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External pH Effects on Delayed Rectifier K^+ Currents of Small Dorsal Root Ganglion Neuron of Rat

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Under certain pathophysiological conditions, such as inflammation and ischemia, the concentration of H^+ ion in the tissue surrounding neurons is changed. Variations in H^+ concentration are known to alter the conduction and/of the gating properties of several types of ion channels. Several types of K^+ channels are modulated by pH. In this study, the whole cell configuration of the patch clamp technique has been applied to the recording of the responses of change of external pH on the delayed rectifier K^+ current of cultured DRG neurons of rat. Outward K^+ currents were examined in DRG cells, and the Charybdotoxin and Mn^{2+} could eliminate Ca^{2+}-dependent K^+ currents from outward K^+ currents. This outward K^+ current was activated around -60 mV by step depolarizing pulses from holding potential -70 mV. Outward K^+ currents were decreased by low external pH. Activation and steady-state inactivation curve were shifted to the right by acidification, while there was small change by alkalization. These results suggest that H^+ could be alter the sensory modality by changing and modifying voltage-dependent K^+ currents, which participated in repolarization.

Key Words: pH, K^+ current, Dorsal root ganglion, Patch clamp technique

INTRODUCTION

Dorsal root ganglion (DRG) neurons could be divided into several groups on the basis of their cell size, morphology, function, peripheral nerve conduction velocity and duration of somatic action potential (Andres, 1961; Harper et al, 1985a, b). It is thought that these properties are determined by the set of ionic channels specifically expressed in the DRG neurons of each group.

Primary afferents are a functionally diverse population of neurons that transduce and encode a variety of stimuli. Some of this diversity may reflect the differential distribution of voltage-dependent K^+ currents, which play an integral role in the regulation of a number of neuronal response properties including spike repolarization, interspike interval, and burst adaptation (Rudy, 1988). Also in most excitable cells with short action potentials, the high K^+ permeability comes from rapidly activating, delayed rectifier K^+ channels. The K^+ currents of mammalian sensory neurons have been described in embryonic, neonatal preparations (Kostyuk et al, 1981) and adult cells (Akins et al, 1993). This distinction is important because the electrophysiologic properties of embryonic and adult neurons differ (Sumeier et al, 1991).

A wide variety of biologic reactions are affected by changes in intracellular and extracellular pH. Proton has been long known as potent algogens and excitatory stimulants of primary nociceptive afferent. Although pH is tightly regulated by intracellular buffers and active transport mechanisms across the plasma membrane, alterations in intracellular or extracellular pH occur under certain pathophysiological circumstance, such as ischemia or high metabolic demands (Moody, 1984). Shifts in the extra-

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cellular pH have also been observed in response to neuronal activity. A prolonged acidification of the extracellular space was detected upon stimulation in many preparations (Chesler, 1992).

Alterations in H^+ concentration are known to alter the conduction and/or the gating properties for several types of ion channel. Acidification of the external medium decreases the flow of membrane current through voltage-dependent channels for Na^+, K^+ and Ca^{2+} (Hille, 1968; Woodhull, 1973; Krafte et al, 1988). In the pathophysiological conditions (pH 6-8), the extracellular H^+ affects voltage-gated Na^+, K^+ and Ca^{2+} currents in rat hippocampal CA1 neurons (Tombaugh et al, 1996). There are some studies concerning the effect of extracellular pH on the voltage-dependent K^+ currents in other cells (Ahn et al, 1997; Rich et al, 1997; Deutsch et al, 1989).

In this report, we tested the effect of extracellular pH on the K^+ currents in adult rat sensory neurons by using the whole-cell patch clamp technique. Our results show that pathophysiologically relevant changes in extracellular pH affects the properties of voltage-gated K^+ currents in adult mammalian neurons.

