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The effect of pressure on potassium currents in the inner hair cells isolated from guinea-pig cochlea

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An increase in hydrostatic pressure in the endolymphatic system causes hydrops-related inner ear diseases such as Meniere's disease or low tone sensorineural hearing loss. In the present study, we investigated the effects of pressure exerted on potassium currents in acutely isolated inner hair cells of the guinea-pig cochlea using whole-cell voltage-clamp techniques. By applying negative or positive pressure via the patch pipette using a syringe, intracellular hydropressure was changed between −40 cm H_2O to +20 cm H_2O. Negative pressure potentiated the amplitude of potassium currents, whereas positive pressure suppressed the amplitude of potassium currents. Gadolinium, a blocker of stretch-activated cation channels, did not influence pressure-dependent changes in potassium currents; however, cinnarizine blocked pressure-dependent changes in potassium currents. The current changes were not dependent on the sign of the pressure change, that is, similar increases in negative pressures (between −10 cm H_2O and −40 cm H_2O) and similar decreases in positive pressures (between +10 cm H_2O and +20 cm H_2O) were observed.

Key words: cochlea, inner hair cell, potassium currents, pressure, gadolinium, cinnarizine

INTRODUCTION

A hydrops in the endolymphatic space causes several inner ear diseases such as Meniere's disease or low tone sensorineural hearing loss. The typical symptoms of these diseases include acute vertigo and temporary or permanent elevations in the low frequency hearing threshold. An increase in hydrostatic pressure in the endolymphatic system may occur as a consequence of an enlarged endolymphatic space (Thomsen et al. 1984) and may be a possible pathophysiological mechanism in hydrops-related inner ear diseases (Bohmer and Dillier 1990). However, it is unclear how hydrostatic pressure may affect the sensory signaling in cochlear hair cells.

There are two types of hair cells in the mammalian cochlea that subserve distinct functions and receive characteristic patterns of innervations. Inner hair cells (IHCs) receive nearly all afferent innervations and are primary acoustic transducers, whereas outer hair cells (OHCs) are involved in the mechanical amplication and fine tuning of cochlear vibrations *via* their electromotile response. In IHCs, three potassium currents are distinguishable by their pharmacology and activation kinetics (Kros and Crawford 1990, Marcotti et al. 2003). The fast activating current, $I_{K,f}$, is blocked by tetraethylammonium (TEA), but is resistant to 4-aminopyridine (4-AP). $I_{K,s}$ is activated more slowly on depolarization and is blocked by 4-AP, but not by TEA. Another potassium current, $I_{K,n}$, is already activated at the resting potential of the cell and, thus, determines the membrane potential and membrane constant (Housley and Ashmore 1992, Marcotti and Kros 1999). Potassium currents are known to participate in the repolarization and discharge behaviors of action potentials in neurons (Sanz et al. 2000, Sumners et al. 2002); therefore, changes in IHC potassium currents at various hydrostatic pressues may affect the IHC presynaptic function.

In the present study, we isolated IHCs from mature guinea-pig cochleae and investigated the effects of pressure exerted on potassium currents in IHCs involved in transduction onto the primary afferent fibers.

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METHODS

Preparation of isolated IHCs

Adult albino guinea-pigs (200–350 g) were killed by rapid cervical dislocation, both bullae were removed, and the cochlea was exposed. The cochlea, fused to the bulla, was placed in a Ca^{2+}-free external solution (mM: 142 NaCl, 4 KCl, 3 $MgCl_2$, 2 NaH_2PO_4, 8 Na_2HPO_4, adjusted to pH 7.4 with NaOH). The otic capsule was opened, allowing the removal of the organ of Corti attached to the modiolus. The organ of Corti was treated with trypsin (0.5 mg/ml, T-4665, Sigma) for 12 min, and gentle mechanical trituration was carried out. Trypsin was rinsed from the specimen by superfusing with a standard external solution (mM: 142 NaCl, 4 KCl, 2 $MgCl_2$, 1 $CaCl_2$, 2 NaH_2PO_4, 8 Na_2HPO_4, adjusted to pH 7.4 with NaOH) for at least 10 min before starting any experiments.

