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Functional significance of channels and transporters expressed in the inner ear and the kidney

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Running title: Transport in ear and kidney

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Abstract

A number of ion channels and transporters are expressed in both, the inner ear and the kidney. In the inner ear, K^+ cycling and endolymphatic K^+, Na^+, Ca^{2+} and pH homeostasis are critical for normal organ function. Ion channels and transporters involved in K^+ cycling include K^+ channels, Na^+,$2Cl^-$,K^+ cotransporter, the Na^+/K^+ ATPase, Cl^- channels, connexins and KCl cotransporters. Further, endolymphatic Na^+ and Ca^{2+} homeostasis depends on the Ca^{2+} ATPase, Ca^{2+} channels, Na^+ channels and a purinergic receptor channel. Endolymphatic pH homeostasis involves H^+ ATPase and Cl^-/HCO_3^- exchangers including pendrin. Defective connexins (GJA1, GJB6), pendrin (SLC26A4), K^+ channels (KCNJ10, KCNQ1, KCNE1, KCNMA1), Na^+,$2Cl^-$,K^+ cotransporter (SLC12A2), KCl cotransporters (KCC3, KCC4), Cl^- channels (BSND, CLCNKA+CLCNKB) and H^+ ATPase (ATP6V1B1, ATPV0A4) cause hearing loss. All these channels and transporters are also expressed in the kidney and support renal tubular transport or signaling. The hearing loss may thus be paralleled by various renal phenotypes including subtle decrease of proximal Na^+ coupled transport (KCNE1/KCNQ1), impaired K^+-secretion (KCNMA1), limited HCO_3^- elimination (SLC26A4), NaCl wasting (BSND, CLCNKB), renal tubular acidosis (ATP6V1B1, ATPV0A4, KCC4) or impaired urinary concentration (CLCNKA). Thus, defects of channels and transporters expressed in the kidney and the inner ear result in simultaneous dysfunctions of these seemingly unrelated organs.

Key words: cochlea, vestibular labyrinth, stria vascularis, deafness, renal tubule

Introduction

The inner ear is the sensory system for sound, motion and gravity. It is housed within the temporal bone and consists of cochlea, vestibular labyrinth and the endolymphatic sac (Fig. 1). The inner ear comprises an array of interconnected fluid compartments that are enclosed by a multitude of highly specialized epithelial cells. The luminal fluid, endolymph, differs in composition between different parts of the inner ear (Table 1). The epithelial cells enclosing the endolymph are highly diverse as shown in more detail for the cochlea in Fig. 2. Among them are the sensory inner and outer hair cells (Fig. 2B,C) and stria vascularis (Fig. 2D). The sensory hair cells transduce mechanical stimuli into electrical signals and release neurotransmitter to activate sensory neurons. Stria vascularis is a multilayered epithelium in the cochlea (Fig. 2A,D), which secretes K^+ into endolymph and generates the endocochlear potential that contributes significantly to the driving force of sensory transduction. In addition, the inner ear contains and depends on a multitude of highly specialized epithelial cells that control the ionic composition of endolymph and the magnitude of the transepithelial potential.

Different compartments of the inner ear serve the transduction of specific stimuli. The cochlea transduces mechanical stimuli associated with sound and provides the basis for hearing. The utricle, saccule and ampullae of the semicircular canals belong to the vestibular labyrinth (Fig. 1), which transduces mechanical stimuli associated with head position and head motion. Vestibular sensory transduction provides input to the vestibular system that controls balance, posture and eye movements. Sensory transduction in the cochlea and the vestibular labyrinth has different electrochemical requirements although all depend on the cycling of K^+ between endolymph and perilymph. In addition to the fluid compartments that house sensory hair cells, the vestibular labyrinth contains another fluid compartment, the endolymphatic sac (Fig. 2), which is devoid of sensory hair cells. The function of the endolymphatic sac is poorly understood although evidence suggests that it controls endolymph fluid volume (219).

Several epithelia in the cochlea appear to have functional equivalents in the vestibular labyrinth. Among such homology pairs are cochlear (Fig. 2A) and vestibular hair cells, strial marginal cells (Fig. 2D) and vestibular dark cells, outer sulcus cells (Fig. 2A, OS), vestibular transitional cells, Reissner's membrane (Fig. 2A) and semicircular canal epithelial cells (163; 303). Several recent reviews have focused on ion transport in different inner ear epithelia (163; 304), hereditary hearing loss (197), cochlear fluid volume regulation (219) and ototoxicity (217).

Similarity between epithelial transport in inner ear and kidney was first suggested by the observation more than 30 years ago that treatment with high doses of the loop diuretic furosemide causes reversible hearing loss (81; 248). Obviously, the inner ear and kidney have very different functions. Nevertheless, most of the genes encoding the epithelial transporters or channels in the inner ear are similarly expressed and/or similarly sensitive to pharmacological intervention in renal tubular epithelia. More importantly, defects of those genes can lead simultaneously to hearing loss and deranged renal tubular transport. Thus, even though several of the channels and transporters expressed in inner ear epithelia are similarly found in other epithelia or even in excitable tissues such as the heart, the pathophysiologically significant overlap is particularly striking between inner ear and kidney. In several channelopathies, the renal defect is subtle and clinically overlooked in face of striking hearing loss or life threatening cardiac arrhythmia. Closer functional analysis reveals, however, the respective defect in renal function. Thus, much can be learned from a comparison of the transport organization in these two organs. The comparison could further serve as a paradigm that channels and transporters could serve different functions in different organs and that genetic defects or pharmacological inhibition of those channels and transporters could lead to seemingly unrelated functional consequences.

The present review first describes the channels and transporters required for inner ear function. The second part of the review is dedicated to the function of those transporters in

renal epithelia. The function and pathophysiological significance of the channels and transporters expressed in both, inner ear and kidney is compiled in Table 2.

