

## Full-length article

**Slack and Slick  $K_{Na}$  channels are required for the depolarizing afterpotential of acutely isolated, medium diameter rat dorsal root ganglion neurons<sup>1</sup>**Shang-bang GAO<sup>2,3</sup>, Ying WU<sup>2,3</sup>, Cai-xia LÜ<sup>2</sup>, Zhao-hua GUO<sup>2</sup>, Chen-hong LI<sup>2,4</sup>, Jiu-ping DING<sup>2,4</sup><sup>2</sup>Key Laboratory of Molecular Biophysics of the Ministry of Education, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China**Key words**Slack; Slick;  $Na^+$ -activated  $K^+$  channels; depolarizing afterpotential; dorsal root ganglion

<sup>1</sup>This work was supported by the National Natural Science Foundation of China (No 30470449 and 30470646), the Nature Science Foundation of Huazhong University of Science and Technology (No 20071986), and the Province Nature Science Foundation of Hubei (No 2003ABA096).

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Received 2008-04-15

Accepted 2008-06-03

doi 10.1111/j.1745-7254.2008.00842.x

**Abstract**

**Aim:**  $Na^+$ -activated  $K^+$  ( $K_{Na}$ ) channels set and stabilize resting membrane potential in rat small dorsal root ganglion (DRG) neurons. However, whether  $K_{Na}$  channels play the same role in other size DRG neurons is still elusive. The aim of this study is to identify the existence and potential physiological functions of  $K_{Na}$  channels in medium diameter (25–35  $\mu$ m) DRG neurons. **Methods:** Inside-out and whole-cell patch-clamp were used to study the electrophysiological characterizations of native  $K_{Na}$  channels. RT-PCR was used to identify the existence of Slack and Slick genes. **Results:** We report that  $K_{Na}$  channels are required for depolarizing afterpotential (DAP) in medium sized rat DRG neurons. In inside-out patches,  $K_{Na}$  channels represented 201 pS unitary chord conductance and were activated by cytoplasmic  $Na^+$  [the half maximal effective concentration ( $EC_{50}$ ): 35 mmol/L] in 160 mmol/L symmetrical  $K^+$ / $K^+$  solution. Additionally, these  $K_{Na}$  channels also represented cytoplasmic  $Cl^-$ -dependent activation. RT-PCR confirmed the existence of Slack and Slick genes in DRG neurons. Tetrodotoxin (TTX, 100 nmol/L) completely blocked the DRG inward  $Na^+$  currents, and the following outward currents which were thought to be  $K_{Na}$  currents. The DAP was increased when extracellular  $Na^+$  was replaced by  $Li^+$ . **Conclusion:** We conclude that Slack and Slick  $K_{Na}$  channels are required for DAP of medium diameter rat DRG neurons that regulate DRG action potential repolarization.

**Introduction**

$Na^+$ -activated  $K^+$  ( $K_{Na}$ ) channels were originally identified in cardiomyocytes and may provide protection against ischemia<sup>[1]</sup>.  $K_{Na}$  channels are accompanied by an increase in intracellular  $Na^+$  and may be involved in action potential shortening during ischemia<sup>[2]</sup>. They have been described to have many different functions in various neurons<sup>[3–7]</sup>.  $K_{Na}$  channels are activated at resting states in quail trigeminal ganglion neuron<sup>[5]</sup>. The accumulation of intracellular  $Na^+$  during a train of action potentials may result in the activation of  $K_{Na}$  channels in the soma of rat motor neurons<sup>[7]</sup>. It has also been proposed that  $Na^+$  influx through voltage-gated  $Na^+$  channels during a single action potential produces

a transient activation of  $K_{Na}$  channels, resulting in action potential repolarization<sup>[8,9]</sup>.