The most important landmarks for identifying IHCs are a tight neck and angle between the cuticular plate and the axis of the cell as described previously (He et al. 2000, Yang et al. 2002, Kimitsuki et al. 2009). In the present study, IHCs were isolated from all turns of the cochlea. IHCs in the basal turn are indistinguishable from those in the apical turn based on shape.

Recording procedures

Membrane currents were measured by conventional whole-cell voltage-clamp recordings using an EPC-10 (HEKA, Lambrecht, Germany). Data acquisition was controlled by the software PatchMaster (HEKA, Lambrecht, Germany). Recording electrodes were pulled on a two-stage vertical puller (PP830 Narishige, Tokyo, Japan) using 1.2 mm outside diameter borosilicate glass (GC-1.2, Narishige, Tokyo, Japan) filled with an internal solution (mM: 144 KCl; 2 $MgCl_2$; 1 NaH_2PO_4; 8 Na_2HPO_4; 2 ATP; 3 D-glucose; 0.5 EGTA; adjusted to pH 7.4 with KOH.). Pipettes showed a resistance of 4-8 MΩ in the bath and were coated with ski wax (Tour-DIA, DIAWax, Otaru, Japan) to minimize capacitance. The capacitance of the cell was 12.2 ± 3.4 pF (mean ± SD) and series resistance was 11.4 ± 3.6 MΩ (n=14). Gadolinium (Gd) chloride (439770, Sigma-Aldrich) and cinnarizine (C5270, Sigma-Aldrich) were applied under pressure (Pressure micro-injector: PMI-200, Dagan, Minneapolis) using pipettes with a tip diameter of 2–4 μm positioned at approximately 50 μm from the IHCs. Cells were continuously perfused with external saline and all experiments were performed at room temperature (20–25°C).

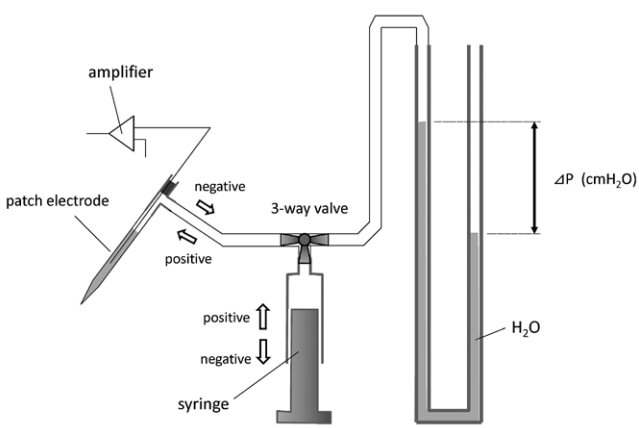

Fig. 1. Schematic illustration of the device used to change the pressure. Intra-pipette (intracellular) pressure was changed by pulling or pushing the pestle of the syringe and the pressure level was detected by measuring the difference between the two surfaces of the water in the U-shaped glass tube (ΔP, cm H_2O)

Pressure control

A negative and positive pressure was applied to the cell via the patch pipette with the apparatus shown in Figure 1. One end of the electrode holder was connected to the patch pipette and another end was connected to a syringe that made a gigaohm seal and whole-cell mode by applying negative pressure. This line could also change the intracellular hydropressure using the syringe. When making a gigaohm seal or whole-cell mode, a three-way valve was fixed only connecting the patch pipette and the syringe. After establishing the whole-cell mode, the valve was turned to connect the patch pipette, the syringe, and the U-shaped glass tube filled with water (H_2O). Patch electrode pressure (intracellular pressure) was changed by pulling or pushing the pestle of the syringe and the pressure level was detected by measuring the difference between the two surfaces of the water in the U-shaped glass tube (ΔP, cmH_2O)

Animal care

The experimental design was reviewed and approved (Accession No. A19-104-0) by the Animal Care and Use Committee, Kyushu University. All

procedures were conducted in accordance with the Guidelines for Animal Care and Use Committee, Kyushu University.