K^+ cycling in the inner ear

Sensory transduction in the cochlea and the vestibular labyrinth depends on the cycling of K^+ between endolymph and perilymph (Fig. 2A). K^+ cycling in the cochlea consists of K^+ flux from endolymph through sensory hair cells into perilymph, uptake of K^+ from perilymph into fibrocytes of the spiral ligament, funneling of K^+ via gap junctions into basal and intermediate cells of stria vascularis, efflux of K^+ from intermediate cells into the intrastrial fluid, and secretion of K^+ by marginal cells of stria vascularis into endolymph (163; 304) (Fig. 2A). Similarly, K^+ cycling in the vestibular labyrinth consists of K^+ flux from endolymph through hair cells into perilymph and uptake of K^+ from perilymph and secretion into endolymph by vestibular dark cells (163; 304). K^+ cycling in the cochlea and vestibular labyrinth, however, is not limited to K^+ efflux through hair cells and K^+ secretion by stria vascularis and vestibular dark cells. Additional pathways accomplish K^+ and Na^+ reabsorption from endolymph. In the cochlea, these additional pathways are provided by Reissner's membrane and by outer sulcus epithelial cells (Fig. 2A), and in the vestibular system, by semicircular canal and by transitional epithelial cells (163; 304).

K^+ flux through hair cells

Sensory transduction in the cochlea and the vestibular labyrinth depends on mechanically-gated ion channels of hitherto elusive molecular identity that are located in the hair bundles of the hair cells (32). Potential candidates include the acid sensing ASIC ion channels (194), members of the epithelial Na^+ channel/degenerin (ENaC/DEG) superfamily, which are widely distributed in the central and peripheral nervous system and are also found in the cochlea (34; 70; 174; 335) and vestibular labyrinth (138; 202; 334). The current view, however, appears to favour the involvement of transient receptor potential (TRP) channels TRPN1, TRPV4, TRPML3 and TRPA1 for mechanotransduction (32). Opening of the transduction channels supports influx of K^+ from endolymph into the hair cells, which depolarizes the basolateral membrane of the hair cell (Fig. 2B,C). Influx of K^+ from endolymph into the hair cells is balanced by efflux of K^+ from the hair cells via K^+ channels into interstitial spaces that are continuous with perilymph. The molecular entities of K^+ efflux channels depend on the type of hair cell.

K^+ efflux from cochlear inner hair cells involves the voltage-gated K^+ channel KCNQ4 and the large conductance Ca^{2+}-activated K^+ channel KCNMA1 (BK channel) (48; 121; 122; 240; 278) (Fig. 2B). In addition, KCNQ4 contributes to the resting membrane potential of inner hair cells and thereby ensures the maintenance of the resting cytosolic Ca^{2+} concentration (156; 157; 189). Several splice variants of KCNQ4 are expressed in the inner ear of which one variant, KCNQ4v3, is preferentially expressed in the high frequency region base of the cochlea (12; 142; 143). Mice lacking KCNQ4 or expressing dominant negative mutations develop normal hearing but later in life suffer progressive hearing loss, which indicates that KCNQ4 is non-essential for basic inner hair cell function but required for maintenance of hearing (107). Consistently, mutations of KCNQ4 cause progressive high frequency hearing loss in people (33; 123; 269). Similarly, mice lacking KCNMA1 develop normal hearing but then suffer progressive hearing loss, indicating that also KCNMA1 is non-essential for basic inner hair cell function (190; 216). Loss of the β-subunit KCNMB1, which associates with the α-subunit KCNMA1, appears to have no effect on hearing (216).

The K^+ channels KCNQ4 and KCNMA1 also mediate K^+ efflux from outer hair cells (Fig. 2C). In contrast to inner hair cells, both channels play a critical role for basic cell function in outer hair cells (24; 87; 155; 158). Mice lacking KCNMA1 or KCNQ4 loose outer hair cells,

but not inner hair cells, during the progressive loss of hearing (52; 107; 216). The K^+ channels KCNMA1 and KCNQ4 are apparently essential for the survival of outer hair cells.

KCNQ4 associates with the β-subunit KCNE1 and possibly with other KCNE subunits that are expressed in hair cells (255). This interaction may be critical for KCNQ4 function given that the KCNE1 mutation KCNE1(D76N) impairs KCNQ4 function and causes Jervell and Lange-Nielsen syndrome (JLNS), life-threatening cardiac arrhythmias and deafness. Other mutations, such as KCNE1(S74L), which does not impair KCNQ4 function, causes Romano-Ward syndrome, arrhythmias without deafness (255).

K^+ buffering near hair cells

Hair cells and neurons in the cochlea and vestibular labyrinth maintain their resting membrane potential via K^+ channels in conjunction with high cytosolic and low extracellular K^+ concentrations. Uncontrolled increases of the K^+ concentration in the extracellular fluid are expected to affect the membrane potential and responsiveness of the hair cells and neurons. Stimulation of cochlear and vestibular hair cells leads to measurable increases in the extracellular K^+ concentration in the surrounding perilymph (104; 282). It is conceivable that K^+ buffering mechanisms limit the magnitude of these increases. In general, multiple mechanisms have been recognized to limit the amplitude of K^+ concentration changes in the extracellular environment near neurons. The predominant mechanism is diffusion into unobstructed open fluid spaces. Current measurements in scala tympani perilymph support the concept that perilymph serves as unobstructed open fluid space in the buffering of K^+ (336). Further, a strategic localization of K^+ channels that differ in their rectification can provide buffering of localized K^+ increases. Inward-rectifying K^+ channels are well suited as uptake mechanisms in K^+ buffering since they conduct K^+ influx more efficiently than K^+ efflux. A local increase in the extracellular K^+ concentration may set the local K^+ equilibrium potential below the membrane potential, which promotes K^+ influx into the buffering cell. The ensuing elevation of the cytosolic K^+ concentration sets the K^+ equilibrium potential above the membrane potential and promotes K^+ efflux preferentially through less inward-rectifying K^+ channels or outward-rectifying K^+ channels. Such a mechanism has been described in Müller glia of the retina (116; 208). It is conceivable that a similar mechanism is present in the organ of Corti. Deiter's cells have a membrane potential of -76 mV (186), which is near the K^+ equilibrium potential. They express the inward-rectifying K^+ channel KCNJ10 (Kir4.1), which is particularly abundant in the membrane area that faces KCNQ4 expressed in outer hair cells (83; 216) (Fig. 2C, DC). K^+ exit mechanisms in Deiter's cells may include outward rectifying K^+ channels (181) and the K/Cl cotransporters SLC12A6 (KCC3) and SLC12A7 (KCC4) (15; 16) (Fig 2C). Moreover, Deiter's cells are connected to neighboring supporting cells via gap junctions. K^+ could thus be dispersed via gap junctions among epithelial cells that include Deiter's cells (Fig 2A, DC), Claudius' cells (Fig2A, CC), Hensen's cells (Fig 2A, HC) and outer sulcus cells (Fig 2A, OC).