METHODS

Preparation of cells

Dissociated DRG (Dorsal Root Ganglion) neurons from 3-week-old Sprague-Dawley rats were prepared by enzymatic and mechanical dissociation by methods described in detail elsewhere. (Wood et al, 1988). Rats were rapidly decapitated and DRG neurons from all levels of thoracic spinal cord were carefully collected and half dissected in sterile cold PBS(phosphate buffer saline, Sigma, 4°C). DRG were washed with culture media, and incubated for 15 min in warm (37°C) culture media containing 0.125% collagenase (Worthington type II). The culture medium was a mixture of DMEM and F-12 solution (Sigma). The DRG were washed two times with PBS. The DRG were incubated in the warm PBS (37°C) containing 0.25% trypsin (Sigma type IX) and shaken gently 10 min. They were then transferred to the culture media containing 10% horse serum (Sigma) and 100 μg/ml DNase (Boehringer DNase I). Cells were isolated by gentle triturating of the ganglia using fire polished Pasteur pipettes with progressively finer tips. Isolated single cells were washed with the culture media containing 10% horse serum, 100 ng/ml nerve growth factor (NGF) 7s and plated on round glass coverslips. The glass coverslips were treated previously with poly-L-lysine and dried. Cells were placed in a 37°C incubator and gassed with 5% CO_2 atmosphere.

Electrophysiology

Experiments were performed on dissociated cell 6~48 hrs after plating on coverslips. Gigaseal was formed with borosilicate glass pipette (TW150F-4, World Precision Instrument, Inc). Patch pipettes were pulled in 2-stage pull on a micropipette puller (Type PP-83, Narishige). The pipettes were fire-polished and had a final resistance of 3~5 MΩ. Whole-cell currents were recorded using a patch-clamp technique with an Axopatch 200B amplifier and digidata 1200B interface. To obtain whole-cell configuration, cell attached patches were formed, and the cell membrane under the patch pipette was ruptured by gentle suction. After forming the whole-cell configuration, the capacitive transients were canceled and series resistance compensation (at least 70%) was routinely employed at the beginning of each recording. Data acquisition and analysis were performed using pClamp 6.0. The current amplitudes were normalized compared to maxium amplitude at +10 mV, and presented as % value in the figure. All experiments were done at room temperature (20~23°C).

Solution

For whole-cell studies, the two types of bath solution were used. One contained (in mM): 140 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES, and 10 glucose (pH 7.3). The other bath solution in which $CaCl_2$ was replaced by $MnCl_2$. In the alkaline solution of pH 7.9, HEPES was replaced with 10 mM Tris (hydroxymethy aminomethane).

The pipette solution contained (in mM): 140 KCl, 2 $MgCl_2$, 1 $CaCl_2$, 10 EGTA, 10 HEPES, 3 Na_2ATP (pH 7.3). Charybdotoxin was dissolved and stored as stock solutions in normal tyrode (100 pM). The acidic solution of pH 6.8 and 5.8 was adjusted with 1N HCl.

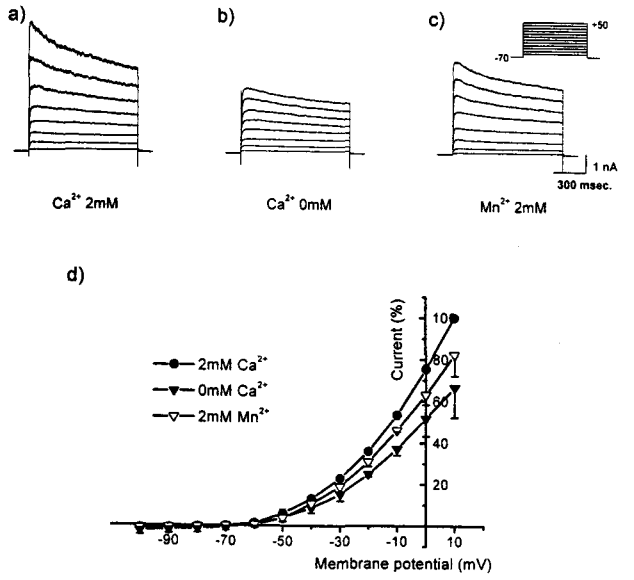

Fig. 1. Outward K^+ currents in different bath solutions. a. Whole cell K^+ currents were evoked by stepping the membrane potential from a holding potential of -70 mV to potential ranging from -100 to $+10$ mV in normal bath solution. b. Outward K^+ currents were decreased in Ca^{2+}-free bath solution, c. bath solution in which $MnCl_2$ was replaced by $CaCl_2$, in order to eliminate contaminating Ca^{2+}-dependent K^+ current. d. Current-voltage relationship of whole cell K^+ currents obtained at different bath solutions (n=10, mean$\pm$S.E).