The molecular identity of native  $K_{Na}$  channels is considered as Slo2, originally called Slack (also termed Slo2.2)<sup>[10]</sup>. The second  $K_{Na}$  channel gene is called Slick (also termed Slo2.1), which is homologous to Slack<sup>[3, 10]</sup>. The Slick  $K_{Na}$  channel is activated rapidly in response to depolarization and cytoplasmic  $Cl^-$ . There is an ATP-binding site in the N-terminal regions of Slick. Slack and Slick  $K_{Na}$  channels could be activated by both  $Na^+$  and  $Cl^-$ . However, the Slick channel has low sensitivity to  $Na^+$ , but high sensitivity to elevating the internal  $Cl^-$  concentration<sup>[3]</sup>.

In rat dorsal root ganglion (DRG) neurons, the largest

cell bodies  $A\alpha$ - and  $A\beta$ -type DRG neurons usually transmit proprioceptive and tactile information, while smaller cell bodies  $A\delta$ - and C-type DRG neurons usually transmit pain and thermal information<sup>[11]</sup>. Scroggs and Fox reported that T-type  $Ca^{2+}$  currents were lower in small (20–27  $\mu\text{m}$ ) diameter DRG cell bodies (100 pA–1 nA) than observed in medium diameter (33–38  $\mu\text{m}$ ) DRG cell bodies (1–6 nA), and were not observed in large (45–51  $\mu\text{m}$ ) diameter DRG cell bodies<sup>[12]</sup>. Their results suggest the different distribution of  $Ca^{2+}$  channels in different size DRG neurons. Bischoff *et al* reported that  $K_{Na}$  channels set and stabilize the resting potential, but do not participate in single action potentials in rat small (20–25  $\mu\text{m}$ ) DRG neurons<sup>[4]</sup>. However, whether  $K_{Na}$  channels play the same role in medium diameter DRG neurons is still unknown.

In the present study, rat medium DRG neurons (25–35  $\mu\text{m}$ ), which were acutely isolated from lumbar segments of vertebrate column (L4–6) were used to study the potential functions of  $K_{Na}$  channels.  $K_{Na}$  channels were detected in ~80% membrane patches which displayed classical characterizations like large single channel conductance, subconductance states, and a block of single channel currents at positive potentials.  $K_{Na}$  channels expressed distinct cytoplasmic  $Na^+$  and  $Cl^-$  concentration-dependent activation in these classes of neurons. Moreover, we demonstrated the existence of Slack and Slick in DRG neurons by RT–PCR. Using tetrodotoxin (TTX, 100 nmol/L) to block  $Na^+$  influx, we found  $K_{Na}$  currents were outward  $K^+$  currents which might contribute to repolarization of DRG action potential. With regards to replacement extracellular  $Na^+$  with  $Li^+$ , we conclude that the outward  $K_{Na}$  currents contribute to the depolarizing afterpotential (DAP) of rat medium diameter DRG neurons.

## Materials and methods

**DRG neuron isolation** Three-to-five-week-old Wistar rats (male) were killed by decapitation. The lumbar segments of the vertebrate column were dissected and the lumbar L4, L5, and L6 DRG, together with the dorsal, ventral roots, and attached spinal nerves were taken out from the outside of the spinal column. These 6 DRG were transferred into iced Dulbecco's modified Eagle's medium (DMEM; Gibco, Grand Island, NY, USA) 13.5 g/L, NaCl 2.15 g/L, HEPES 2.0 g/L pH 7.4, 320 mOsm immediately. After the removal of attached nerves and surrounding connective tissues, DRG were minced with iridectomy scissors and incubated with enzymes, including 1 mL collagenase (type I; Sigma-Aldrich, St. Louis, MO, USA) 2 mg/mL, 1 mL trypsin (Type IX, Sigma) 0.5 mg/mL, and 50  $\mu\text{L}$  DNase, 4 mg/mL [in calcium-free buffer with 4 mg/mL BSA (bovine serum albumin)] in a 37 °C shaking

bath (170 r/min) for 35–40 min with gently mechanical trituration every 10 min. The addition of 8 mL of pre-incubated DMEM [including 20% FBS (fetal bovine serum)] was used to stop the enzymatic digestion. The isolated neurons were plated on 0.5 mg/mL poly-lysine coated glass coverslips and maintained in a 37 °C humidified incubator with 5%  $CO_2$  for at least 2 h before use. The medium neurons with a diameter of 25–35  $\mu\text{m}$  were used in the experiments.