SLC12A6 and SLC12A7 may serve as a release mechanism for KCl not only in K^+ buffering but also in cell volume regulation (131). The recent claim that SLC12A6 and SLC12A7 serve as a K^+ uptake mechanism in Deiter's cells, however, would require an unusually low cytosolic Cl^-, which has not been shown thus far (15; 16). Consistent with a role of SLC12A6 and SLC12A7 in cell volume regulation is the finding that mice lacking either transporter hear normal at the onset of hearing but suffer from a more or less early onset of hearing loss (15; 16).

K^+ uptake from perilymph

K^+ released from the sensory hair cells may travel along multiple pathways toward the spiral ligament in the lateral wall (246) (Fig 2A). Pathways that avoid supporting cells or that involve buffering by Deiter's or neighboring cells and lead through the open perilymph space

of scala tympani are supported by current measurements (336). An additional pathway may involve uptake of K^+ into Deiter's cells, dispersion of K^+ among Deiter's, Hensen's, outer sulcus and root cells (Fig 2A) via gap junctions and release of K^+ from root cells into the interstitial space of the spiral ligament that is continuous with perilymph (110).

Uptake of K^+ from interstitial space of the spiral ligament occurs via specialized fibrocytes (named I-V within the spiral ligament in Fig 2A). Fibrocytes types II, IV and V express Na^+/K^+ ATPase, the $Na^+,2Cl^-,K^+$ cotransporter SLC12A2 (NKCC1) and the Cl^- channels CLCNKA and CLCNKB (36; 154; 177; 206; 230) (Fig 2D). Although functional data from fibrocytes are lacking, the resemblance of this array of transporters with the basolateral membrane of strial marginal cells and vestibular dark cells suggests that fibrocytes take up K^+ from perilymph. Gap junctions, in particular GJB2 (CX26) and GJB6 (CX30), connect fibrocytes types II, IV and V among each other as well as to fibrocytes type I, basal and intermediate cells of stria vascularis. Gap junctions form a network in the lateral wall that is thought to provide a pathway for K^+ from the sites of uptake into fibrocytes types II, IV and V to the sites of release from strial intermediate cells into the intrastrial fluid space.

K^+ secretion into endolymph

Strial marginal cells and vestibular dark cells take up K^+ from the intrastrial fluid space and secrete it into endolymph (Fig. 2D). K^+ secretion by strial marginal cells and vestibular dark cells occurs via equivalent mechanisms (311). Both epithelial cells take up K^+ across the basolateral cell membrane via the $Na^+,2Cl^-,K^+$ cotransporter SLC12A2 (NKCC1) and the Na^+/K^+ ATPase and secrete K^+ across the apical membrane via the K^+ channel KCNQ1/KCNE1 (Fig. 2D). Na^+ and Cl^- taken up via the $Na^+,2Cl^-,K^+$ cotransporter is recycled in the basolateral membrane via the Na^+/K^+ ATPase and the Cl^- channels CLCNKA/BSND (ClC-Ka/barttin) and CLCNKB/BSND (ClC-Kb/barttin) (Fig 2D). The following paragraphs focus on the $Na^+,2Cl^-,K^+$ cotransporter, the K^+ channel and the Cl^- channels that are essential for K^+ secretion in strial marginal cells and vestibular dark cells.

Na^+/K^+ ATPase and K^+/H^+ ATPase

Strial marginal cells and vestibular dark cells absorb K^+ from the intrastrial space and from perilymph via the Na^+/K^+ ATPase and the $Na^+,2Cl^-,K^+$ cotransporter (170; 306). The Na^+/K^+ ATPase takes up K^+ and establishes a Na^+ gradient that energizes further uptake of K^+ via SLC12A2. The Na^+/K^+-ATPase in strial marginal cells and vestibular dark cells as well as in fibrocytes of the spiral ligament consists of the subunits ATP1A1, ATP1B1 and ATP1B2 (173; 230) (Fig 2D)

Inhibition of Na^+/K^+ ATPase with ouabain inhibits K^+ secretion and consequently abolishes the endocochlear potential (126; 129). Strial marginal cells appear to express gastric K^+/H^+ ATPase in addition to Na^+/K^+-ATPase (135; 235). The functional significance of K^+/H^+ ATPase for the generation of the endocochlear potential is currently unclear since very high concentrations of K^+/H^+ ATPase inhibitors were necessary to affect the endocochlear potential.

$Na^+,2Cl^-,K^+$ cotransporter

Strial marginal cells and vestibular dark cells absorb K^+ from the intrastrial space and from perilymph via the $Na^+,2Cl^-,K^+$ cotransporter SLC12A2 (NKCC1) (162; 306; 313) (Fig 2D). SLC12A2 is sensitive to the loop-diuretics furosemide and bumetanide and to their analog piretanide (162; 313). SLC12A2 is an essential transporter for K^+ secretion and endolymph production. Mice that lack SLC12A2 fail to produce endolymph, which leads to the collapse of Reissner's membrane onto stria vascularis and the organ of Corti (41; 43; 57).

