (RBI, Natick, MA, USA). Unless otherwise stated, all drugs were prepared daily in ultrapure water (MilliQ, Millipore, Bedford, MA, USA) just before the experiments and protected from the light. Indomethacin and quinine were dissolved in absolute ethanol at 10 mM. Glibenclamide and nifedipine were prepared in dimethyl sulfoxide (DMSO) at 10 mM.

3. Results

3.1. Tension changes induced by the K^+ channel inhibitors

The inhibitor of K_{ATP}, glibenclamide, the inhibitor of the BK_{Ca}, iberiotoxin, had no effect on the basal tension in the indomethacin-treated mouse trachea, neither did the non-selective K^+ channel inhibitors like procaine, quinine and tetraethylammonium. In contrast, the inhibitor of the K_{dr}, 4-aminopyridine (1 μM–2 mM), induced concentration-dependent contraction. This action of 4-aminopyridine

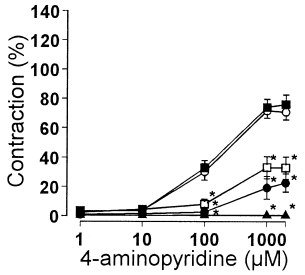

Fig. 1. The effects of nifedipine (1 μM □), tetrodotoxin (2 μM ●) and atropine (1 μM ▲) on 4-aminopyridine-induced contraction of the mouse-isolated trachea. Each point represents mean ± S.E.M. ($n = 6–8$). Statistically significant difference: * $P < 0.05$ vs. the respective control (water ○; DMSO ■).

was abolished by atropine (1 μM). Pretreatment with tetrodotoxin (2 μM) and nifedipine (1 μM) significantly reduced the contraction induced by 4-aminopyridine (Fig. 1).

3.2. Effects of K^+ channel inhibitors on contractions induced by methacholine and KCl

Both methacholine (0.01–100 μM) and KCl (20–60 mM) induced concentration-dependent contraction of the mouse-isolated trachea. 4-Aminopyridine (200 μM but not 20 μM) potentiated KCl- and methacholine-induced contractions. Glibenclamide (10–33 μM) failed to modify KCl- and methacholine-induced contractions. Iberiotoxin (10–100 nM) potentiated KCl- and methacholine-induced contractions (Fig. 2). Nifedipine (10–33 μM), an antagonist of L-type voltage-dependent calcium channels, inhibited KCl- and methacholine-induced contractions in a concentration-dependent manner. Procaine (20–200 μM) concentration-dependently inhibited KCl-induced contraction, and also methacholine-induced contraction without suppressing maximum contraction. Quinine (20–200 μM) inhibited KCl- and methacholine-induced contractions. Tetraethylammonium inhibited (200 μM–2 mM) KCl-induced contraction, and also methacholine-induced contraction without changing maximum contraction (Fig. 3).

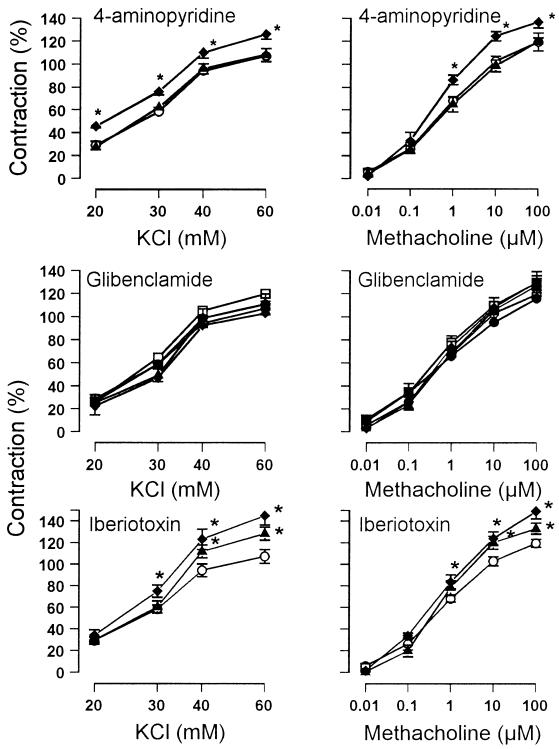

Fig. 2. The effects of 4-aminopyridine (20 μM ▲; 200 μM ◆), glibenclamide (10 μM ▲; 33 μM ◆) and iberiotoxin (10 nM ▲; 100 nM ◆), on KCl- or methacholine-induced contraction of the mouse-isolated trachea. Each point represents mean ± S.E.M. ($n = 6$–8). Statistically significant difference: * $P < 0.05$ vs. the control (○).