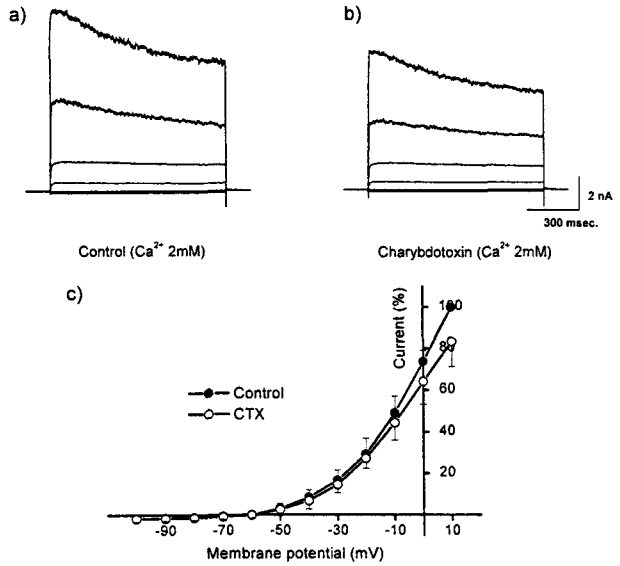

Fig. 2. Effect of CTX on outward K^+ currents in normal bath solution. a. Outward K^+ currents were recorded under control bath solution with 2 mM Ca^{2+}. b. Outward K^+ currents after addition of 100 pM Charybdotoxin (CTX). c. Current-voltage relationship in control and CTX treated cell. Peak currents were decreased in the presence of CTX. Pulse protocols were same as described in Fig. 1 (n=5, mean$\pm$S.E).

RESULTS

Delayed rectifier K^+ currents in small DRG

The variability of voltage-dependent K^+ currents in small size cells (diameter smaller than 25 μm) was striking. For whole-cell current recordings, the pipettes were filled with high-K^+ solution and normal external solution was used. The depolarizing steps from -70 mV activated large outward currents with threshold at about $-50 \sim -60$ mV. Figure 1a shows K^+ current recorded from a small DRG cells in normal bath solution. In order to eliminate the contamination of Ca^{2+}-dependent K^+ currents, currents were recorded in various bath solutions. The outward K^+ current decreases in Ca^{2+}-free bath solution (Fig. 1b) and in 2 mM Mn^{2+} containing bath solution (Fig. 1c). The current-voltage relationship (Fig. 1d) clearly indicates that the currents decrease at all voltages in the presence of Mn^{2+} and Ca^{2+}-free bath solution. These results show that the outward current was contaminated by Ca^{2+}-dependent K^+ current in normal bath solution, and that the Ca^{2+}-dependent K^+ current was blocked by Mn^{2+}. We examined the effects of Charybdotoxin (CTX), a potent inhibitor of Ca^{2+}-activated K^+ channel, on the outward K^+ current. Figure 2a and 2b show the current measured in the absence and presence of 100 pM CTX in normal bath solution, respectively. Fig. 2c shows the current-voltage relationship for outward K^+ currents. The outward K^+ currents were decreased by CTX, indicating the existence of Ca^{2+}-dependent K^+ currents. In order to verify that these Ca^{2+}-dependent K^+ currents were completely eliminated by 2 mM Mn^{2+}, we included 2 mM Mn^{2+} in bath solution. In this case, the addition of CTX had no effect on the outward K^+ current further (Fig. 3a, b). The current-voltage relationship was not changed at all (Fig. 3c). Thus, we confirmed that the use of Mn^{2+} containing external solutions effectively minimizes current due to Ca^{2+}-activated K^+ channels.

The voltage-dependent outward K^+ current in small DRG cells was reported to consist of fast inactivation and slow inactivation components (Kostyuk et al. 1981b). To test whether the outward current has fast inactivating component, we used different pulse-pro-