K^+ channels

Strial marginal cells and vestibular dark cells secrete K^+ into endolymph via the K^+ channel KCNQ1/KCNE1 (165; 306) (Fig 2D). KCNQ1/KCNE1 is a slowly activating delayed rectifier that carries the IKs current and requires the assembly of the pore-forming α-subunit KCNQ1 with the β-subunit KCNE1 (11; 223). Mice lacking functional KCNE1 or KCNQ1 fail to produce endolymph, which leads to a collapse of Reissner's membrane onto stria vascularis and the organ of Corti due to loss of K^+ secretion in the presence of ongoing reabsorptive processes (22; 139; 140; 294). Similar observations have been made in human patients (61). Homozygous or heterozygous compounding mutations of KCNE1 or KCNQ1 lead to Jervell and Lange-Nielsen syndrome, characterized by deafness, prolonged cardiac action potentials and potentially fatal cardiac arrhythmias (103; 182; 231; 233). Consistently, pharmacologic inhibition of the KCNQ1/KCNE1 channel leads to hearing loss (79).

Transepithelial currents and currents through the apical KCNQ1/KCNE1 K^+ channel are enhanced by lowering the apical or increasing the basolateral K^+ concentration or by lowering the osmolarity on the basolateral side (161; 306; 308; 317). Further, the rate of K^+ secretion is increased by β_1-adrenergic receptors via cAMP dependent stimulation of the KCNQ1/KCNE1 K^+ channel (258; 259; 309; 310). Conversely, muscarinic and purinergic receptors suppress K^+ secretion (307). Purinergic $P2Y_4$ receptors decrease currents through the KCNQ1/KCNE1 K^+ channel via protein kinase C (160; 166). Finally, KCNE1/KCNQ1 K^+ channel activity is stimulated by the serum and glucocorticoid inducible kinase SGK1 (20; 50), which may contribute to the stimulation of cochlear ion transport and hearing improvement by glucocorticoids and mineralocorticoids (137; 280). KCNE1 is inhibited by estrogens (298), which may contribute to the inhibitory effect of those hormones on cochlear transport (136).

The rate of K^+ secretion may further be regulated by trafficking of KCNE1/KCNQ1 K^+ channels to the apical membrane of strial marginal cells, which requires the participation of LIMPII (115). LIMPII is a transmembrane glycoprotein that is mainly located in lysosomal and endosomal membranes (127). Mice lacking LIMPII suffer from progressive hearing loss correlated with a loss of surface expression of KCNQ1/KCNE1 in the apical membrane of the marginal cells (115). In addition, mice lacking LIMPII suffer from uni- or bilateral hydronephrosis due to hypertrophy of the smooth muscle layer at the ureteropelvic junction (65).

Cl^- channels

K^+ secretion by strial marginal cells and vestibular dark cells require Cl^- to recycle in the basolateral membrane via a Cl^- conductance (306; 314) (Fig. 2D). This Cl^- conductance is comprised of the Cl^- channels CLCNKA/BSND (ClC-Ka/barttin) and CLCNKB/BSND (ClC-Kb/barttin) (6; 53; 154; 167; 206; 218; 264; 265). The Cl^- channels CLCNKA/BSND and CLCNKB/BSND consist of the pore-forming α-subunits CLCNKA and CLCNKB and the β-subunit BSND (53; 228). Mutations of BSND reduce channel conductivity and surface expression and thereby cause Bartter's syndrome type 4, which is characterized by deafness and renal salt wasting (14; 53). Similarly, simultaneous mutations of CLCNKA and CLCNKB also lead to Bartter's syndrome type 4, whereas mutations of CLCNKB lead to Bartter's syndrome without deafness (171; 226; 237). This observation is consistent with the finding that CLCNKA and CLCNKB are coexpressed in cells of the inner ear but not the kidney and with the notion that the two channels can substitute for each other in the inner ear (206) but not in the kidney (see below).

K^+ and Na^+ reabsorption

Homeostasis of the high K^+ and low Na^+ concentrations in endolymph is maintained by K^+ secretion and Na^+ and K^+ reabsorption. Reabsorption of K^+ is not limited to the pathways

through inner, outer and vestibular hair cells. Indeed, currents generated by the stria vascularis in the cochlea flow not only through hair cells but also through the outer sulcus and through Reissner's membrane (222; 336). Consistently, outer sulcus and Reissner's membrane epithelial cells reabsorb Na^+ and K^+ from the endolymph (138; 159). Outer sulcus cells take up Na^+ and K^+ via apical non-selective cation channels, large conductance (BK) and small conductance K^+ channels as well as $P2X_2$ receptor-gated non-selective cation channels. They release Na^+ and K^+ across the basolateral membrane via a Na^+/K^+ ATPase and K^+ channels, respectively (25; 26; 136). Subunits of ENaC may contribute to the apical non-selective cation channels (Fig 2A), although the channel involved is not the typical Na^+ selective and amiloride-sensitive ENaC channel (25; 70).

Reissner's membrane epithelial cells take up Na^+ via the amiloride-sensitive Na^+ channel ENaC and extrude Na^+ across the basolateral membrane via the Na^+/K^+ ATPase (138) (Fig 2A). The endocochlear potential contributes to the driving force of cation reabsorption in outer sulcus and Reissner's membrane epithelial cells much like it contributes to the transduction current through inner and outer hair cells.

Na^+ and K^+ reabsorption has also been found in the vestibular labyrinth. Cation reabsorption in vestibular transitional cells and semicircular canal epithelial cells bear some resemblance to cation reabsorption in outer sulcus and Reissner's membrane epithelial cells, respectively. Vestibular transitional cells reabsorb Na^+ and K^+ via apical $P2X_2$ receptor-gated non-selective cation channels and extrude Na^+ and K^+ across the basolateral membrane via the Na^+/K^+ ATPase and K^+ channels, respectively (136; 312; 318).

Semicircular canal epithelial cells in the vestibular labyrinth reabsorb Na^+ via the ENaC, release Na^+ across the basolateral membrane via the Na^+/K^+ ATPase and recycle K^+ in the basolateral membrane via K^+ channels (201; 202). Na^+ reabsorption in semicircular canal epithelial cells is under the control of glucocorticoids but not mineralocorticoids (201; 202). ENaC is activated by the transmembrane serine protease TMPRSS3 (72). A defect of TMPRSS3 leads to deafness (72), which may, however, involve dysregulation of further transporters or channels besides ENaC activity. Loss of function mutations of ENaC do not lead to an inner ear phenotype, which is consistent with the presence of alternative Na^+ reabsorption pathways in outer sulcus epithelia cells and transitional cells (136; 159).