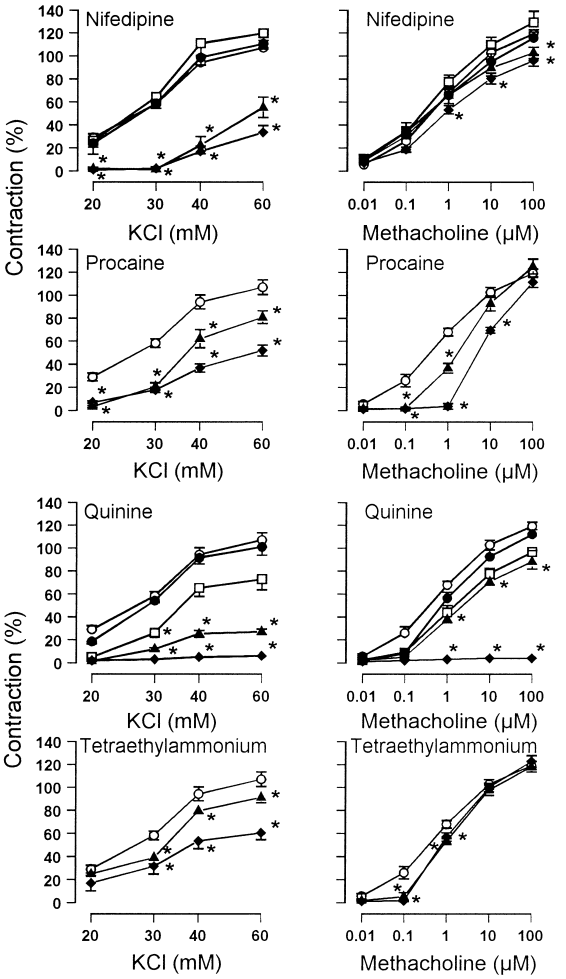

Fig. 3. The effects of nifedipine (10 μM ▲; 33 μM ◆), procaine (20 μM ▲; 200 μM ◆), quinine (20 μM ▲; 200 μM ◆) or tetraethylammonium (200 μM ▲; 2 mM ◆) on KCl- or methacholine-induced contraction of the mouse-isolated trachea. Each point represents mean ± S.E.M. ($n = 6$–8). Statistically significant difference: * $P < 0.05$ vs. the respective control (water ○; or the low concentration of DMSO or ethanol ●; or the high concentration DMSO or ethanol □).

4. Discussion

The present study for the first time describes the effects of K^+ channel inhibitors on the mouse trachea and on the contractions induced by methacholine and KCl. Airway smooth muscle of most species is characterized by electrical stability. This stability is thought to be attributable to the presence of different K^+ channels, especially the BK_{Ca} on the plasma membrane that rectifies any tendency to depolarization. This is supported by the evidence showing that the blockade of K^+ channels by K^+ channel inhibitors like tetraethylammonium, charybdotoxin and iberiotoxin causes action potential and depolarization in normal air-

way smooth muscle tissue in vitro (Kroeger and Stephens, 1975; Kannan et al., 1983; Marthan et al., 1989; Issac et al., 1996). However, in the present study, neither the non-specific K^+ channel inhibitors like procaine, quinine and tetraethylammonium, nor the inhibitor of the K_{ATP}, glibenclamide and the inhibitor of the BK_{Ca}, iberiotoxin, induced contraction of the mouse trachea under the resting tone. This suggests that under resting conditions very few of the BK_{Ca} are open and other K^+ channels may play more important role in determining the resting plasmalemmal K^+ permeability in the mouse smooth muscle.