**Electrophysiology** For whole-cell clamp, the pipette solution contained the following (in mmol/L): 140 K-gluconate, 20 KCl, 10 HEPES, 5 EGTA, 2 MgATP, and 0.3  $Na_2GTP$  (pH 7.2 with KOH, and 300 mOsm). The external solution contained (in mmol/L): 145 NaCl, 2.5 KCl, 4  $MgCl_2$ , 1 EGTA, 10 HEPES, and 10 glucose (pH 7.3 with NaOH, and 310 mOsm). To make the  $Na^+$ -free saline, 145 mmol/L NaCl was replaced with 145 mmol/L LiCl. For the inside-out recordings, the pipette extracellular solution contained (in mmol/L): 140 methanesulfonic acid, 150 KOH, 10 KCl, 10 HEPES, and 2  $MgCl_2$  (pH 7.2 with methanesulfonic acid). Testing solutions bathing the cytoplasmic face of the patch membrane contained (in mmol/L): 100 KCl, 60 KOH, 60 methanesulfonic acid, 5 EGTA, and 10 HEPES; 0, 20, 40, and 80 mmol/L NaOH was added for different concentrations of the  $Na^+$  solution (pH 7.2 with methanesulfonic acid). For different concentrations of  $Cl^-$ , redundant  $Cl^-$  was replaced with same quantity of methanesulfonic acid to make 10, 100, and 160 mmol/L  $Cl^-$ . Osmolarity was measured by a vapor pressure osmometer (Wescor INC., Logan, Utah, USA) and adjusted to 300–310 mOsm (pipette solution) and 310–330 mOsm (extracellular solution). All experiments were performed at room temperature (22–25 °C)<sup>[13]</sup>.

**RT–PCR** The RNeasy Mini Kit (QIAGEN, Valencia, CA, USA) was used to extract the total RNA from the rat DRG<sup>[14]</sup>. The cDNA of the Slack and Slick were amplified by RT–PCR with the Qiagen OneStep RT–PCR kit (QIAGEN, Valencia, CA, USA). Two primers for amplifying Slack and Slick (the upstream primer 5'-CATAACTGCTATGAGGATGC-3' and the downstream primer 5'-GTCTTGCCATCTGCCATGTAGTC-3') were used in the RT–PCR reaction. The RT–PCR products were extracted by QIAquick Gel Extraction Kit (QIAGEN, Valencia, CA, USA) and then ligated into a pCR2.1-TOPO vector (Invitrogen, Carlsbad, CA, USA) for the sequence analysis.

**Data analysis** Data were analyzed with Igor 5.03 (Wavemetrics, Lake Oswego, OR, USA), Clampfit (Axon Instruments Inc., Foster City, CA, USA), and SigmaPlot (SPSS, Chicago, IL, USA). Unless stated otherwise, the data are presented as mean  $\pm$  SEM. Significance was tested by Student's *t*-test, and differences in the mean values were considered

significant at a probability of  $P < 0.05$ .

The dose–response curve for the open probability ( $P_o$ ) of  $K_{Na}$  was drawn according to the Hill equation  $P_o = P_{(max)} / (1 + [EC_{50} / [Na^+]_i]^n)$ , where  $P_{(max)}$  is the maximum  $P_o$  of the  $K_{Na}$  currents, and  $[Na^+]_i$  is the concentration of cytoplasmic  $Na^+$ .  $EC_{50}$  and  $n$  denote the  $Na^+$  concentration of the half-maximal effect and the Hill coefficient, respectively.