RESULTS

Negative pressure potentiated potassium currents in IHCs

Currents in response to hyperpolarizing and depolarizing voltage steps from a holding potential of −60 mV were recorded in IHCs. Typical current records are shown in the left of Figure 2A (control). IHCs had outwardly rectifying currents ($I_{K,f}$) in response to depolarizing voltage pulses, with only a slight inward current ($I_{K,n}$) when hyperpolarized. Negative pressure (−20 cm H_2O) into the cytoplasm of the IHC increased outward potassium currents (middle in Fig. 2A), and these were returned to the control level by releasing the pressure (right in Fig. 2A). The outward currents at a membrane potential of +110 mV were 9.9 nA, 12.5 nA, and 10.2 nA under control, −20 cm H_2O, and pressure-release states, respectively. These pressure-dependent current changes were not induced by the change of series resistance, because the initial current at the beginning of the voltage jump did not change by the negative pressure. If the series resistance changes, the initial current cannot be compensated and shows some spiked currents. The activating kinetics in each voltage-dependent outward K current preserved a fast rising rate (Fig. 2B, expanded time scale). Figure 2C represents the steady-state current-voltage (I–V) relationships measured at 80 ms command steps under control (open circle), −20 cm H_2O (closed circle), and pressure release states (open triangle). Each curve showed marked outward rectifications with maximal slope conductances of 63.4 nS, 83.0 nS, and 67.7 nS under control, −20 cm H_2O and pressure release states, respectively. Negative pressure potentiated the amplitude of potassium currents in fourteen of fifteen cells examined.