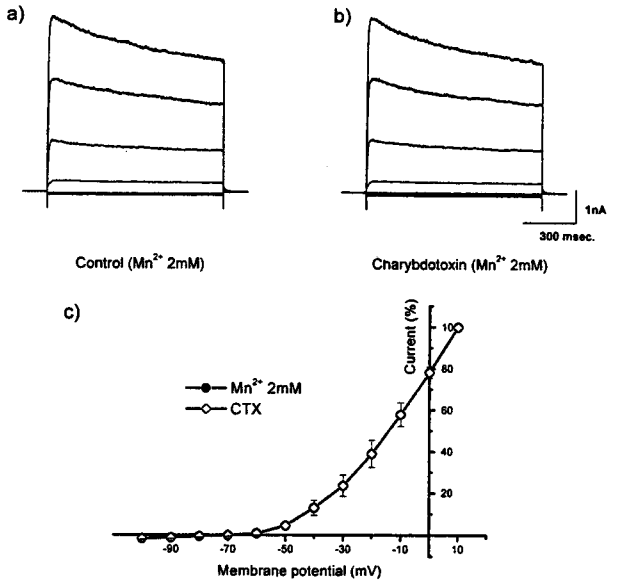

Fig. 3. Effects of CTX on outward K^+ currents in 2 mM Mn^{2+} containing bath solution. a. Outward K^+ currents in 2 mM Mn^{2+} containing solution were elicited by pulse protocols as in Fig. 1. b. The addition of CTX did not decrease outward K^+ currents further. c. Current-voltage relationship is shown. There were no effects of CTX (n=5, mean±S.E).

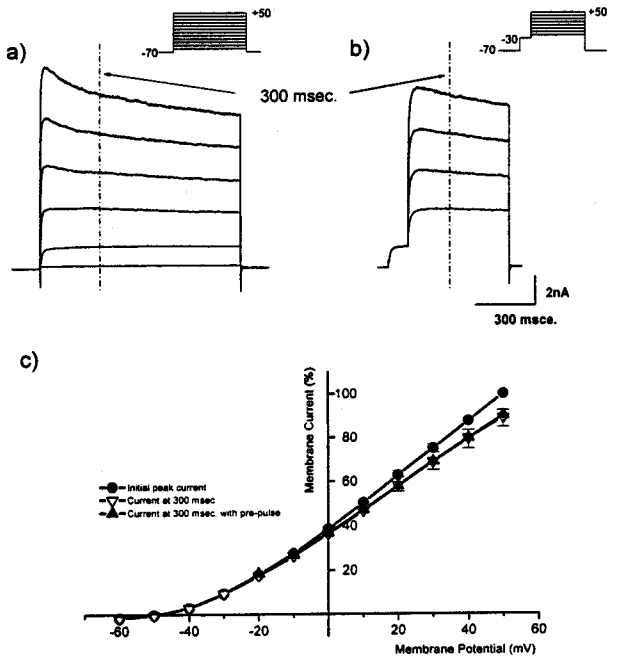

Fig. 4. Fast inactivating component of outward K^+ current. a. Whole-cell K^+ currents were evoked by stepping the membrane potential from a holding potential of −70 mV to potentials ranging from −100 to +10 mV increments. b. Fast inactivating component of outward K^+ current was inactivated by pre-pulses to −30 mV for 100 ms before the test pulse to +10 mV was given. c. The current-voltage relationship curve was fitted at peak current and in (a) at 300 ms after the start of the pulse in (a) and (b) (n=7, mean±S.E).

tocols. The small DRG neuron was held at −70 mV, and the whole cell K^+ current was elicited as described in Fig. 1 (Fig. 4a). On the other hand, the pre-pulse to −30 mV for 100 ms was applied before the command pulse was given (Fig. 4b). In Fig. 4c, the current-voltage relationships of the initial peak current of Fig. 4a, the current levels at 300 ms after the start of command pulse of Fig. 4a and 200 ms after the start of command pulse of Fig. 4b were compared. There is no significant difference between current levels after 300 ms in Fig. 4a and 4b, indicating that the fast inactivating current was inactivated during −30 mV pre-pulses. We obtained all the current-voltage relationship of the currents at 300 ms after the start of command pulse.

Effect of external pH on the delayed rectifier K^+ currents

We tested the effect of external pH change on the delayed rectifier K^+ currents. In some cells, the currents did not change by acidic treatment (4 out of the 10 cells). Fig. 5a, 5b, 5c show a typical response of these cells. The current-voltage relationship of the