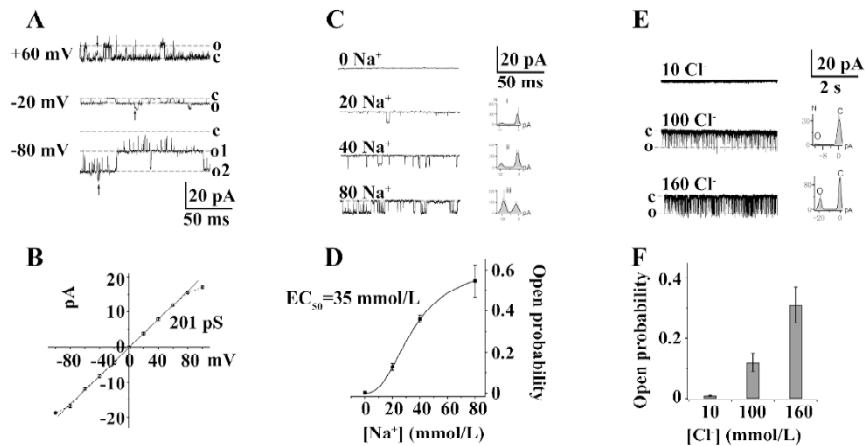
## Results

**$K_{Na}$  channels in DRG neurons** In our experiments,  $K_{Na}$  channels were present in approximately 80% in all inside-out patches. The representative single-channel currents were evoked by 80 mmol/L cytoplasmic  $Na^+$  ( $Na^+_i$ ) at different holding potentials which contained 2 opened  $K_{Na}$  channels (Figure 1A). The unitary chord conductance of the  $K_{Na}$  channel was  $201 \pm 3.8$  pS ( $n=8$ ) by fitting the current–voltage relationship curve through the line function (Figure 1B). Under this condition,  $K_{Na}$  channels displayed linear open characterization from  $-100$  to  $0$  mV. When the membrane potential was more positive than the potassium equilibrium potential, the single-channel currents exhibited inward rectification and opened in bursts (Figure 1A;  $+60$  mV), during which they fluctuated between the fully open, closed, and the substates. This was proposed as the result of the  $Na^+$  block of outward

$K_{Na}$  currents at positive potentials.

$K_{Na}$  channels exhibited different  $Na^+$  concentration-dependent activation in various neurons. The effect of different  $Na^+_i$  concentrations on the  $P_o$  of  $K_{Na}$  channels was studied in medium diameter DRG neuron cell bodies. Single-channel currents were not activated in the absence of  $Na^+_i$ , but could be gradually evoked in 20, 40, and 80 mmol/L  $Na^+_i$  (Figure 1C), although the activity of  $K_{Na}$  channels was not completely open in 80 mmol/L  $Na^+_i$  ( $n=12$ ). The best fit of the data using the Hill equation obtained the following parameters:  $P_{max}$  (maximum  $P_o$ ) is 0.62,  $EC_{50}$  is 35 mmol/L, and  $n$  (Hill coefficient) is 2.4 (Figure 1D). One possible explanation for the steep relationship between  $P_o$  and the  $Na^+_i$  concentration is that the binding of 2–3  $Na^+$  was necessary to open a  $K_{Na}$  channel. These results suggested that Slack  $K_{Na}$  channels exist in medium diameter DRG neurons.

Slack and Slick  $K_{Na}$  channels are reported to have overlapping distribution in the central neural system<sup>[6,15]</sup>. In order to understand the existence of  $Cl^-$ -activated Slick channel in medium diameter rat DRG neurons, different concentrations of cytoplasmic  $Cl^-$  (10, 100, and 160 mmol/L) were used to study the single-channel currents in an inside-out clamp (Figure 1E). The single channel conductance of  $Cl^-$ -activated  $K^+$  channels is  $182 \pm 1.2$  pS at  $-100$  mV with fre-