Generation of the endocochlear potential

Mechanical stimuli associated with sound, head position or gravity are transduced into electrical signals by the sensory hair cells in the cochlea and the vestibular labyrinth. Mechanically-induced channel openings permit an influx of K^+ from endolymph into the hair cell. The driving force of this current is roughly the sum of the basolateral membrane potential of the hair cell and the transepithelial potential. The transepithelial potential in the cochlea, called the endocochlear potential is as high as + 80 mV (Fig 2A). For cochlear inner and outer hair cells the driving force for sensory transduction is 145 mV (145 mV = 65 mV + 80 mV), respectively (38; 189). Driving forces for sensory transduction in the vestibular labyrinth are smaller due to the smaller endovestibular potential of 3-7 mV (130; 185; 220).

The endocochlear potential is a transepithelial potential that is generated by the stria vascularis (275; 295; 316). The stria vascularis is functionally a two layered epithelium comprised of a layer of marginal cells and a layer of basal cells that is penetrated by a capillary network (99). Marginal cell junctions contain a multitude of different claudins, whereas tight junctions between basal cells contain only CLDN11 (claudin 11) (58; 114). Tight junctions among basal cells define an inner membrane facing the intrastrial space and an outer membrane facing the spiral ligament (Fig. 2). The inner membrane is connected via gap junctions to strial intermediate cells and strial intermediate cells are connected via gap junctions to strial

pericytes and endothelial cells (108; 262). Gap junctions ensure that intermediate cells are electrically a part of the basal cell barrier. The outer membrane of basal cells is connected by gap junctions to type I fibrocytes of the spiral ligament.

The endocochlear potential is essentially a K^+ equilibrium potential that is generated by the K^+ channel KCNJ10 (Kir4.1) in intermediate cells of stria vascularis (Fig 2D) in conjunction with a very low K^+ concentration of intrastrial fluid and a high cytosolic K^+ concentration in intermediate cells (169; 263). A number of key findings provide support for this model. First, the endocochlear potential and the KCNJ10 K^+ channel in intermediate cells share the same sensitivities to a panel of K^+ channel blockers (164; 262; 266). Second, the endocochlear potential can be measured across the basal cell barrier (221). Third, expression of KCNJ10 correlates with the presence of the endocochlear potential in KCNJ10 knockout and pendrin knockout mouse models and in normal development (82; 169; 215; 305; 315). Fourth, loss of CLDN11 (claudin 11), which is the only known claudin in the basal cell tight junctions, renders the basal cell barrier leaky and leads to a loss of the endocochlear potential (67; 114). Fifth, increases of the K^+ concentration in the intrastrial fluid space suppress the endocochlear potential. Such increases can be achieved by vascular perfusion of solutions containing elevated K^+ concentrations, inhibitors of the Na^+/K^+ ATPase (ouabain) or inhibitors of the $Na^+,2Cl^-,K^+$ cotransporter (furosemide or bumetanide) (118; 126; 128; 129; 164). Sixth, loss of GJB6 (CX30), which renders the capillaries in stria vascularis leaky to the intrastrial space, leads to a loss of the endocochlear potential (31). Collectively, these findings support the model that the endocochlear potential is a K^+ equilibrium potential that is generated by the K^+ channel KCNJ10.

Marginal cells of stria vascularis and fibrocytes of the spiral ligament play important supporting roles in the generation of the endocochlear potential. Fibrocytes of the spiral ligament, which are connected via basal cells to intermediate cells, ensure a high cytosolic K^+ concentration in strial intermediate cells. Strial marginal cells reabsorb K^+ from the intrastrial fluid spaces and keep the K^+ concentration in the intrastrial fluid spaces as low as 2 mM (164; 263; 306).

Gap-junctional networks

Several major networks of cells that are connected by gap junctions have been recognized in the cochlea (109). Notably excluded from these networks are marginal cells of stria vascularis, inner hair cells and outer hair cells that are neither connected among each other nor to any of their neighbors. The importance of gap junctions for cochlear function is underscored by the fact that mutations of GJB2 (CX26) and GJB6 (CX30) are the most prevalent causes of hereditary childhood deafness consistent with the contribution of GJB2 and GJB6 to all major gap junctional networks in the cochlea (39; 42; 68; 73; 191; 193; 331).

One major network of gap junction interconnected cells links different types of fibrocytes in the spiral ligament as well as basal and intermediate cells, pericytes and endothelial cells of stria vascularis (Fig 2A, spiral ligament). A major purpose of this network is to connect sites of K^+ uptake in fibrocytes types II, IV and V to the site of K^+ release in intermediate cells of stria vascularis. Most gap junctions in this network are formed by heteromeric complexes of GJB2 and GJB6 (2; 59; 109; 134; 325). In addition, endothelial cells of stria vascularis express GJA1 (CX43) and GJA7 (Cx45) (29; 134; 260) and fibrocytes of spiral ligament express GJB3 (CX31) and GJB1 (CX32) (150; 326). Mutations of GJA1, GJB1 and GJB3 are also associated with deafness (147; 148; 251; 326).

Mice that lack GJB6 are profoundly deaf despite the continued presence of GJB2 (277). The assumed limited gap junction coupling mediated by the remaining GJB2 and other connexins appears to be sufficient for the cycling of K^+ but insufficient to prevent leakiness of

strial capillaries and breakdown of the endocochlear potential (31). Consequently, mice lacking GJB6 failed to develop an endocochlear potential but had normal endolymphatic K^+ concentrations at least at young age (277). Interestingly, the insufficiency of gap junction coupling, which is associated with leaky capillaries in mice lacking GJB6 can be restored by overexpression of GJB2. Mice lacking GJB6 and overexpressing GJB2 develop a normal endocochlear potential and have normal hearing (3).

Two further networks are formed by the epithelial cells in and adjacent to the organ of Corti, the medial and the lateral network (98; 109; 247). Most gap junctions in these networks are formed by GJB2 and GJB6 (2; 59; 109; 134; 325). In addition, some cells express GJA1 (147; 260). The lateral network of gap junction interconnected cells in the organ of Corti includes outer pillar cells, Deiter's, Hensen's, Claudius', outer sulcus and root cells (98; 109) (Fig 2A). The major purpose of this network may be metabolic coupling in addition to buffering of K^+ that is released from outer hair cells in response to sound stimulation (104).