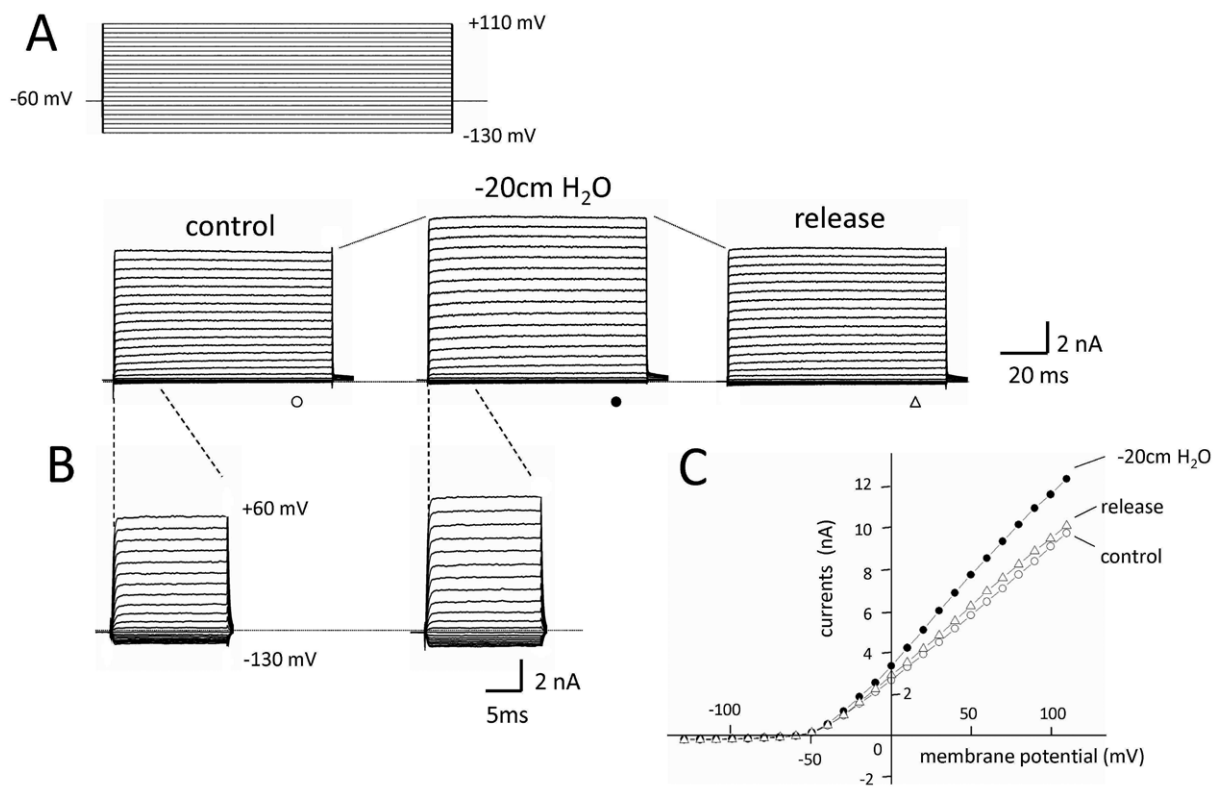

Fig. 2. Potassium currents in IHCs under negative pressure in the patch pipette. (A) The left panel shows control currents from the holding potential of −60 mV to various test potentials. The upper panel shows the voltage step protocol. The middle panel shows the currents under −20 cm H_2O and the right panel shows those after releasing the pressure to the control 0 level. (B) Initial activating phase in expanded time scales. (C) Steady-state current-voltage relationships for control (open circles), −20 cm H_2O (closed circles), and after releasing the pressure (open triangles). Currents were measured at 80 ms during the test pulses as shown in A (○, ●, Δ).

Effects of gadolinium on pressure-dependent potassium currents in IHCs

By adding negative pressure *via* the patch pipette, the cell membrane was stretched and may have activated stretch-activated cation channels. Stretch-activated channels were blocked by Gd (Yeh et al. 1998); gadolinium chloride was perfused and the pressure effects on potassium currents were examined. In 100 μM Gd solutions, the outward currents at a membrane potential of +110 mV were 5.4 nA, 6.7 nA, and 6.0 nA under control, −30 cm H_2O, and pressure-release states, respectively (Fig. 3). Increases in currents by the negative pressure were preserved, which suggested that stretch-activated channels were not involved in pressure-dependent changes.

Effects of cinnarizine on pressure-dependent potassium currents in IHCs

In vestibular type II hair cells, pressure-sensitive potassium currents ($I_{K.p}$) induced by increasing the hydrostatic pressure facing the cells have been previously reported (Düwel et al. 2003). Cinnarizine, a Ca^{2+} channel blocker, inhibited $I_{K.p}$ at lower concentrations than that required to block Ca^{2+} channels (Düwel et al. 2005, Haasler et al. 2009). In 10 μM cinnarizine solutions, negative pressure was applied in order to investigate whether the negative pressure changed potassium currents in IHCs or not. Before applying cinnarizine, −20 cm H_2O increased the outward current at a membrane potential of +110 mV from 10.8 nA to 11.4 nA (5.6% increase, left two traces in Fig. 4) and this was reversed to 10.8 nA by releasing the pressure (third trace from the left in Fig. 4). In 10 μM cinnarizine solutions, the amplitude of potassium currents did not change with the negative pressure (no increase, fourth trace from the left in Fig. 4). After washing cinnarizine in the external solutions, pressure-induced increases reappeared from 9.9 nA to 10.5 nA (6.1% increase, right two traces in Fig. 4). The relative values of the outward current amplitudes under the −20 cm H_2O state to that of the control were 1.11 ± 0.07 (mean ± SD) and 1.01 ± 0.03 in standard solutions and 10 μM cinnarizine solutions, respectively (n=10), which was significantly different (P<0.01, student's t-test).

