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Inwardly Rectifying K^+ Currents in Gastric Myocytes of Guinea-pig

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To identify the presence of inwardly rectifying K^+ channels and its characteristics, membrane currents were measured using a whole-cell patch clamp from isolated gastric myocytes of guinea-pig. Change of external K^+ concentration from 5 to 90 mM induced an inward current at a holding potential of −80 mV. The high K^+-induced inward current was blocked by Ba^{2+} and Cs^+, but not by glibenclamide. With 90 mM K^+ in bath, the Ba^{2+}- and Cs^+-sensitive currents showed strong inward rectification. Ten mM TEA weakly blocked the inward current only at potentials more negative than −50 mV. With 90 mM K^+ in bath, hyperpolarizing step pulses from −10 mV induced inward currents, which were inactivated at potentials more negative than −70 mV. Reduction of external K^+ to 60 mM decreased the amplitudes of the currents and shifted the reversal potential to more negative potential. The inactivation of inward K^+ current at negative clamp voltage was not affected by removing external Na^+. These results suggest that the inwardly rectifying K^+ channels may exist in gastric smooth muscle.

Key Words: Inwardly rectifying K^+ channels, Ba^{2+}-sensitive currents, Gastric myocytes

INTRODUCTION

The K^+ channels of smooth muscle regulate membrane potential and cell excitability. The close of K^+ channels produces membrane depolarization and leads to activation of L-type voltage-dependent Ca^{2+} channels, thereby increasing muscle tension. In contrast, the opening of K^+ channels produces membrane hyperpolarization, which closes voltage-dependent Ca^{2+} channels and decreases muscle tension. There are four types of K^+ channels in smooth muscle (Bolton & Beech, 1992): (1) The Ca^{2+}-dependent K^+ channel is opened by membrane depolarization and intracellular Ca^{2+}. It is inhibited by low concentrations of tetraethylammonium (TEA). (2) The voltage-dependent K^+ channel is opened by membrane depolarization and inhibited by 4-aminopyridine. (3) The ATP-sensitive K^+ channel is opened, when the concentrations of intracellular ATP are depleted. It is inhibited by sulfonylureas (glibenclamide and tolbutamide) and activated by K^+-channel openers (lemakalim, cromakalim and pinacidil). (4) The inwardly rectifying K^+ (K_{IR}) channel is opened by membrane hyperpolarization and external high K^+, and inhibited by external Ba^{2+}.

K_{IR} channels only in vascular smooth muscle cells have been reported (Quayle et al, 1997). In addition, these channels are known to be restricted to only arterioles and small arteries (Edwards & Hirst, 1988; Quayle et al, 1993; 1996). Blocking of these channels in arterioles leads to substantial depolarization (Edwards et al, 1988.) Thus, K_{IR} channels are thought to be important for setting and stabilizing the resting membrane potential of vascular smooth muscle cells and for permitting long depolarizing responses. In gastric smooth muscle cells, glibenclamide-insensitive and Ba^{2+}-sensitive K^+ currents have been recorded by high external K^+ concentrations (Jun et al, 1998), consistent with those of vascular smooth muscle (Knot et al, 1996). This finding suggests that gastric smooth muscle also may have K_{IR} channels.

Therefore, the present study was undertaken to identify the presence of K_{IR} channels and their characteristics, using a whole-cell patch clamp from isolated gastric myocytes of guinea-pig.

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METHODS

Cell isolation

Guinea-pig of either sex, weighing approximately 200∼250 g, were stunned and bled. The stomachs were isolated and cut in the longitudinal direction along the lesser curvature in Krebs-Ringer solution. The antral part of stomach was cut and the mucosal layer was separated from the muscle layer. The circular muscle layer was dissected from the longitudinal muscle layer and cut into small segments in nominal Ca^{2+}-free physiological salt solution (PSS) for 30 min at room temperature. Then, these segments were transferred to Krebs-Ringer solution containing 0.1% collagenase (Wako), 0.1% trypsin inhibitor (Sigma) and 0.2% bovine serum albumin (Sigma), and incubated for 20∼30 min at 36°C. After digestion, the supernatant was

discarded and muscle segments were transferred into the modified Kraft-Brühe (K-B) medium (Isenberg & Klöckner, 1982). Single cells were obtained by gentle agitation with wide-bored glass pipette. Isolated gastric myocytes were kept in the modified K-B medium at 4°C until use. All experiments were carried out within 12 hours of harvesting cells and performed at room temperature.

Membrane currents recording

Isolated cells were transferred to a small chamber (400 μl) on the stage of an inverted microscope (IX-70, Olympus). The chamber was perfused at 2~3 ml/min with PSS. The standard whole-cell patch clamp technique was used to record currents (Hamill et al, 1981). Glass pipettes with a resistance of 3~5 MΩ were used. Membrane currents were amplified by an Axopatch 1-D (Axon Instruments), and command pulses were applied using an IBM-compatible computer and pCLAMP software v.6.0 (Axon Instruments). The data were filtered at 5 kHz and displayed on an oscilloscope (National), a computer monitor, and a pen recorder (Recorder 220, Gould), and analyzed using pCLAMP and Origin software (Microcal).