**Figure 1.**  $Na^+$  activated  $K^+$  conductance in DRG neurons. (A) single-channel currents were recorded from an inside-out patch activated by internal 80 mmol/L  $[Na^+]_i$  and 100 mmol/L  $[Cl^-]_i$  in 160 mmol/L symmetrical  $K^+ / K^+_i$  solution at different holding potentials. C and O indicate the close and open states of the channel, and arrows indicate the subconductance states. (B) current–voltage relationship of single channel from multiple patches. Slope conductance is  $201 \pm 3.8$  pS ( $n=8$ ) fitted by the line function. (C) currents activated by 0, 20, 40, and 80 mmol/L  $[Na^+]_i$  at the cytoplasmic face of the patch (with 100 mmol/L  $[Cl^-]_i$ ). Membrane potential was stepped to  $-100$  mV from a holding potential of  $0$  mV. Point histograms taken from the current traces are shown on the right. Bin width is  $0.25$  pA, and the data were fitted by the sum of 2 Gaussian curves (i: 20 mmol/L  $[Na^+]_i$ , ii: 40 mmol/L  $[Na^+]_i$ , iii: 80 mmol/L  $[Na^+]_i$ ). (D)  $P_o$  as a function of  $[Na^+]_i$ .  $P_o$  was calculated from 100–200 traces of different  $[Na^+]_i$ . Data were expressed as the mean  $\pm$  SEM ( $n=12$ ) and fitted with the equation:  $P_o = P_{max} / (1 + [EC_{50} / [Na^+]_i]^n)$ , where  $P_{max}$  (maximum  $P_o$ ) is 0.62,  $EC_{50}$  is 35 mmol/L, and  $n$  (Hill coefficient) is 2.4. (E) currents activated by 10, 100, and 160 mmol/L  $[Cl^-]_i$  at the cytoplasmic face of the patch (with 20 mmol/L  $[Na^+]_i$ ). (F) open probability ( $P_o$ ) as a function of  $[Cl^-]_i$  was calculated from more than 200 traces of different  $[Cl^-]_i$  ( $n=6$ ).



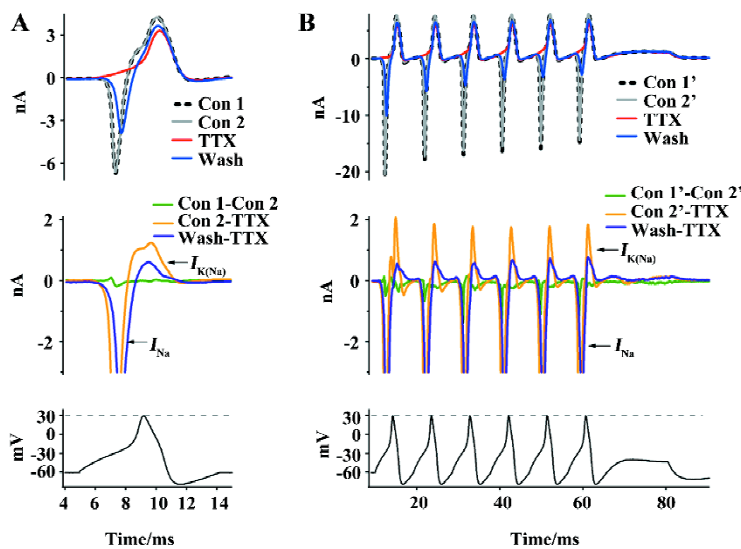
suggested that they play an important role in medium diameter DRG action potentials transferring.

**K<sub>Na</sub> channels contribute to DAP in medium diameter DRG neurons** The replacement of extracellular Na<sup>+</sup> with Li<sup>+</sup> is usually performed to study the assumed contribution of K<sub>Na</sub> channels in the regulation of action potential in current clamps. Single action potentials were evoked by short (30 ms) current pulses of 0.5 nA. The shape of action potential (AP) waveforms was compared from a certain cell in 145 mmol/L Na<sup>+</sup> or replacement by 145 mmol/L Li<sup>+</sup> and washout with 145 mmol/L Na<sup>+</sup> at intervals of 1–2 min, respectively (Figure 4A).