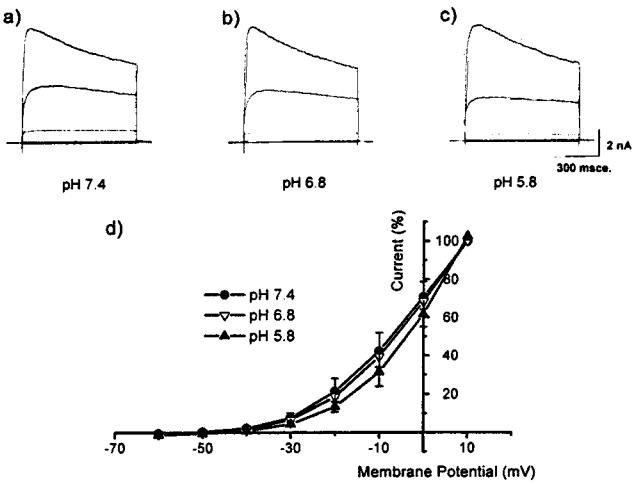

Fig. 5. Acidic pH did not change outward K^+ currents in some cells. a. Whole cell K^+ currents evoked by command pulse in bath solution containing 2 mM Mn^{2+} at pH 7.4, b. in pH 6.8 bath solution, c. in pH 5.8. d. Current-voltage relationship was obtained in control and low external pH conditions. (n=4, mean±S.E).

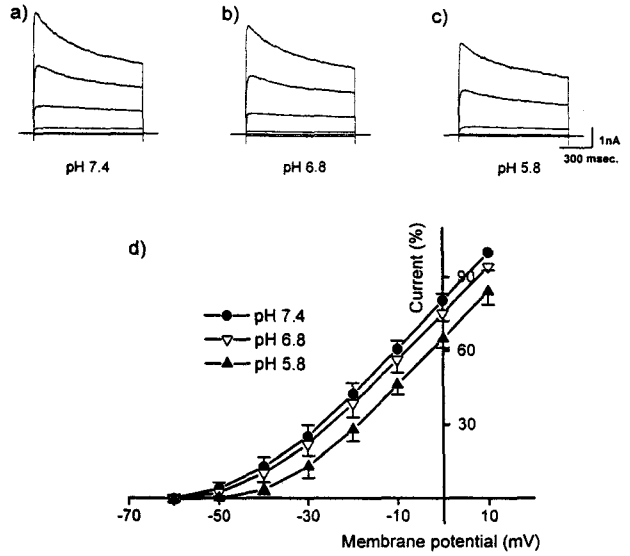

Fig. 6. Acidic pH decreased outward K^+ current in some cells. a. Outward K^+ currents were elicited at pH 7.4, b. at pH 6.8, c. at pH 5.8. Outward K^+ currents were decreased as pH decreased. d. Current-voltage relationship at 300 ms after the start of the pulses. The reversal potential was shifted to the depolarized direction about +15 mV (n=6, mean±S.E).

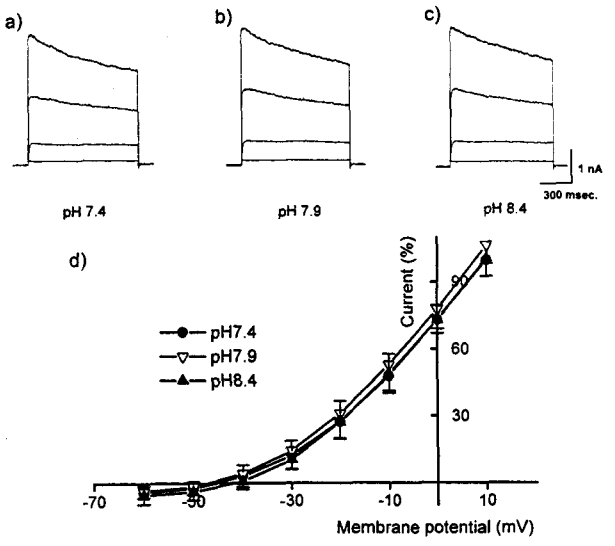

Fig. 7. Alkalization of external solution did not change outward K^+ current. a. Outward K^+ currents evoked by command pulse in bath solution containing 2 mM Mn^{2+} at pH 7.4, b. at pH 7.9, c. at pH 8.4. d. Current-voltage relationship was obtained at different pH levels (n=6, mean±S.E).

currents (Fig. 5d) shows that external pH change had little or no effect on the outward K^+ currents. In some cells, however, lowering external pH from 7.4 to 6.8, and 5.8 resulted in the decrease of K^+ currents (6 out of the 10 cells; Fig. 6a, b, c.). The current-voltage relationships of the currents are shown in Fig. 6d. At any given voltage, maximum currents were smaller at pH 5.8 than at pH 6.8. The threshold for activation of current shifted from approximately −60 mV at pH 7.4 to −45 mV at pH 5.8.