Solutions

Krebs-Ringer solution contained (in mM): NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 24, EDTA 0.026 and glucose 11.1 (pH 7.4, bubbled with 5% CO_2 : 95% O_2). PSS contained (in mM): NaCl 135, KCl 5, $MgCl_2$ 1, $CaCl_2$ 1.8, glucose 5, HEPES 5 and pH was adjusted to 7.4 by Tris. $CaCl_2$ was simply omitted in the Ca-free PSS. The high K^+-low Ca^{2+} external solution contained (mM): NaCl 52 (or 82), KCl 90 (60), $MgCl_2$ 1, HEPES 10, $CaCl_2$ 0.2 and pH was adjusted to 7.4 by NaOH. The internal pipette solution contained (mM): NaCl 10, KCl 102, $CaCl_2$, 1, GTP 1, HEPES 10, EGTA (ethyleneglycol-*bis* (β-aminoethyl ether)-N,N,N',N'-tetraacetic acid)10, ATP 0.1, $MgCl_2$ 1 and pH was adjusted to 7.2 by KOH (38 mM). Modified K-B solution contained (mM): L-glutamate 50, KCl 50, taurine 20, KH_2PO_4 20, $MgCl_2$ 3, glucose 10, HEPES 10, EGTA 0.5 and pH was adjusted with KOH.

Drugs

The following drugs were used. Glibenclamide, $BaCl_2$, CsCl and TEA were purchased from Sigma. Glibenclamide was dissolved in dimethylsulfoxide.

RESULTS

Inwardly rectifying current

A high-K^+-low-Ca^{2+} external solution has been used to increase the currents through K_{IR} channels and to reduce the attribution of voltage-dependent Ca^{2+} and Ca^{2+}-dependent K^+ channels, as described in a variety of cells (Bauer et al, 1990; Quayle et al, 1993). As shown in Figure 1A, change of external K^+ concentrations from 5 to 90 mM induced steady-state inward currents at a holding potential of −80 mV in gastric myocytes. The contribution of ATP-sensitive K^+ currents in the steady-state currents, was ruled out, because glibenclamide (10 μM) did not block the steady-state currents (Fig. 1B). To examine the role of inwardly rectifying K^+ channels in the steady-state currents,

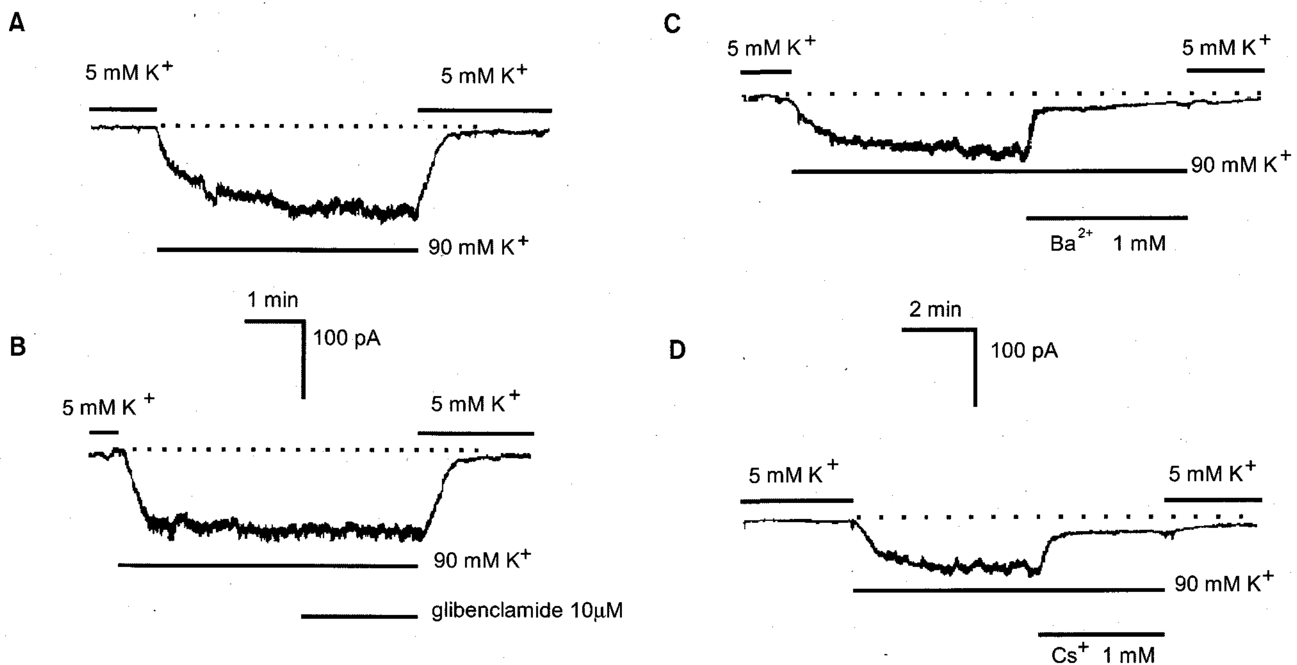

Fig. 1. Effects of glibenclamide, Ba^{2+} and Cs^+ on the steady-state inward currents in gastric myocytes of guinea-pig. A; changing external K^+ concentrations from 5 to 90 mM K^+ produced steady-state inward currents at −80 mV of holding potential. B; the treatment of glibenclamide (10 μM) did not affect the steady-state currents under this condition. C and D; Ba^{2+} (1 mM) and Cs^+ (1 mM) blocked the steady-state currents induced by external 90 mM K^+ at −80 mV of holding potential. Dotted line indicates zero current level.