The inhibitor of the K_{dr}, 4-aminopyridine contracted the mouse trachea concentration-dependently. 4-Aminopyridine-induced contraction was significantly reduced but not abolished by nifedipine, suggesting that part of the 4-aminopyridine-induced contraction may be explained by membrane depolarization with Ca^{2+} influx through L-type voltage-dependent Ca^{2+} channels. 4-Aminopyridine-induced contraction was only partially reduced by tetrodotoxin but abolished by atropine, suggesting that 4-aminopyridine may promote the neural release acetylcholine and interacts indirectly and directly with muscarinic receptors in the mouse trachea. Drukarch et al. (1989) has shown that 4-aminopyridine can promote the neural release of acetylcholine in rat striatal slices. Such findings support our results that 4-aminopyridine may cause the neural release of acetylcholine in the mouse-isolated trachea. Our results are also supported by the fact that 4-aminopyridine inhibits the specific biding of [^{3}H]dexetimide to rat striatal muscarinic receptor binding sites (Drukarch et al., 1989). In the guinea pig trachea, 4-aminopyridine potentiated histamine-induced but not carbachol- or KCl-induced contraction (Issac et al., 1996). However, the potentiation of KCl- or methacholine-induced contraction by 4-aminopyridine in the mouse trachea can also be explained by its indirect or direct muscarinic action. Taken together, our results indicate that 4-aminopyridine may act indirectly or directly as a muscarinic agonist. Thus, we conclude that the effects of 4-aminopyridine on the mouse trachea reflect chiefly activation of muscarinic receptors but not interference with K^+ channels. But we cannot exclude that the 4-aminopyridine-induced release of acetylcholine results from membrane depolarization due to the blockade of the K_{dr} in cholinergic nerve terminals.

The inhibitor of the K_{ATP}, glibenclamide, failed to modify KCl- or methacholine-induced contraction. This agrees with the action of glibenclamide in the guinea pig trachea (Issac et al., 1996). However, it is possible that the K_{ATP} exist in the mouse trachea because in our previous study, the opener of K_{ATP} lemakalim induces relaxation of the isolated mouse trachea, and this action of lemakalim is significantly inhibited by glibenclamide (Li et al., 1997). The inhibitor of the BK_{Ca}, iberiotoxin, potentiated KCl- and methacholine-induced contractions. This agrees with the action of iberiotoxin in the guinea pig trachea (Issac et al., 1996). In contracting tissues, membrane depolarization associated with action potentials enhances $[Ca^{2+}]_i$ and induces tissue contraction. In response both to the rise in $[Ca^{2+}]_i$ and to the depolarization, the BK_{Ca} opens, thus reducing the contraction (Kotlikoff, 1993). Therefore, the potentiation of methacholine-induced contraction by iberiotoxin could be explained by its inhibitory action on the BK_{Ca}.

In contrast, the non-specific K^+ channel inhibitors like procaine, quinine and tetraethylammonium inhibited KCl- and methacholine-induced contractions. However, the inhibitory actions of procaine, quinine and tetraethylammonium cannot be attributed to inhibition of K^+ channels because they behave differently from glibenclamide and iberiotoxin and the closure of K^+ channels should not lead to the inhibition of contraction. The site at which procaine, quinine and tetraethylammonium inhibit contraction is not easily defined.

Contractile mechanisms in airway smooth muscle can be divided into depolarization-induced contraction and receptor-operated contraction. The contraction evoked by KCl in airway smooth muscle is due to membrane depolarization with influx of Ca^{2+} through voltage-dependent Ca^{2+} channels (Knox and Tattersfield, 1994). Nifedipine, a classical antagonist of L-type voltage-dependent Ca^{2+} channels, inhibited KCl-induced contraction of the mouse trachea. This, thus, suggests that nifedipine could inhibit Ca^{2+} influx through voltage-dependent Ca^{2+} channels in the mouse airway smooth muscle. Procaine, quinine and tetraethylammonium inhibited KCl-induced contraction of the mouse trachea, being less potent than or as potent as nifedipine. This inhibitory action of procaine, quinine and tetraethylammonium agrees with the following results. Both procaine and quinine inhibit Ca^{2+}-induced contraction of the guinea pig taenia (Spedding and Berg, 1985). Procaine inhibits KCl-induced contraction of the canine trachea, the dog coronary artery, the rabbit aorta and the guinea pig taenia (Imaizumi and Watanabe, 1982; Imai et al., 1984; Ahn and Karaki, 1988). Quinine inhibits KCl-induced contraction of the rat-isolated rectum and the rat-isolated aorta (Savage and Akinlalu, 1985; Del Pozo et al., 1996). Our results thus suggest that procaine, quinine and tetraethylammonium could inhibit Ca^{2+} influx through voltage-dependent Ca^{2+} channels in the mouse airway smooth muscle.