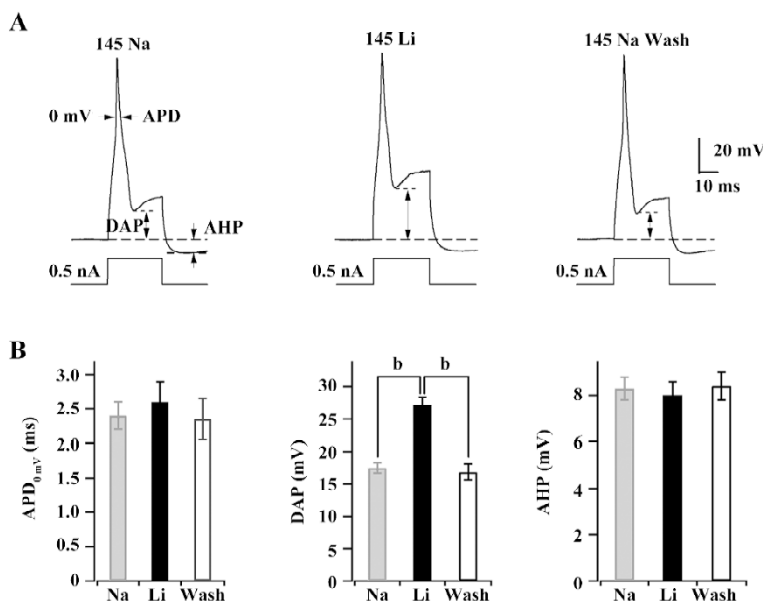
The absolute value of DAP was increased from 17.5±0.8 mV to 27.1±1.2 mV after the replacement of extracellular Na<sup>+</sup> with Li<sup>+</sup>, but action potential duration (APD) at 0 mV (APD<sub>0mV</sub>) and after hyperpolarizing potential (AHP) were not affected (Figure 4B). Washing out with 145 mmol/L Na<sup>+</sup> could recover the DAP of action potentials. The results indicated that K<sub>Na</sub> channels are required for action potential repolarization in medium diameter rat DRG neurons.

**Discussion**

DRG neurons transfer much complex sensory informa-



**Figure 3.** TTX blocked K<sub>Na</sub> currents evoked by action potentials. (A) representative whole-cell currents evoked by a single action potential. Con 1 and Con 2 were 2 control currents recorded at intervals of 1 min which had no difference. TTX completely blocked the inward Na<sup>+</sup> current and the following outward K<sub>Na</sub> current. TTX-sensitive inward Na<sup>+</sup> current and following Na<sup>+</sup>-dependent outward K<sub>Na</sub> current were obtained by Con 2-TTX (n=6). Na<sup>+</sup> currents and following outward K<sub>Na</sub> current were restored partially after washing out TTX (wash-TTX, n=6). A single action potential stimulation waveform is shown at the bottom. (B) a train of action potentials (6 action potentials) as a stimulation waveform was used to simulate and evoke the rough physiological inward Na<sup>+</sup> currents. Con 1' and Con 2' were 2 control currents recorded at intervals of 1 min which had no difference. Continuous Na<sup>+</sup> and K<sub>Na</sub> currents were the same as in (A) (Con 2'-TTX, n=6). A stimulation waveform of 6 action potentials is shown at the bottom. Data were recorded at intervals of 1 min.



**Figure 4.** K<sub>Na</sub> channels were required for DRG DPA. (A) representative single action potentials evoked by a 0.5 nA current pulse for 30 ms were recorded in 145 mmol/L Na<sup>+</sup>, and placement by 145 mmol/L Li<sup>+</sup> and 145 mmol/L Na<sup>+</sup> washout solutions in free Ca<sup>2+</sup> extracellular solution, respectively. (B) characteristic parameters of a single action potential were compared in Na<sup>+</sup>, Li<sup>+</sup>, and washout extracellular solution: APD<sub>0mV</sub>, DAP absolute value, AHP absolute value. DAP increased after extracellular Na<sup>+</sup> was replaced with Li<sup>+</sup>, but APD<sub>0mV</sub> and AHP did not change (n=8). <sup>b</sup>P<0.05.