Positive pressure suppressed potassium currents in IHCs

Positive pressure suppressed outward potassium currents (Fig. 5). The amplitudes of outward currents at a membrane potential of +110 mV were 8.7 nA and 7.7 nA under control and +10 cm H_2O states, respectively (Fig. 5A). Figure 5B represents the I–V relationships measured at the end of 100 ms command steps under control (open circle) and +10 cm H_2O states (closed circle). The maximal slope conductance was 56.8 nS under the control state, and 50.2 nS under the +10 cm H_2O state. Four of five cells showed an apparent suppression of potassium currents when positive pressure was applied.

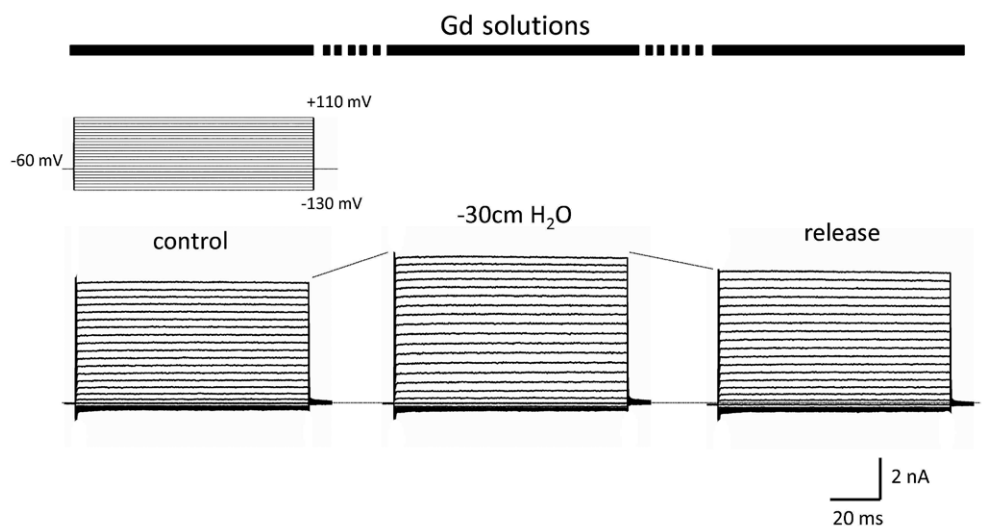

Fig. 3. Potassium currents under −30 cm H_2O pressure in 100 μM Gd solutions. The upper left panel shows the voltage step protocol.