Receptor-operated contraction of airway smooth muscle results from binding of a contractile agonist to its receptor and activation of the inositol phospholipid second messenger system to mobilize Ca^{2+} from intracellular stores (Chilvers et al., 1994). Activation of airway smooth muscle cells by receptor agonists induces a rise in $[Ca^{2+}]_i$ that consists of two phases, a transient release from intracellular stores and a sustained influx across plasma membrane. Most of the contractile agents such as cholinergic agonists and histamine activate this pathway (Murray and Kotlikoff, 1991; Knox and Tattersfield, 1994). Nifedipine

suppressed the mouse tracheal contraction induced by methacholine much less than by KCl. This agrees with the fact that receptor-operated contraction of airway smooth muscle is not readily inhibited by the classical L-type voltage-dependent Ca^{2+} channel antagonists (Barnes, 1985; Knox and Tattersfield, 1994). The concentration of nifedipine (33 μM) is considered to be sufficient in blocking most L-type voltage-dependent Ca^{2+} channels as it almost totally abolished KCl-induced contraction. This suggests that only part of receptor-agonist-induced contraction is due to influx of Ca^{2+} through voltage-dependent Ca^{2+} channels and the rest is due either to the release of Ca^{2+} from the intracellular stores or influx of Ca^{2+} through voltage-independent channels. On this basis, it is possible that inhibition of methacholine-induced contraction by procaine, quinine and tetraethylammonium may be partly due to their effects on voltage-dependent Ca^{2+} channels

Inhibition of methacholine-induced contraction by procaine, quinine and tetraethylammonium may be partly due to their effects on muscarinic receptor sites because procaine, quinine and tetraethylammonium have been shown to interact directly with muscarinic receptors (Mirro et al., 1980; Drukarch et al., 1989; Hisayama et al., 1989). However, procaine inhibits histamine-induced contraction of the guinea pig trachea and taenia and noradrenaline-induced contraction of the rabbit aorta (Wanna and Gergis, 1978; Ahn and Karaki, 1988); and quinine inhibits 5-hydroxytryptamine-, endothelin-1- or noradrenaline-induced contraction of rat-isolated aorta (Del Pozo et al., 1996). The inhibitory effects induced by procaine and quinine on different membrane receptors can not be explained by an interference with the muscarinic receptors but with a process(es) beyond receptor activation. This is consistent with the following findings. Procaine inhibits Ca^{2+}-induced Ca^{2+} release from the intracellular Ca^{2+} store in the guinea pig taenia caeci and in the rat vas deferens (Iino, 1989; Garcia and Schneider, 1995). Procaine also inhibits the hydrolysis of phosphatidylinositol 4,5-bisphosphate activated by acetylcholine, thus reducing the amount of inositol-1,4,5-trisphosphate and the release of Ca^{2+} from the store site (Ueno et al., 1987). Quinine inhibits Ca^{2+} release from inositol-1,4,5-trisphosphate-sensitive stores in dog brain microsomes and in macrophages (Lee and Go, 1996; Misra et al., 1997). Tetraethylammonium inhibits Ca^{2+} release from inositol-1,4,5-trisphosphate-sensitive stores and the increase in $[Ca^{2+}]_i$ induced by acetylcholine (Palade et al., 1989; Cook et al., 1992). Thus it is possible that inhibition of methacholine-induced contraction by procaine, quinine and tetraethylammonium is partly due to their inhibitory effects on the release of Ca^{2+} intracellular stores.

Taken together, the inhibition of methacholine-induced contraction by procaine, quinine and tetraethylammonium can be attributed to interference with voltage-dependent Ca^{2+} channels, muscarinic receptors or Ca^{2+} release from internal stores or with their combination. For this reason care should be exercised when using procaine, quinine and tetraethylammonium as a pharmacological tool for inhibiting K^+. However, the mechanism of the inhibitory action of procaine, quinine and tetraethylammonium on methacholine-induced contraction still remains open because they may also interfere with other steps of receptor-operated contraction.

In conclusion, we have shown in the present study for the first time that under resting tone the inhibitors of the K_{ATP} and the BK_{Ca} cause no contraction of the mouse tracheal smooth muscle. The closure of the BK_{Ca} can increase the mouse tracheal smooth muscle sensitivity to KCl and methacholine. The effects of 4-aminopyridine on the mouse trachea reflect chiefly activation of muscarinic receptors but not interference with K^+ channels. Procaine, quinine and tetraethylammonium inhibit both depolarization-induced and receptor-operated contraction of the mouse-isolated trachea.

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