the effects of Ba^{2+} and Cs^{+} were tested. Ba^{2+} (1 mM) and Cs^{+} (1 mM) were found to block the steady-state currents (Fig. 1C and D). Pure Ba^{2+}-sensitive current obtained by ramp pulse from −130 to 30 mV showed strong inward rectification and the reversal potential of −9.3±3.2 mV (n=3) in current-voltage relationship, which is close to equilibrium potentials of K^{+} (Fig. 2A and B). These results indicated that the steady-state currents induced by external K^{+} might be K_{IR} currents. Therefore, to identify the presence of these channels, the whole-cell currents were recorded using a hyperpolarizing step pulse. Whole-cell patch clamp measurement in external 90 mM K^{+} revealed the presence of hyperpolarization-activated currents in gastric myocytes. As shown in Fig. 2C, the inward currents elicited by the hyperpolarizing voltage steps from −130 to 30 mV at a holding potential of −10 mV showed fast activation and inactivation kinetics. The activation and inactivation of the inward currents were time- and voltage-dependent. Maximum inward currents occurred in 10~20 ms after the onset of the hyperploarizing voltage steps at a holding potential of −130 mV. Inactivation occurred at potentials more negative than −70 mV and was more pronounced at higher negative potentials. Time constant of inactivation was 53.7±2.1 ms, 103.7±5.7 ms, and 215.5±12.3 ms (n=5) at holding potentials of −130, −110, and −90 mV, respectively. The time constants decreased with increasing amplitude of hyperpolarizing pulse. Current-voltage relationship for the peak amplitudes of inward currents are shown in Fig. 2D. The peak currents were increased at more negative potentials and revealed strong inward rectifying properties.

Ionic selectivity of inwardly rectifying currents

To investigate the ionic selectivity of hyperpolarization-activated currents, external K^{+} concentrations were changed. As shown in Fig. 3A and B, the amplitudes of inward and outward currents were decreased at whole test potentials