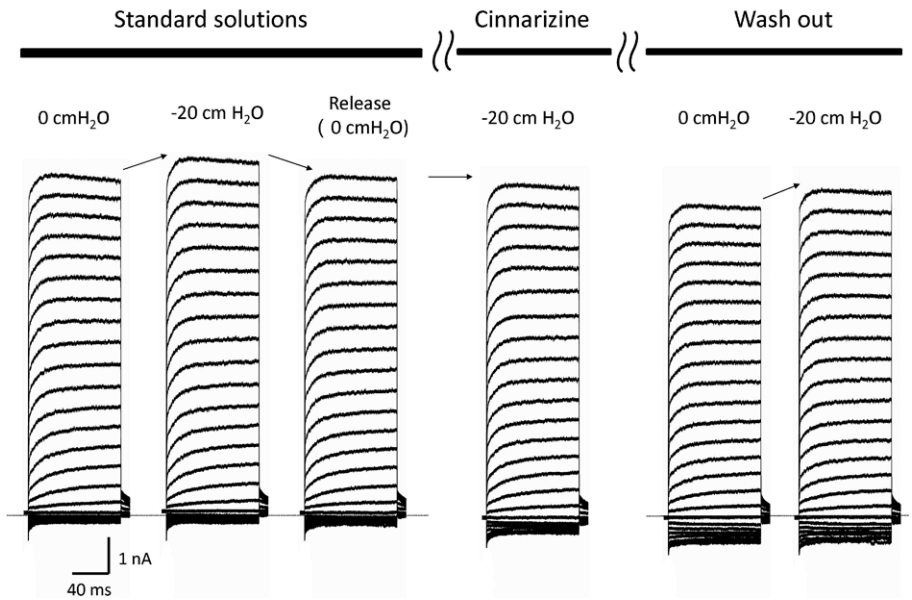

Fig. 4. Effects of cinnarizine on pressure-dependent potassium currents. The left three traces were recorded in standard solutions. The right two traces were recorded after washing-out the 10 μM cinnarizine solutions. Cinnarizine inhibited the augmentation in the amplitude of potassium currents induced by −20 cm H_2O.

Responses of potassium currents to various pressures in IHCs

Relative conductances measured at the membrane potential of +110 mV were calculated between −40 cm H_2O and +20 cm H_2O and plotted against the various pressures in Figure 6. The amplitude of potassium current changes was not pressure-dependent manner, that is, similar increases in negative pressures (mean ± SD were 1.25 ± 0.01, 1.29 ± 0.12, 1.26 ± 0.06, and 1.22 ± 0.08 under −40 cm H_2O, −30 cm cm H_2O, −20 cm H_2O, and −10 cm H_2O, respectively) and similar decreases in positive pressures (0.84 ± 0.07 and 0.93 ± 0.02 under +10 cm H_2O and +20 cm H_2O, respectively) were observed.

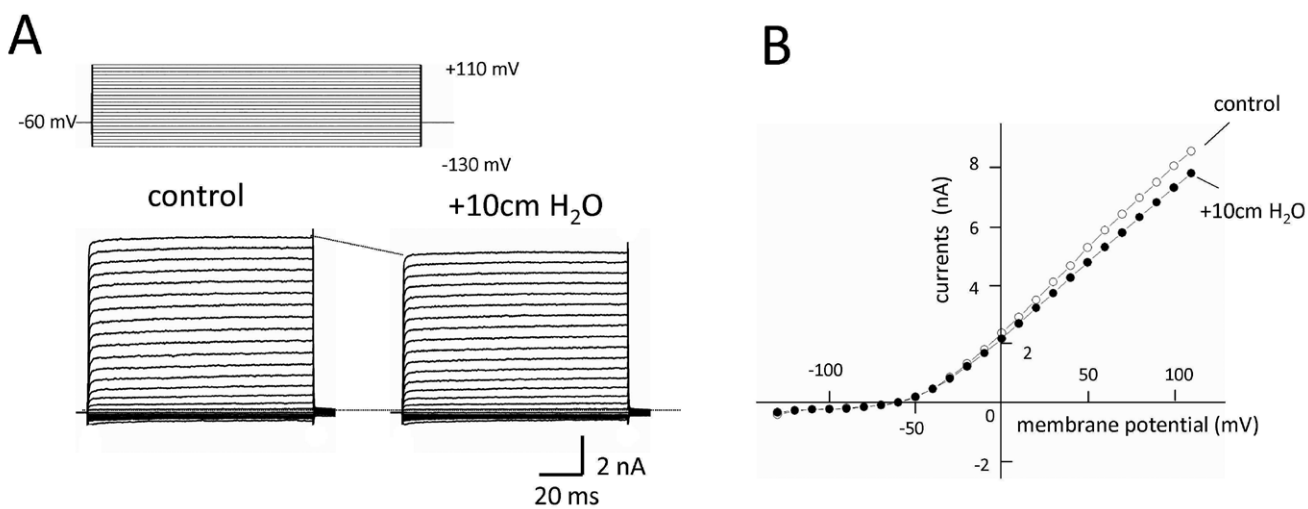

Fig. 5. Potassium currents under positive pressure in the patch pipette**.** (A) The left panel shows control currents and the right panel shows currents under +10 cm H_2O. The upper panel shows the voltage step protocol. (B) Steady-state current-voltage relationships for control (open circles) and +10 cm H_2O (closed circles). Currents were measured at the end of 100 ms test pulses.