The medial network includes inner pillar cells, supporting cells of the inner hair cells and interdental cells (Fig 2A,B). A major purpose of this network is to buffer glutamate, which is the neurotransmitter released from the inner hair cell. Expression of the glutamate uptake transporter SLC1A3 (GLAST) is limited to the immediate neighbor of the inner hair cell, whereas glutamine synthase, a key enzyme in the detoxification of glutamate, is mainly expressed in adjacent cells but not in SLC1A3-expressing cells (55). Gap junctions between SLC1A3-expressing cells and their glutamine synthase expressing neighbors may be required for transcellular metabolism of glutamate. Support for the concept of transcellular glutamate buffering comes from the finding that mice lacking SLC1A3 fail to buffer glutamate, which leads to an accumulation of glutamate in scala tympani perilymph during sound stimulation (76). SLC1A3-expressing supporting cells are also the first cells in the organ of Corti to undergo apoptosis in mice that lack GJB2 in this region of the cochlea (30). Further, several deafness-causing mutations of GJB2 and GJB6 impair the transfer of organic molecules but do not impede ionic coupling, which implies that these mutations do not affect K^+ cycling but could impair metabolic coupling and glutamate buffering (31; 332). It is not clear, why glutamate is not metabolized in the cells immediately adjacent to the hair cells. One could speculate that the accumulation of glutamate with accompanying cations would impose a considerable osmotic burden, eliciting untoward cell swelling.

Several reasons may account for the intriguing observation that the loss of function of either GJB2 or GJB6 leads to deafness rather than simply being compensated by the remaining connexin forming homomeric gap junctions (30; 124; 277). First, loss of GJB6 has been shown to suppress protein expression of GJB2, which reduces intercellular coupling more than predicted by the simple omission of GJB6 (3). Mutations may also exert dominant negative effects on the function of wildtype isoforms (68; 210). Second, heteromeric gap junctions formed from GJB2 and GJB6 have slightly different biophysical properties than homomeric gap junctions (257). The finding that overexpression of GJB2 can rescue hearing of mice lacking GJB6 suggests that the biophysical differences between hetero- and homomeric GJB2 gap junctions are less important than the fact that loss of GJB6 leads to a loss of GJB2 expression and a reduction in intercellular coupling (3).

Ca^{2+} homeostasis

The transduction channel in hair cells is a Ca^{2+}-permeable non-selective cation channel. Although K^+ is the major charge carrier, the transduction current is in part carried by Ca^{2+} and the reliability of the transduction process itself depends on the constancy of Ca^{2+} concentrations in endolymph (Table 1). Both, elevated and reduced concentrations of Ca^{2+} have been shown to suppress transduction currents and microphonic potentials (187; 271). Further, Ca^{2+}

homeostasis of vestibular endolymph during development affects the formation of otoconia, that are necessary for the detection of gravity and linear acceleration (106; 152). Consistent with the importance of Ca^{2+} homeostasis in endolymph are the observations that mice and guinea pigs with reduced or elevated endolymphatic Ca^{2+} concentrations are deaf and have vestibular deficits (120; 185; 315; 324).

The endolymphatic Ca^{2+} concentration appears to be controlled by secretory and reabsorptive mechanisms. Ca^{2+} reabsorption may occur through paracellular and transcellular pathways and may at least in part be driven by the endocochlear potential (91). In general, transepithelial Ca^{2+} transport may employ Ca^{2+} permeable channels as Ca^{2+} uptake mechanisms, Ca^{2+} binding proteins as Ca^{2+} buffers in the cytosol, and Ca^{2+} ATPases or Na^{+}/Ca^{2+} exchangers as Ca^{2+} extrusion mechanisms. Ca^{2+} ATPases appear to be most suitable for Ca^{2+} extrusion into endolymph due to the low Na^{+} concentration in endolymph (Table 1), which does not provide a driving force for Ca^{2+} extrusion via Na^{+}/Ca^{2+} exchangers. Consistently, Ca^{2+} secretion into endolymph has been shown to depend on Ca^{2+} ATPases rather than on Na^{+}/Ca^{2+} exchangers (92; 324) and loss of function of the Ca^{2+} ATPase ATP2B2 (PMCA2) leads to deafness and to a reduction in the endolymphatic Ca^{2+} concentration (253; 324).

Among the many different epithelial cells lining cochlear and vestibular endolymph, cells best understood to be involved in the homeostasis of endolymph Ca^{2+} include the outer hair cells in the cochlea and the semicircular canal duct epithelial cells in the vestibular labyrinth, although it is currently unclear whether outer hair cells contribute to the homeostasis of bulk endolymph or only to the homeostasis of endolymph in the nearest vicinity of the hair bundle. Nevertheless, outer hair cells have been shown to secrete Ca^{2+} into endolymph (328). This Ca^{2+} secretion is required to remove Ca^{2+} from the cytosol of the hair bundle and to maintain an appropriate Ca^{2+} concentration in endolymph surrounding the bundle (7; 84). Outer hair cells express the Ca^{2+} ATPase ATP2B2 in the stereocilia (49; 64) (Fig 2C), a high concentration of Ca^{2+} binding proteins in the cytosol (74), and Ca^{2+} permeable channels in the basolateral membrane including TRPC, TRPV1, TRPV4, L-type and non-L-type Ca^{2+} channels (45; 144; 157; 207; 234; 333). Mice lacking TRPV4 develop normal hearing consistent with a redundancy of Ca^{2+} permeable channels. However, they suffer from a delayed-onset hearing loss and vulnerability to acoustic injury (261). It is currently unclear whether the delayed-onset hearing loss and vulnerability to acoustic injury is due to the loss of TRPV4 in outer hair cells or due to the loss of the channel from other cells including inner hair cells, and spiral ganglion neurons (234).