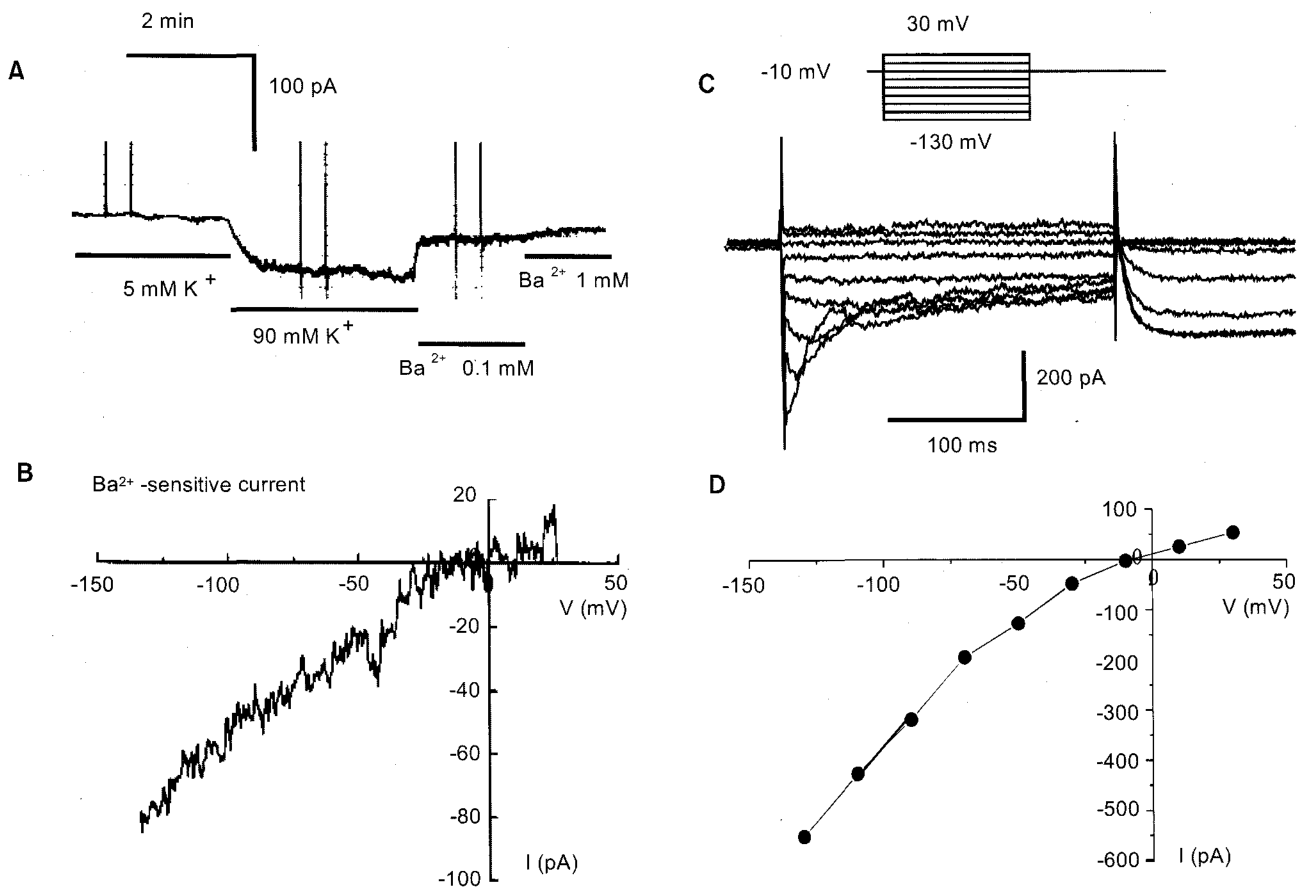

Fig. 2. Ba^{2+}-sensitive currents recorded by ramp pulse in the gastric myocytes of guinea pig. A; current trace of steady-state inward currents induced by external 90 mM K^{+} at −80 mV of holding potential. External Ba^{2+} inhibited the steady-state inward current. B; current-voltage relationship of Ba^{2+}-sensitive current. Ramp stimulation pulses from −130 to 30 mV were applied in the presence of Ba^{2+}. The current after Ba^{2+} was subtracted from the current before Ba^{2+} to obtain the Ba^{2+}-sensitive current. The Ba^{2+}-sensitive current showed strong inward rectification. The estimated equilibrium potential for K^{+} was −11 mV with 90 mM external K^{+}. The real reversal potential of Ba^{2+}-sensitive current was about −10 mV. C; whole-cell inwardly rectifying currents were recorded by external 90 mM K^{+} in the gastric myocytes of guinea-pig. The hyperpolarizing voltage step protocol was indicated above the current traces. The currents showed rapid activation and inactivation at potentials negative more than −70 mV. D; current-voltage relationship of the peak amplitudes of the inward currents showed strong inward rectification.

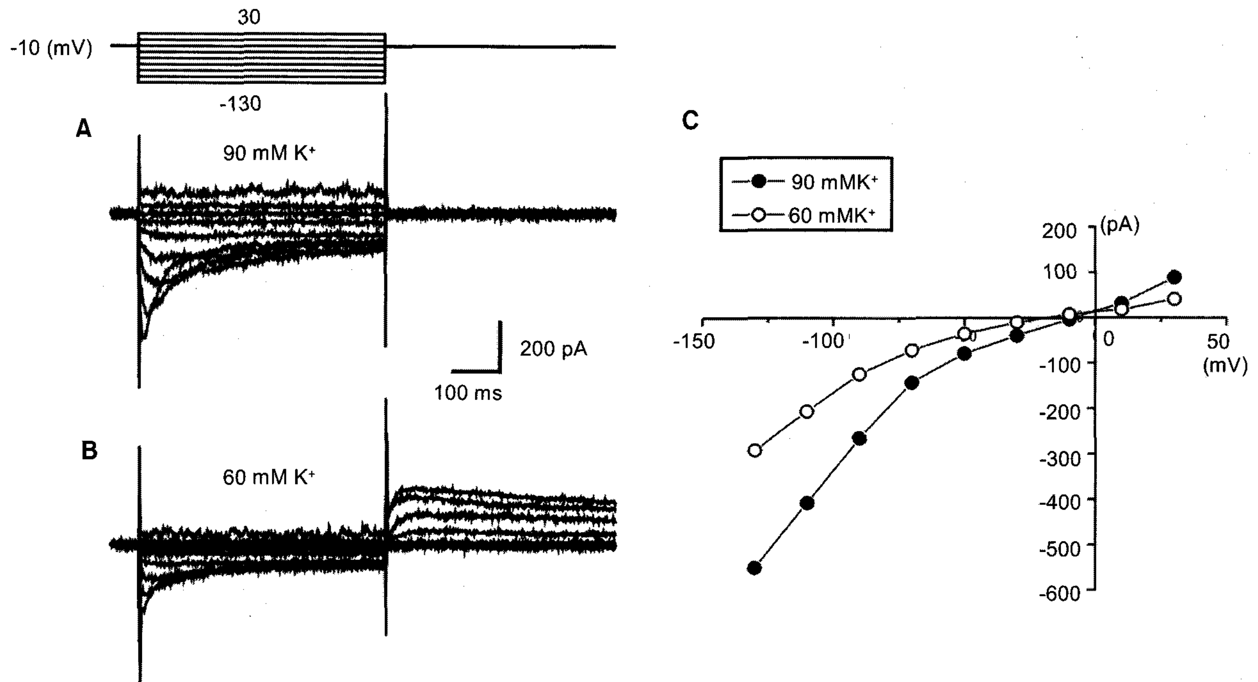

Fig. 3. Whole-cell inwardly rectifying currents recorded by external 60 mM K^+ in the gastric myocytes of guinea-pig. A; control current traces in external 90 mM K^+. B; current traces in external 60 mM K^+. The amplitude of inwardly rectifying currents in external 60 mM K^+ was smaller than in external 90 mM K^+. C; current-voltage relationship of the peak amplitudes of the inward currents. The inward and outward currents were decreased and the reversal potential shifted to more negative potential in external 60 mM K^+.