On the other hand, external high pH has no effects on the outward K^+ currents (Fig. 7). When the external pH was changed from 7.4 to 7.9 and 8.4, there was no change in currents (Fig. 7a, b, c). The current-voltage relationship of the currents shows no effect by increasing external pH (Fig. 7d). However, in some cells (4 out of the 10 cells), increasing external pH from 7.4 to 7.9 resulted in 5~10% increase of the current (Fig. 8b, c).

To investigate how changes in extracellular pH could modulate K^+ current, we examined the effects of external pH on the voltage-dependence of steady-state activation and steady-state inactivation. Fig. 8a, b, c show an example of K^+ currents superfused with extracellular solutions of pH 5.8, 7.4 or 7.9. Fig. 8d shows the activation curve of the current at different external pH. The activation curve at 7.9 was almost identical to that of at pH 7.4. However, the external pH 5.8 caused a positive shift in the voltage-dependence of activation. The threshold of activation was about −60mV at either of pH 7.4 and pH 7.9. It shifted to −45mV at pH 5.8.

To study the steady-state inactivation of the current, the holding potential of the cells was varied from −70 to 0 mV in +10 mV increments and then command pulses to 0 mV were applied for 300 ms. The outward K^+ current was not fully inactivated during 20 s pre-pulses. The steady-state inactivation curve of outward K^+ current was shifted to depolarizing direction by acidification, while there was only small change by alkalization (Fig. 8e). At pH 5.8, half of the channel is inactivated at about −15 mV, while at external pH 7.9, it is shifted to about −40 mV from −35 mV.

DISCUSSION

K^+ currents have a major impact on the firing properties of neurons. For example, Ca^{2+}-dependent K^+ currents are required for burst firing, whereas fast

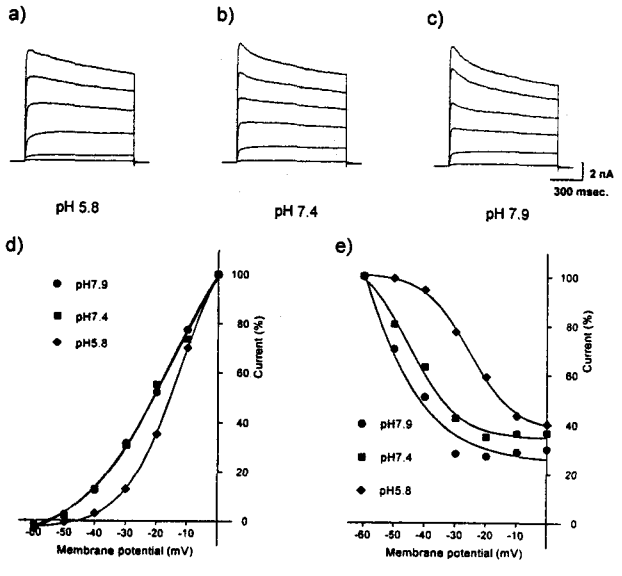

Fig. 8. The comparison of steady-state activation and inactivation of outward K^+ current by low and high external pH. a. Outward K^+ current recorded at pH 5.8, b. at pH 7.4, c. at pH 7.9. The bath solution containing 2 mM Mn^{2+}. The voltage dependence of steady-state activation and inactivation was determined using a double-pulse protocol. In holding potential −70 mV, voltage pulses were applied for 20 s to potentials between −60 and 0 mV in +10 mV increments and then then test pulses were applied to 0 mV during 300 ms, resulting in activating and steady-state inactivating outward currents. d. Activation curve was not sensitive to external pH 7.9. However, at pH 5.8 it shifted to the right, +15 mV. e. The outward K^+ current inactivated by a 20 s conditioning pulse to 0 mV. Low external pH moved inactivation curve to the depolarized direction, but high external pH showed opposite effect.

inactivating (A-type) are needed for slow repetitive firing (Rudy, 1988). Adult rat sensory neurons heterogeneously express transient and sustained K^+ currents. A Ca^{2+}-dependent K^+ current was also known to be present (Akins et al, 1993). Furthermore, five types of K^+ currents, one type of fast inactivating A current and four types of delayed rectifier K^+ currents, have been identified underlie voltage-gated K^+ conductance in small DRG neurons. Four types of delayed rectifier K^+ channels were found at a high density. These channels activated in the same voltage range between −60 and −10 mV. Deactivation of the channels at −80 mV lasted tens of milliseconds. The channels were separated on the basis of their sensitivities to TEA. (Safronov et al, 1996).