Semicircular canal duct epithelial cells in vestibular labyrinth have been shown to reabsorb Ca^{2+} from endolymph (180). Ductal epithelial cells express Ca^{2+} permeable TRPV5 and TRPV6 channels, Ca^{2+} binding proteins, Na^{+}/Ca^{2+} exchangers and Ca^{2+} ATPases (327). Consistent with an apical membrane expression of the pH-sensitive TRPV5 and TRPV6 Ca^{2+} channels is the finding that the transepithelial Ca^{2+} flux was pH-sensitive and that the endolymph Ca^{2+} concentrations were elevated in mice that have acidic endolymph due to loss of pendrin (180).

Other epithelial cells in the cochlea and vestibular labyrinth may be involved in endolymph Ca^{2+} homeostasis since they express Ca^{2+} ATPases and Ca^{2+} permeable channels. Whether these cells secrete or reabsorb Ca^{2+} is currently not clear. Inner hair cells, in contrast to outer hair cells, may be involved in Ca^{2+} reabsorption (84). The transduction channel may serve as an uptake channel and the Ca^{2+} ATPase ATP2B1 (PMCA1) in the basolateral membrane may serve as a release mechanism (49). Similarly, vestibular hair cells express in their basolateral membrane ATP2B1 and ATP2B3 (PMCA3). However, inner and vestibular hair cells express also ATP2B2 in hair bundles (49) (Fig 2B). It is thus unclear whether inner and vestibular hair cells support a transcellular Ca^{2+} flux. The stria vascularis expresses ATP2B1 and Ca^{2+} permeable TRPV4, TRPV5 and TRPV6 channels (1; 37; 144; 268; 315;

324). Reissner's membrane and interdental cells express Ca^{2+} ATPases (37; 64; 324). Outer sulcus cells express ATP2B2 (64) and inner and outer sulcus epithelial cells as well as ductal epithelial cells of the semicircular canals express TRPV5 and TRPV6 Ca^{2+} channels (180; 315). The TRPV5 and TRPV6 Ca^{2+} channels may be located in the apical membrane of at least some cochlear epithelial cells (315).

pH homeostasis

The pH of endolymph varies greatly between different regions in the inner ear. In the cochlea and utricle the endolymphatic pH is slightly alkaline [pH 7.5] (93; 180; 315). In the endolymphatic sac, on the other hand, the pH is more acidic [pH 6.6 -7.1] (35; 281). The functional significance of these differences is largely elusive. The presence of these differences, however, underscores that fluid homeostasis in different compartments of the inner ear is controlled by local ion transport in the adjacent epithelia rather than via a fluid flow between different compartments of the inner ear (219).

Homeostasis of the endolymphatic pH depends on the secretion of H^+ and HCO_3^-. Epithelial cells that express H^+ ATPase in their apical membrane include interdental cells of the spiral limbus (Fig. 2A), strial marginal cells (Fig. 2D) and endolymphatic duct and sac epithelial cells (46; 105; 250). Further, epithelial cells that express in their apical membrane the HCO_3^- permeable anion exchanger SLC26A4 (pendrin) include spiral prominence and outer sulcus epithelial cells, spindle cells of stria vascularis and endolymphatic duct and sac epithelial cells (46; 54; 305; 330).

The main buffer, at least in cochlear endolymph, appears to be CO_2 and HCO_3^-. Glycosaminglycans, which are found in high concentrations in endolymph of the endolymphatic sac, may contribute to pH buffering (89; 203). Proteins, however, which contribute to the buffering capacity of blood plasma, appear to play a lesser role in the buffering of cochlear endolymph due to their low concentration (Table 1). Marginal cells of the stria vascularis are a significant local source of CO_2 due to their high metabolic rate and their use of the hexose monophosphate pathway (168). Carbonic anhydrases in stria vascularis, spiral ligament and spiral limbus capture metabolically-derived CO_2 and convert it to HCO_3^- (146; 188; 245). HCO_3^- generated within the fibrocyte gap junction network may be secreted into endolymph via the HCO_3^- permeable anion exchanger pendrin (SLC26A4). Consistent with HCO_3^- secretion into endolymph is the observation that mice lacking pendrin have an acidic endolymphatic pH consistent with a lack of HCO_3^- secretion (180; 315). Further, increased metabolic rates during acoustic stimulation cause an alkalization of endolymph, which is consistent with an increased rate of HCO_3^- secretion (92).

Endolymphatic pH homeostasis is necessary for hearing and the prevention of hearing loss, although effects of pH may be indirect. For example, acidification of endolymph inhibits Ca^{2+} reabsorption via pH-sensitive TRPV5 and TRPV6 Ca^{2+} channels and elevates the endolymphatic Ca^{2+} concentration, which impairs cochlear function (180; 315). Further, acidification enhances free radical stress and promotes hearing loss (270).

Whether mutations of the B1 subunit (ATP6V1B1) or the A4 subunit (ATPV0A4) of H^+-ATPase cause an alkalinization of endolymph pH is currently unknown. Nevertheless, mutations of either subunit may cause in humans a progressive sensorineural hearing loss in addition to renal tubular acidosis (105; 252; 288). The etiologies of these hearing losses, however, are unclear, in particular, since mice lacking the B1 subunit (ATP6V1B1) develop normal hearing and show no overt morphological abnormalities in the inner ear (44).

Water transport

Water transport follows osmotic gradients that are established by the transport, metabolism or catabolism of solutes (131). Water can permeate most membranes freely with the notable exception of the apical membrane of thick ascending limb and of the cortical collecting duct of the kidney in the absence of the antidiuretic hormone, vasopressin. The water permeability of cell membranes depends to a significant extent on the presence of aquaporins, which are water-permeable channels. According to a recent review, thirteen different aquaporins (AQP0-12) have so far been identified (184).

A multitude of aquaporins is expressed in the inner ear including AQP1, AQP2, AQP3, AQP4, AQP5, AQP7 and AQP9 (88; 149; 175; 176; 224; 249; 267; 334). The functional significance of inner ear water channels is largely unclear. Loss of function of AQP1 associated with the Colton blood group does not cause an overt clinical phenotype although it is associated with a reduction of the urinary concentration capacity (113; 205). Hearing loss or balance difficulties have not been reported in association with the Colton blood group. Neither have hearing loss or balance disorders been reported to be associated with diabetes insipidus due to loss of AQP2. Mice lacking AQP1, AQP3 or AQP5 have normal hearing, however, mice lacking AQP4 have a minor hearing loss of 10 dB at 4-5 weeks of age (141) (Fig. 2A). Whether hearing was impaired at the onset of hearing, is currently unknown.