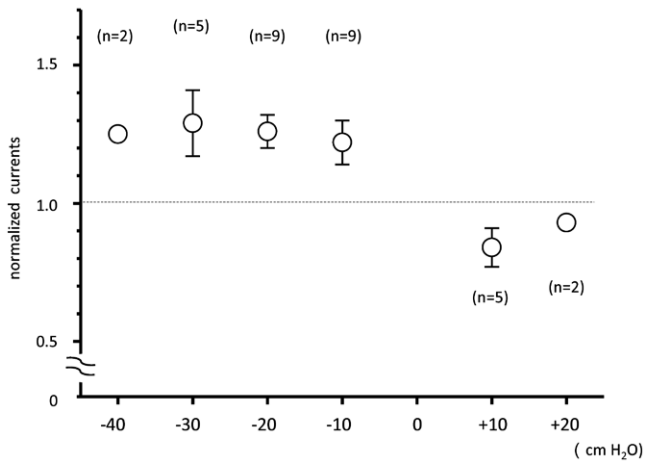

Fig. 6. Current-pressure relationships. The relative conductances of potassium currents measured at the membrane potential of +110 mV were calculated and plotted against the pressures of −40, −30, −20, −10, +10, and +20 cm H_2O. Open circles indicate the mean values and vertical lines indicate the SD.

DISCUSSION

Negative pressure through the patch pipette potentiated the amplitude of potassium currents in IHCs, whereas positive pressure suppressed the amplitude of potassium currents. Stretch-activated cation channels that are typically stimulated by the application of positive and negative intra-pipette pressures have been reported, e.g. in OHCs (Ding et al. 1991, Iwasa et al. 1991), in Reissner's membrane epithelial cells (Yeh et al. 1998), and in inner ear dark cells (Vetter et al. 1996). Stretch-activated cation channels may exist in IHCs; however, the pressure-dependent current changes reported in this study were not involved in stretch-activated channels because Gd, a stretch-activated channel blocker (Yeh et al. 1998), had no influence on pressure-induced current changes (Fig. 3).

Potassium outward currents in type II vestibular hair cells significantly increased by raising the hydrostatic pressure ($I_{K,p}$) (Düwel et al. 2003, 2005, Haasler et al. 2009). An increase in the hydrostatic pressure from 0.2 to 0.5 cm H_2O led to a sizable current increase that could be further enhanced by a pressure of 0.7 cm H_2O. They changed the hydrostatic pressure by varying the height of the bath solutions. In the present study, higher pressure was needed to observe the current changes, and the amplitude of current changes was not pressure-dependent (Fig. 6). This discrepancy may be attributed to differences in the methods for changing cell membrane pressures. The pressure in the pipette may not directly reflect that of cell's whole membranes, due to the various intracellular organelles that exist between the pipette tip and the cell membrane. Maintaining the stability of the whole-cell patch configuration is difficult especially under a positive pressure in the pipette because of the easy detachment between the rim of the patch pipette and the cell membrane, which causes an increase in leak currents. Negative pressure evoked an immediate increase in the amplitude of potassium currents in IHCs, was non-inactivating during depolarizing pulses, and promptly receded after the return to normal pressure, which corresponding to the properties of $I_{K,p}$ in vestibular type II hair cells (Düwel et al. 2003).

The outward K currents in IHCs mostly consist of $I_{K,f}$, which resemble Ca^{2+}-activated K^+ currents (BK currents) due to their kinetics and pharmacology (Lewis and Hudspeth 1983, Art and Fettiplace 1987). Several types of BK channels, such as those in osteoblasts (Rezzonico et al. 2003), chromaffin cells (Macdonald 1997), vascular smooth muscle cells (Kirber et al. 1992), colonic smooth muscle (Wang et al. 2010), intestinal neurons (Kunze et al. 2000), and neuroepithelium (Mienville et al. 1996) have been identified as mechanosensitive. Pressure increased the probability of channels being open and also increased the minimum number of channels apparent in the patches (Macdonald 1997). It was concluded that pressure acted directly on the channel proteins and/or their modulating reactions. Charybdotoxin, a blocker of Ca^{2+}-sensitive potassium currents, induced the complete inhibition of $I_{K,p}$ in vestibular type II hair cells (Düwel et al. 2003), which suggests that $I_{K,p}$ is attributable to the BK channel.