In this experiment, outward K^+ currents recorded in high K^+-pipette solution and were sensitive to 0.4 M TEA (data is not shown). The amplitude of currents was decreased differently in Ca^{2+}-free bath solution and 2 mM Mn^{2+} containing bath solution. CTX blocks some part of the outward current. Because CTX, a scorpion venom component, blocks mainly Ca^{2+}-dependent K^+ currents, the outward K^+ currents were contaminated Ca^{2+}-dependent K^+ current though even the pipette solution contains 10 mM EGTA. It is apparent that there are many types of Ca^{2+}-activated K^+ channels, which differ in their conductance and sensitivity to activation by both intracellular Ca^{2+} concentration and membrane voltage. Thus Ca^{2+}-activated K^+ channel could be open by depolarizing at low intracellular Ca^{2+} concentration such as 2 nM (Cow et al, 1997). Since CTX showed no effect in Mn^{2+} containing bath solution, this result indicates that outward K^+ current did not have Ca^{2+}-dependent K^+ current in the presence of Mn^{2+}. There were fast inactivating component and slow inactivating component in outward K^+ currents in small DRG neuron. In order to examine the fast inactivating component, we used double pulse protocols. It was inactivated by 30 mV pre-pulse. We could not observed the fast inactivating component at 300 ms after the start of test pulse.

Many of the effects of changes in extracellular pH have been attributed to changes in a variety of other cells. Extracellular pH shifts expert profound effects on intrinsic neuronal excitability. Such shifts in excitability may reflect changes in the properties of voltage-dependent membrane Na^+, K^+ or Ca^{2+} channels. Extracellular acidic solutions have been found to induced sustained pain and nociceptor excitation that is likely due to a non-selective cation current which has recently been identified in a subpopulation of DRG cells. These cells are sensitive to capsaicin and thus may represent nociceptor in culture (Issberner et al, 1996; Kress et al, 1996a; 1997b).

The effects of external pH on delayed rectifier K^+ currents in small DRG are qualitatively similar other preparations including squid giant axon (Hille, 1968) and frog node of Ranvier (Drouin, 1969). The effects of external low pH caused a positive shift in the voltage dependence of K^+ current activation and reduced amplitude, whereas elevated pH were not effective in K^+ current activation curve. These DRG cells which response to external low pH seem to have nociceptor. The inactivation kinetics of delayed rectifier K^+ current was sensitive to external low and high

pH. Extracellular acidification shifted the inactivation curve of K^+ current in depolarizing direction, whereas extracellular alkalinization shifted them in opposite direction. The left shift of steady-state inactivation would excite the small DRG cells. The activation and steady-state inactivation properties of K^+ currents at external low pH described in the present study closely match those reported in different neurons (Numann et al, 1987, Tombaugh et al, 1996). Assuming that the same pH sensitivity exists *in situ,* reduced external pH could, in principle, favor the reactivation of more K^+ current following an action potential, reducing the likelihood of recurrent spikes and burst firing (Cornner et al, 1971).

Elevated H^+ may be affected K^+ current inactivation via a sort of specific interaction with the channel in addition to the surface charge screening effect, though titration of specific protein residues can not be ruled out. Several theories have been proposed to explain these H^+ mediated effects (reviewed in Hille, 1992). As for changes in Na^+ current amplitude, H^+ can make voltage-dependent block by binding in the pore. Exisiting theories consider three effects; 1) low external pH might alter the gating kinetics so that even for large depolarization fewer channels are open at the peak, 2) might lower the single channel conductance by titrating distributed negative charge, 3) might lower single channel conductance by titrating an essential acid group within the pore itself.

Although a few studies have charicterized H^+ concentration effects on the delayed rectifier K^+ currents, the underling mechanism have not yet been identified clearly in DRG cells. This report demonstrates that moderate shifts in external pH alter the activation or inactivation properties of delayed rectifier K^+ current in isolated adult mammalian neurons. The K^+ channels determine the threshold for action potential firing, their contribution to the repolarizing phase of the action potential and the setting of the resting potential in small DRG neurons (Safronov et al, 1996). Thus, external pH changes could contribute to the effect on neuronal excitability

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