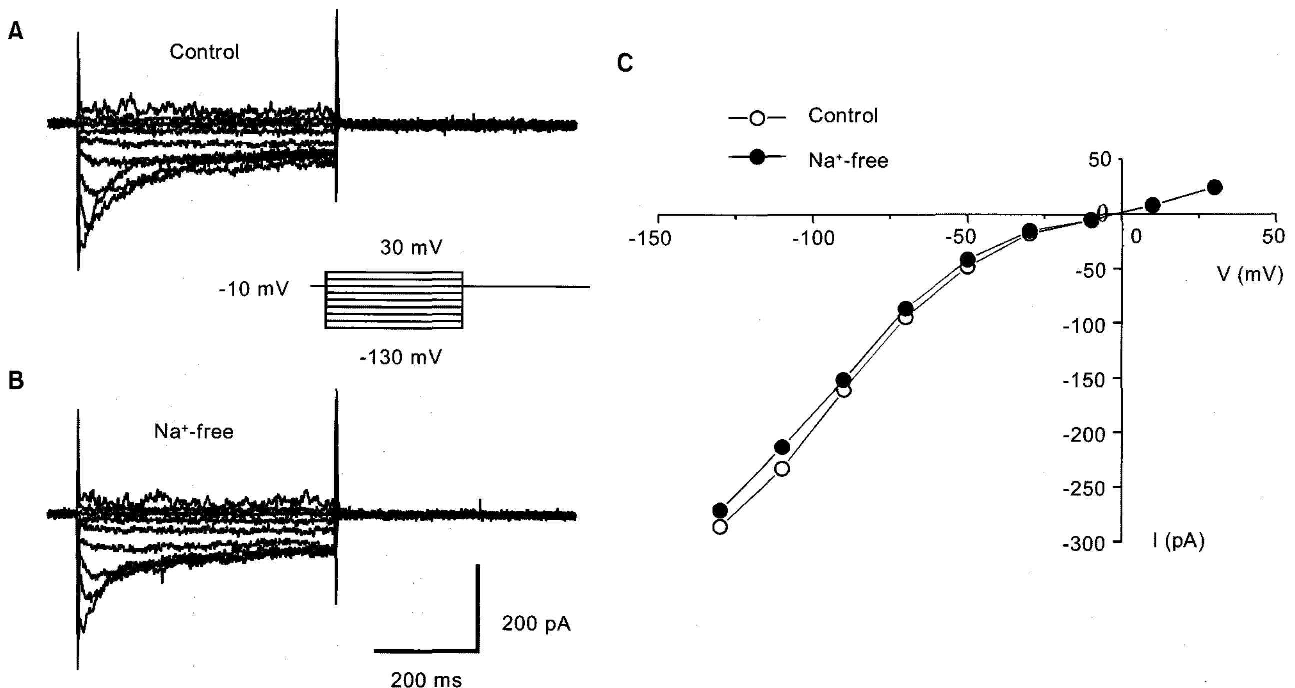

Fig. 4. Effects of external Na^+ -free on the inwardly rectifying currents in gastric myocytes of guinea-pig. A; control membrane currents recorded by external 90 mM K^+. B; membrane currents recorded in the absence of external Na^+. External Na^+ was replaced with NMDG. The current amplitude was affected little by Na^+-free. External Na^+-free did not influence inactivation of the inwardly rectifying current. C; current-voltage relationship of the peak inward currents, shown in A and B. The reversal potential was not changed in the absence of external Na^+.

when the external K^+ changed from −90 to −60 mM, and the reversal potential was shifted to more negative in current-voltage relationship in Fig. 3C. In 60 mM K^+, the reversal potential revealed -19 ± 3 mV (n=4). The estimated reversal potential for 60 mM K^+ by the Nernst equation was −21 mV. These results indicate that hyperpolarization-activated currents are highly selective for K^+. To examine possible effects of Na^+ on the hyperpolarization-activated currents, external Na^+ was replaced with N-methyl-D-glucamine (NMDG). The replacement of external Na^+ with NMDG had very little effect on current amplitudes (Fig. 4A and B). Furthermore, the inactivation process still continued and the reversal potential in current-voltage relationships was not changed (n=4) (Fig. 4C).

Effects of TEA, Ba^{2+} and Cs^+

The effects of TEA on K_{IR} channels varied from cells to cells. In rat spinal cord astrocytes, K_{IR} currents were inhibited by 90% with external 10 mM TEA (Ransom & Sontheimer, 1995). But in lens epithelial cells, K_{IR} currents were inhibited only 53% by external 20 mM TEA (Cooper et al, 1991). As shown in Fig. 5A, 5 mM TEA had no effect, while 10 mM TEA inhibited K_{IR} currents at potentials more