tion like pain, temperature, proprioceptive, and tactile information<sup>[8,9]</sup>. Different sensory information might depend on different size DRG neurons. Sensory information transfer was thought to be coded on the DRG action potential firing frequency, amplitude, and firing pattern. The shape of neuron action potentials was dependent on the opening of various ion channels on the cell periphery. In this study, the results showed that the Slack and Slick Na<sup>+</sup>-activated K<sup>+</sup> channels existed and contributed to action potential DAP in acutely isolated, medium diameter rat DRG neuron cell bodies. Native K<sub>Na</sub> channels had distinct properties similar with the cloned Slack and Slick channels, including a large single channel conductance (201 pS; Figure 1), sensitivity to intracellular Na<sup>+</sup> and Cl<sup>-</sup> (Figure 1), multiple subconductance states, and a block of single channel currents at high positive potentials (Figure 1)<sup>[3,10]</sup>. RT-PCR demonstrated that both Slack and Slick K<sub>Na</sub> channels existed in the DRG neurons (Figure 2). This method has been successfully used to demonstrate that the β2-subunit, but not β3-subunit, induces the inactivation of calcium-activated potassium (BK) channel in small DRG neurons<sup>[14]</sup>. However, how K<sub>Na</sub> channels are opened under physiological conditions and whether K<sub>Na</sub> channels contribute to regulate the physiological functions in medium diameter rat DRG neurons is unknown. Using a real action potential stimulation waveform, whole-cell K<sub>Na</sub> currents appeared to be activated by Na<sup>+</sup> influx through TTX-sensitive Na<sup>+</sup> channels (Figure 3). The transient currents did not appear to be the results of the lack of space clamp because the neurons examined were small with very short processes and their series resistance was compensated. Additionally, Na<sup>+</sup> current was blocked reversibly by TTX. In a current clamp, we demonstrated that the K<sub>Na</sub> channels were required for action potential DAP in medium diameter rat DRG neurons by replacing Na<sup>+</sup> with Li<sup>+</sup> (Figure 4). The effect of replacing Na<sup>+</sup> on the DAP did not appear to be a result of an action of the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger or the Na<sup>+</sup>-H<sup>+</sup> exchanger because of the intracellular solution containing EGTA or a high HEPES concentration.

**Functions of K<sub>Na</sub> channels** Over the past several years, many physiological functions of K<sub>Na</sub> channels have been proposed. One of the surprises is that such channels can act over a wide range of time scales to influence the action potential firing pattern of neurons. The physiological roles of K<sub>Na</sub> channels have been difficult to characterize because of the lack of specific K<sub>Na</sub> channel blockers. However, there have been several studies showing that K<sub>Na</sub> channels contribute to the regulatory neuronal activity and the action potential waveform to produce adaptation of firing rates and to set the resting membrane potential<sup>[5,16]</sup>. The kinetic prop-

erties of Slack channels suggest that they contribute to currents that develop slowly during maintained neuronal firing. Na<sup>+</sup>-dependent slow AHP lasting many seconds have been described in various neurons depending on Na<sup>+</sup> influx and following repetitive neuronal firing<sup>[18,19]</sup>. K<sub>Na</sub> channels participate in the DAP following a single action potential in rat hippocampal CA1 pyramidal cells<sup>[20]</sup>. The size of the DAP was controlled by the activation of an opposing K<sub>Na</sub> conductance that was detected as early as 5–10 ms after a single action potential<sup>[20]</sup>. In this work, we found that the K<sub>Na</sub> channels were activated by a Na<sup>+</sup> influx evoked by a single action potential in normal Ca<sup>2+</sup> free extracellular saline in medium diameter DRG neurons. The activated K<sub>Na</sub> currents were outward following Na<sup>+</sup> influxes. Using ionic replacement, we demonstrated that K<sub>Na</sub> channels were required for DAP, but not APD<sub>0,mv</sub> or AHP.

A recent study that found that the activity of Slack channels can be enhanced by estradiol raises the possibility that the activation of K<sub>Na</sub> channels contributes to estradiol-dependent neuroprotection in ischemia<sup>[21]</sup>. Although evidence of the possible role of K<sub>Na</sub> in pathologies is circumstantial, it raises that possibility that these channels could be therapeutically useful drug targets. Similarly, the existing function of Slack and Slick K<sub>Na</sub> channels in medium diameter rat DRG neurons may be useful in the research of therapeutic drugs for the treatment of pain.

## Author contributions

Shang-bang GAO and Jiu-ping DING designed research; Shang-bang GAO and Ying WU performed research; Cai-xia LÜ and Zhao-hua GUO contributed new analytical reagents and tools; Shang-bang GAO and Chen-hong LI analyzed data; Shang-bang GAO and Jiu-ping DING wrote the paper.

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