

The positive resting membrane potential of non-excitable fibrocytes in the mammalian cochlea

It is schoolbook knowledge that both excitable and non-excitable cells are stably hyperpolarized at -25 mV to -80 mV in the resting state *in vivo* and *in vitro*. This negative resting membrane potential (RMP), a fundamental cell property necessary for the physiological responses and homeostasis of a variety of tissues and organs, stems primarily from the high K^+ permeability of the cell membrane. However, an atypical cell type against the dogma was found in the mammalian inner ear. This is “cochlear fibrocyte”, which achieves a significantly positive RMP *in vivo* with unique ion permeable property.

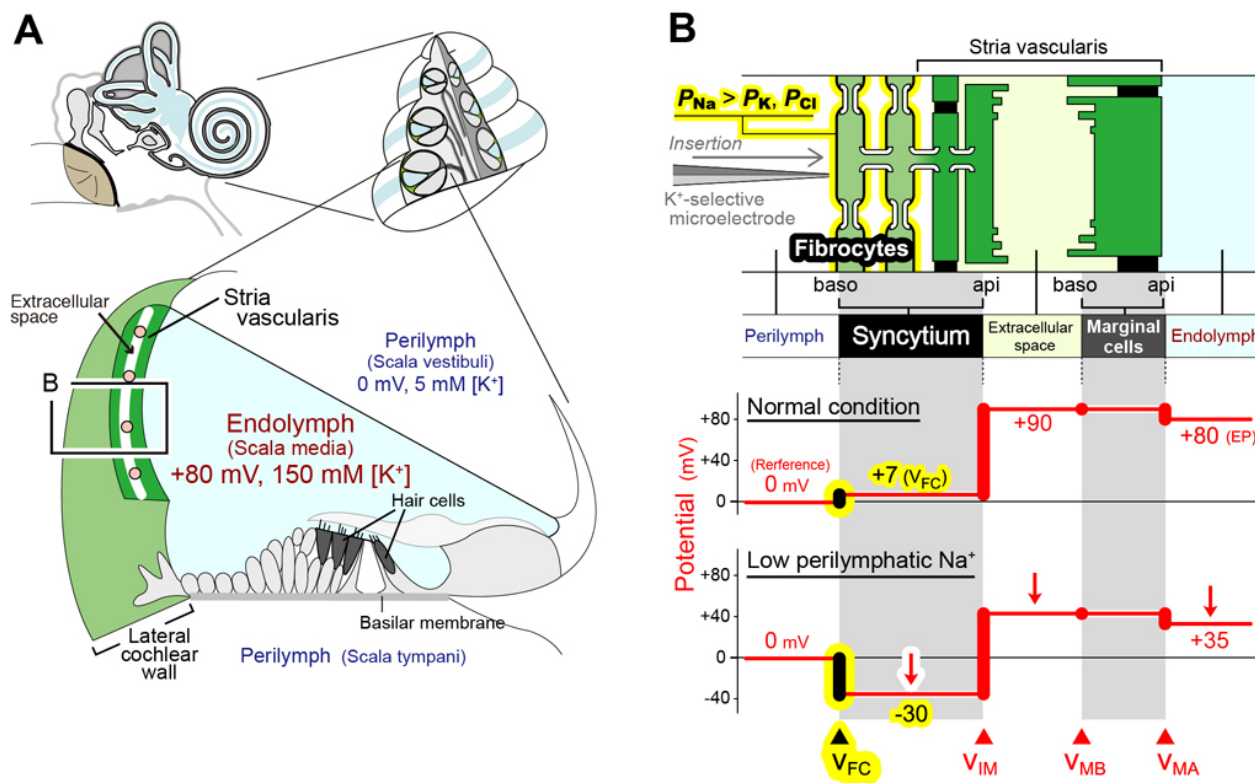


Fig. 1. Mammalian cochlea and its unique electrical properties

A, Morphology and electrochemical profile of the cochlea. A cross-section of the cochlea, which has a spiral shape (top panels), shows that this organ contains the three chambers: the scala vestibule, scala media, and scala tympani (bottom panel). The scala media is filled with an endolymph characterized by a high $[K^+]$ and an endocochlear potential (EP) of $\sim +80$ mV. **B**, Cellular components of the lateral cochlear wall (boxed region in the bottom panel of **A**). Fibrocytes and the neighboring cells are interconnected and thereby form a syncytium (top panel). Middle and bottom panels show potential of each compartment of the lateral wall. In the fibrocyte membranes, Na^+ permeability (P_{Na}) exceeds the K^+ and Cl^- permeabilities (P_K and P_{Cl}) (top panel). Therefore, the fibrocyte membrane potential (v_{FC}) is continuously depolarized at $\sim +7$ mV at resting

state (middle panel). When Na^+ was artificially depleted in the perilymph, vFC was remarkably hyperpolarized (bottom panel). vIM, vMB, and vMA represent the membrane potentials of intermediate cells, the basolateral and apical surface of marginal cells, respectively; these cells are other components of the lateral wall. Reproduced and modified from Yoshida et al. (2016) and Nin et al., (2016).

The cochlea is filled with two different fluids, the perilymph and endolymph (Fig. 1A). The K^+ -rich endolymph exhibits an endocochlear potential (EP) of +80 mV, relative to the perilymph that conserves ion contents of a regular extracellular fluid (Nin et al., 2016). Sensory hair cells lie between the two lymph fluids. Acoustic stimulation permits endolymphatic K^+ to enter into the hair cells, exciting them. The highly positive EP amplifies the K^+ -inflow, thereby greatly sensitizing the hair cells. This EP stems from an electrical property of the lateral cochlear wall, an epithelial-like tissue that contains fibrocytes (Fig. 1B). The fibrocyte, which is bathed in the perilymph, belongs to a non-excitabile cell type; nevertheless, it is constantly depolarized at +5 mV to +12 mV *in vivo*. This unusual RMP plays a key role in the formation of the EP. Although histochemical studies have detected several ion channel and transporter types in the fibrocytes, none of the experimental approaches have revealed how the fibrocytes establish the positive RMP values.

We investigated the ion permeability of the fibrocyte membrane *in vivo* (Yoshida et al., 2016). We prepared a double-barreled K^+ -selective microelectrode sensitive to the potential and $[\text{K}^+]$ and inserted it into the fibrocytes to monitor their membrane potential over time (Fig. 1B). The RMP of the fibrocytes in living guinea pigs was $\sim +9$ mV when an artificial control perilymph was perfused to the cells. Strikingly, application of a solution containing low $[\text{Na}^+]$ (1 mM) to the perilymphatic space markedly hyperpolarized the fibrocyte membrane potential to ~ -30 mV (Fig. 1C). Simultaneously the EP was reduced. Little change in the RMP was observed during the perfusion of a low $[\text{Cl}^-]$ solution or a high $[\text{K}^+]$ solution. Accordingly, the fibrocyte membrane are more permeable to Na^+ than K^+ and Cl^- (Fig. 1B). This unique profile critically contributes to the positive RMP and thus the EP.

To our knowledge, cell types that are dominated by Na^+ permeability under resting conditions have not been detected in other tissues and organs. Evidences described in the present study may not only advance the principle of cells and hearing but also help to understand the pathological processes of deafness that afflicts 15% of world population.

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Publication

[The unique ion permeability profile of cochlear fibrocytes and its contribution to establishing their positive resting membrane potential.](#)

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Pflugers Arch. 2016 Sep