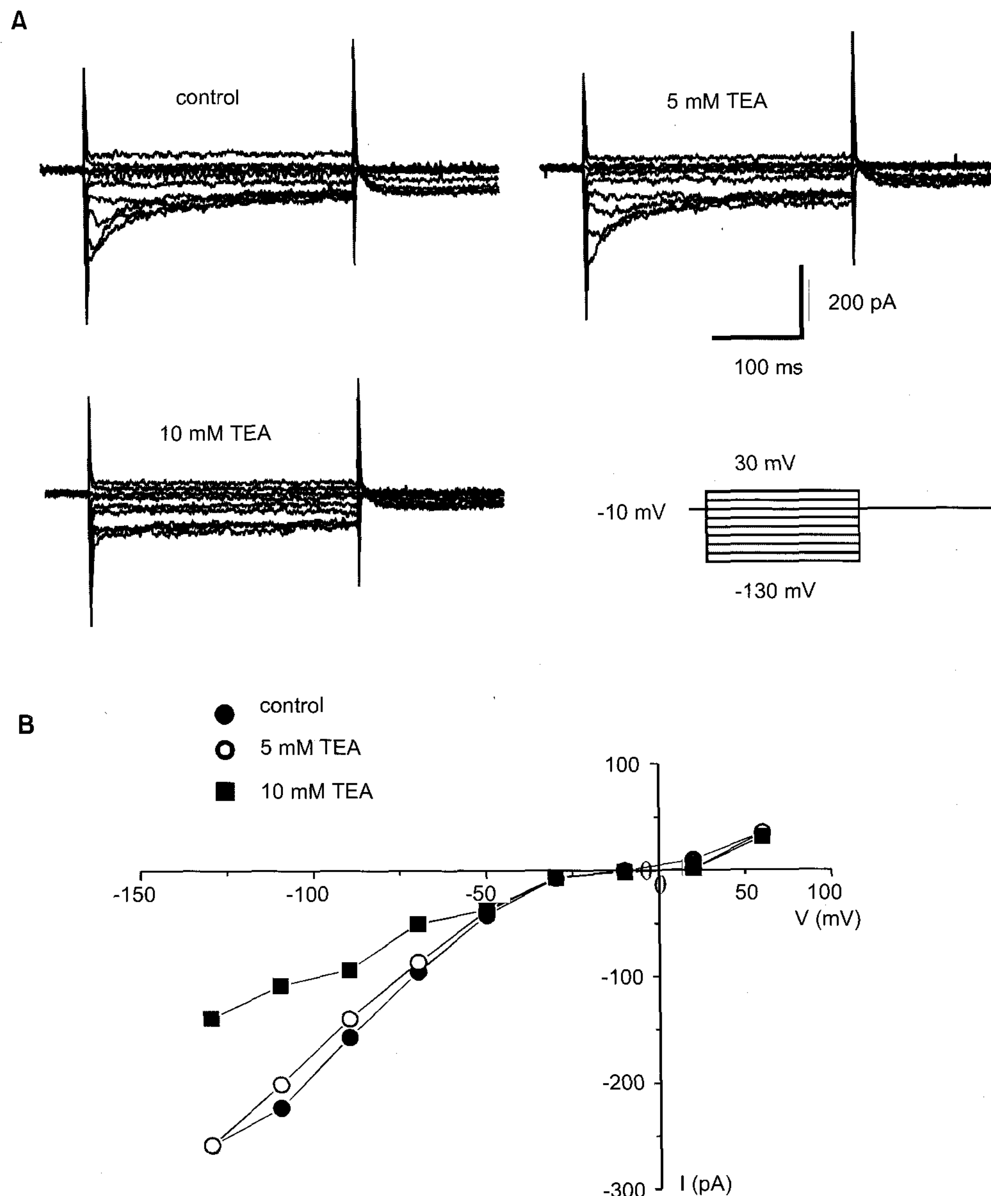

Fig. 5. Effects of TEA on the inwardly rectifying currents in gastric myocytes of guinea-pig. A; current traces in the control and after the application of TEA. Five mM TEA did not affect the control currents, while 10 mM TEA decreased the control currents. B; current-voltage relationship was obtained by plotting the peak amplitudes of the currents. Ten mM TEA decreased the currents at potentials more negative than −70 mV.

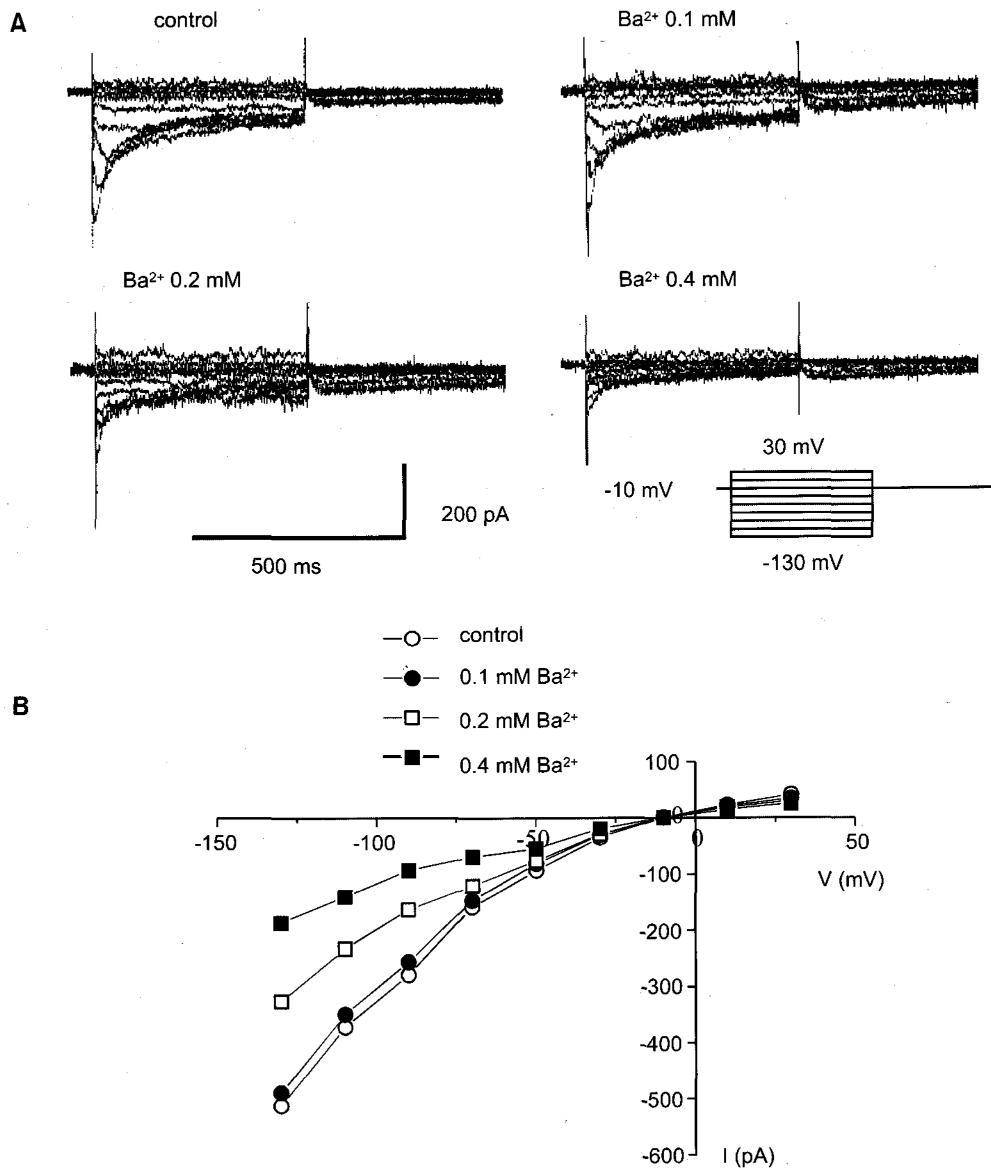

Fig. 6. Effects of external Ba^{2+} on the inwardly rectifying currents in gastric myocytes of guinea-pig. A; current traces in the control and after the application of Ba^{2+}. Ba^{2+} of 0.1 to 4 mM dose-dependently inhibited the currents. B; current-voltage relationship was obtained by plotting the peak amplitudes of the currents.