The effects of high pressure on several cell functions have been previously examined. Pressure has drastic effects on the release of synaptic vesicles; high pressure exponentially reduced the frequency of miniature end-plate currents in the neuromuscular junction (Ashford et al. 1982). Heinemann and coauthors (1987) reported the pressure dependence of nicotinic acetylcholine receptor channels in isolated membrane patches from cultured muscle cells. The mean amplitude of the single-channel current was not markedly influenced by pressure; however, both the mean closed time and mean open time were markedly increased by high pressure. In contrast, voltage-gated Ca^{2+} currents were not altered by hydrostatic pressure in type II vestibular hair cells (Düwel et al. 2003).

In 10 μM cinnarizine solutions, the amplitude of potassium currents did not change by applying negative pressure (Fig. 4). Cinnarizine is known as a Ca^{2+} channel blocker (Arab et all. 2004); however, the drug inhibited $I_{K,p}$ at lower concentrations than required for a Ca^{2+} channel block (Düwel et al. 2005). The inhibition of $I_{K,p}$ in pharmacologically relevant concentrations of cinnarizine elicited depolarization and increased the voltage-dependent activation of Ca^{2+} currents, which enhanced transmitter release (Haasler et al. 2009). The effects of other potassium channel blockers on $I_{K,p}$ have been examined in vestibular hair cells (Düwel et al. 2003). TEA abolished all outward currents including $I_{K,p}$. 4-AP partly (40 ± 10%) and reversibly inhibited $I_{K,p}$. Dihydrostreptomycin, a blocker of the transduction channel, left $I_{K,p}$ unaffected.

Changing potassium currents by pressure may have an important pathophysiological role in Menière's disease because an increase in hydrostatic pressure in the endolymphatic space has been implicated as a key mechanism in this condition. An increase of less than 1.0 cm H_2O was sufficient to cause nystagmus and vertigo in animal models after experimentally induced hydrops (Bohmer and Dillier 1990). $I_{K,p}$ are attributable to Ca^{2+}-sensitive potassium currents as described above. Ca^{2+}-sensitive potassium currents are known to take part in terminating Ca^{2+}-induced neurotransmitter release from hair cells, which being crucial at the same time for the frequency behavior of these cells because it prepares them for renewed depolarization (Ramanathan et al. 1999). Ca^{2+}-sensitive potassium currents in IHCs allow the cells to perform high frequency transduction by greatly shortening the membrane time constant (Kros and Crawford 1990) and consequent rapid repolarization. Mice with a gene deletion of the α subunit of the BK channel ($BK\alpha^{-/-}$) showed progressive high frequency hearing loss starting at 8 weeks (Oliver et al. 2006). The enhancement of potassium currents in IHCs by pressure will lead to a more rapid repolarization, thereby preserving a higher frequency of transmitter release. Therefore, the low frequency transduction may be relatively disadvantageous, and also result in the low-tone hearing loss characteristically observed in Menière's disease. The pharmacological modification of these pressure-dependent potassium currents may be a promising therapeutic principle that should be considered in the further development of drugs.

CONCLUSIONS

Negative intracellular pressure potentiated the amplitude of potassium currents, whereas positive pressure suppressed the amplitude of potassium currents in IHCs of the guinea-pig cochlea. Cinnarizine directly blocked these pressure-dependent changes in potassium currents; however, gadolinium did not influence the potassium currents. Pressure-dependent changes influence the IHCs' excitability and may have an important pathophysiological role in Menière's disease or low tone sensorineural hearing loss.

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