negative than −70 mV. Ten mM TEA reduced the currents by 53.5±3.4% and 48.2±2.8% (n=4) at holding potentials of −130 and −110 mV, respectively (Fig. 5B).

Ba^{2+} is an effective inhibitor of K_{IR} currents, however, the current sensitivity to block by external Ba^{2+} is different from cells to cells. In vascular smooth muscle (Edwards & Hirst, 1988; Quayle et al, 1993), neuron (Yamaguchi et al, 1990) and corticotropes (Kuryshev et al, 1997), Ba^{2+} blocks K_{IR} currents completely at μM concentrations. On the other hand, higher external Ba^{2+} (mM) was needed to block K_{IR} currents in pituitary (Bauer et al, 1990) and parotid secretory cells (Ishikawa & Cook, 1993). In the present study, Ba^{2+} did not completely inhibit K_{IR} currents evens at mM concentrations. Fig. 6A shows the control and the hyperpolarization-activated inward currents before and after the addition of Ba^{2+} to the bath. Ba^{2+}, ranging from 0.1 to 4 mM inhibited the hyperpolarization-activated inward currents dose-dependently. Four mM Ba^{2+} reduced the current by 67.4±4.1% and 52.9±2% (n=4) at holding potentials of −130 and −90 mV, respectively (Fig. 6B). Cs^{+} is known to block K_{IR} currents by voltage-dependent manner in a variety of tissues (Hagiwara et al, 1976; Yamaguchi et al, 1990). Representative hyperpolarization-activated inward currents before and after the addition of Cs^{+} to the bath are shown in Fig. 7A. Cs^{+} from 1 to 5 mM inhibited the inwardly rectifying K^{+} currents, dose-dependently. In this case, 5 mM Cs^{+} reduced current by 63.2±3.7% and 47.5±6.4% (n=4) at holding potentials of −130 and −90 mV, respectively. The pure Cs^{+}-sensitive currents are shown in Fig. 7B. Its current-voltage relationship (Fig. 7C) shows

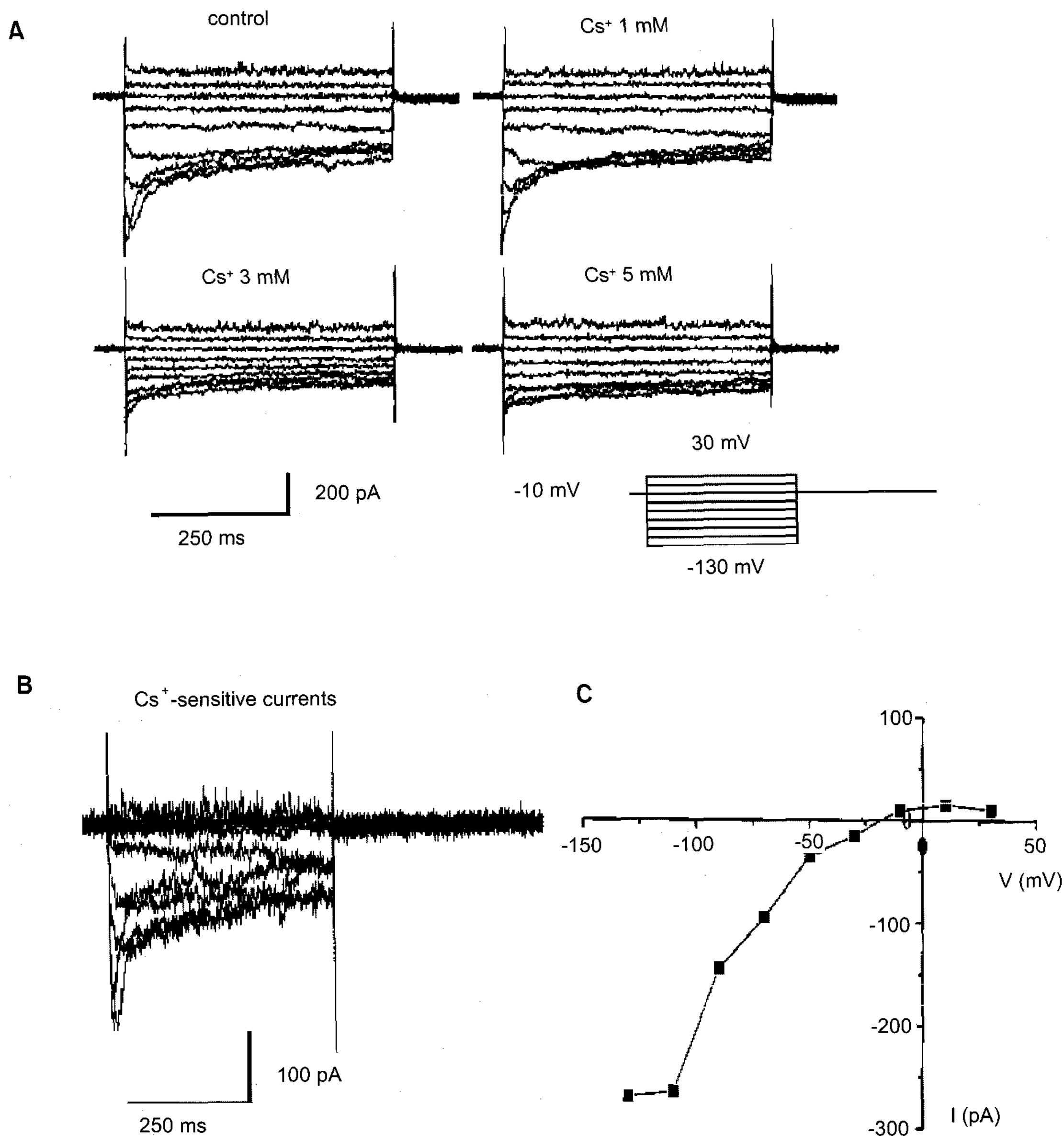

Fig. 7. Effects of external Cs^+ on the inwardly rectifying currents in gastric myocytes of guinea-pig. A; current traces in the control and after the application of Cs^+. Cs^+ of 1 to 5 mM dose-dependently inhibited the currents. B; pure Cs^+ -sensitive currents obtained by subtraction of the control current traces from those of 5 mM Cs^+ treatment. C, current-voltage relationship was obtained by plotting the peak amplitudes of the currents.

inward rectification.

DISCUSSION

In a variety of cell types, K_{IR} currents have been observed, even though their behavior and pharmacological effects are different. The current study demonstrated the presence of K_{IR} channels in gastric myocytes.

The common properties characteristic to K_{IR} currents are as follows: (1) the kinetics of inactivation is voltage- and time-dependent. The inactivation is faster and more complete at more negative potentials and shows single exponential time course (Bauer et al, 1990; Hoyer et al, 1991; Barros et al, 1992; Corrette et al, 1996). In our experiment, hyperpolarization-activated currents showed time- and voltage-dependent inactivation. Also, the inactivation showed single exponential time course. (2) K_{IR} currents are highly selective for K^+ and increasing external K^+ concentrations increases conductance (Hagiwara & Takahashi, 1974; Yamaguchi et al, 1990; Quayle, et al, 1996; Tare et al, 1998). In the present experiment, the reduction of external K^+ from 90 to 60 mM decreased conductance with a shift of reversal potential according to the estimated K^+ equilibrium potential. (3) K_{IR} currents are sensitive to both external Ba^{2+} and Cs^+ and show strong inward rectifi-

cation. Ba^{2+} and Cs^{+} inhibit K_{IR} currents and their inhibition is voltage dependent, the extent of inhibition increasing with membrane hyperpolarization (Edward & Hirst, 1988; Quayl et al, 1996; 1993; Jow & Numann, 1998). In the present experiment, K_{IR} currents were suppressed by external application of Ba^{2+} and Cs^{+}. The inhibition was enhanced at more negative potentials and Ba^{2+}- and Cs^{+}-sensitive currents showed strong inward rectification.

The inwardly rectifying properties of gastric myocytes can be distinguished from those of rabbit jejunum (Benham et al, 1987) and rat bladder (Green et al, 1996) smooth muscle, which have characteristics of the hyperpolarization-activated cation currents (I_h) described in the cells of the sinoatrial node (Difrancesco, 1985) and neuron (Pape, 1996): The inwardly rectifying current of jejunal and bladder smooth muscle shows a slow activation, a non-inactivating current, and is relatively insensitive to blockade by external Ba^{2+}. In addition, it represents Na^{+}-permeable cationic currents. In the present study, the reduction of external Na^{+} concentrations shifted reversal potentials to more negative potentials from the control values. However, the reversal potential of the inwardly rectifying current in gastric myocytes was not significantly changed by the absence of Na^{+} and shifted only by changing external K^{+} concentrations, indicating high selectivity to K^{+}.

Underlying mechanisms of the inactivation in several cells have been reported. In skeletal muscle, the inactivation gating is due to time-dependent changes of conductance caused by depletion of external K^{+} (Standen & stanfield, 1979), whereas the inactivation gating in neuron is due to time-and voltage-dependent blockade by external Na^{+} (Standen & Stanfield, 1979). On the other hand, in ventricular cells the inactivation gating is due to intrinsic voltage dependence (Sakmann & Trube, 1984). In the present study, K_{IR} currents were inactivated continuously in the absence of external Na^{+} and in the reduced external K^{+}. Thus, it seemed that the inactivation in gastric myocytes was caused by intrinsic time- and voltage-dependent gating process. The intrinsic voltage-dependent gating of K_{IR} currents has also been reported in cholinergic neurons from rat brain (Yamaguchi et al, 1990) and neuroblastoma cells (Hu & Shi, 1997).

In summary, the hyperpolarization-activated inward currents were recorded in gastric myocytes of guinea-pig. These currents showed rapid activation and inactivation, high K^{+}-selectivity, strong inward rectification and Ba^{2+}- and Cs^{+}-sensitive block, which are similar to those of K_{IR} currents as described in other tissues. These results suggest that the presence of K_{IR} channel in gastric myocytes. We, therefore, propose that K_{IR} channels similarly modulate electrophysiological and mechanical activity in gastric smooth muscle as they do in vascular smooth muscles.

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