Function of inner ear channels and transporters in renal epithelia

Many of the channels, carriers, and pumps accomplishing tranport in the inner ear are similarly expressed in the kidney and participate in renal tubular transport. Accordingly, the hearing loss in patients carrying genetic defects of defined transport molecules may be paralleled by deranged renal acid or electrolyte excretion that affects acid-base or electrolyte homeostasis of the body. Moreover and possibly related to the different organization and function of the two organs, some of the transport proteins are used for quite different cellular functions in the inner ear and the kidney as discussed below.

The proximal tubule of the kidney (Fig. 3A) reabsorbs about 60% of the filtered NaCl and fluid and most of the filtered amino acids and glucose. K^+ channels in the apical cell membrane of proximal tubules (Fig. 3A) contribute to the maintenance of the cell membrane potential during depolarizing Na^+-coupled transport (e.g. cotransport of Na^+ with amino acids or glucose), thereby stabilizing the electrical driving force for electrogenic Na^+ reabsorption.

The Henle´s Loop contributes to the generation of a hypertonic kidney medulla, a prerequisite for urinary concentration. Most importantly, the thick ascending limb of Henle´s Loop reabsorbs about 25% of the NaCl filtered by the glomeruli without accompanying water reabsorption, thus enhancing interstitial osmolarity (Fig. 3B). The medullary collecting ducts (Fig. 3D) pass the hypertonic kidney medulla. During water retention water channels allow water to leave the lumen of the collecting ducts thus leading to urinary concentration.

The distal convoluted tubule (Fig 3C), the connecting tubule (not explicitly shown) and the collecting duct (Fig 3D,E) allow the fine tuning of renal acid, fluid, and electrolyte excretion. In all nephron segments, proximal tubule, Henle´s Loop, distal tubule and collecting duct K^+ channels maintain the cell membrane potential and thus the driving force for electrogenic transport.

K^+ channels

K^+ channels expressed in both inner ear and kidney include KCNE1/KCNQ1, KCNJ10 and BK channels (KCNMA1/KCNMB1) (Table 2)

KCNE1 and KCNQ1 have been localized to the brush border of the mid to late proximal tubule (256; 283) (Fig. 3A). Besides their potential role in net K^+ secretion into the early proximal tubule (284), they may polarize the brush border membrane and thus maintain

the electrical driving force for Na^+ coupled transport (132; 133). Studies in knockout mice indeed revealed that lack of functional KCNE1/KCNQ1 K^+ channels leads to moderate impairment of electrogenic Na^+,glucose cotransport in proximal tubules (283; 284) (see Fig. 3A). KCNE1 may interact with additional K^+ channels especially in the early proximal tubule where most of the glucose, amino acids and phosphate is reabsorbed by electrogenic cotransport with Na^+ and where KCNE1 but not KCNQ1 was detected. In the early proximal tubule KCNE1 is likely to coassemble with another KCNQ isoform (Fig 3A) similar to what was recently shown for the outer hair cells (255). KCNQ1-independent function of KCNE1 may explain the more severe phenotype (e.g. renal Na^+ and glucose loss) in mice lacking KCNE1 compared with KCNQ1 (283; 284). Thus, whereas KCNQ1/KCNE1 K^+ channels serve to establish high K^+ concentrations in the endolymph of the inner ear, they serve the very different function of stabilizing the membrane potential and thus electrogenic reabsorption of Na^+ in the proximal tubule of the kidney, with the secreted K^+ being subsequently reabsorbed by paracellular routes.

KCNJ10 is expressed in the basolateral cell membrane of renal distal tubules including the thick ascending limb (97; 151; 272; 273) (see Fig. 3B). The channels are highly sensitive to cytosolic pH and are thus thought to link K^+ metabolism with acid-base balance (21). To our knowledge, however, no data are available on K^+ or acid-base balance in mice lacking KCNJ10. Whereas KCNJ10 is considered to be of primary importance for the endocochlear potential of the inner ear, its precise role in the kidney remains to be defined.

BK channels (KCNMA1) are expressed in the renal vasculature and the tubular system (71; 198) (Fig 3D). In the latter, they contribute to K^+ secretion into the luminal fluid. BK channels in the luminal membrane of the distal nephron (Fig. 3D) are involved in K^+ homeostasis in response to a high K^+ diet (9; 179; 212) and mediate renal K^+ excretion in response to enhanced tubular flow rates (71; 198-200; 212; 274; 323). In the mouse, the β1-sbunit KCNMB1 was found exclusively in the connecting tubule (200). Notably, this β1-subunit confers protein kinase G activation of BK channels, dramatically increases the Ca^{2+} sensitivity of the channel, and leads to activation of the channel at more negative potentials, thereby presumably enhancing the ability of the pore-forming α-subunit to induce significant K^+ excretion in the distal nephron under physiological conditions (for review see (198)). Moreover, mice lacking the α-subuniț (KCNMA1) (212) but also mice deficient in the β1-subunit (KCNMB1) (199) exhibited blunted flow-induced renal K^+ excretion. These studies implied a role for BK channels (KCNMA1/KCNMB1) in flow-induced renal K^+ excretion and K^+ homeostasis. BK channels are also expressed in other tubular segments where their function is less clear. Whether circulation or flow of endolymph similarly affects BK channel activity in the inner ear remains to be determined.

Na^+,$2Cl^-$,K^+ cotransporter

The Na^+,$2Cl^-$,K^+ cotransporter NKCC1 (SLC12A2) is highly expressed in glomeruli of more mature nephrons (286) and may participate in the macula densa-dependent regulation of renin release (23; 66; 302). A closer look at SLC12A2 knockout mice more recently revealed that they suffer from hypotension, which was proposed to relate in part to an impaired responsiveness of the kidney to aldosterone and vasopressin (302).

The Na^+,$2Cl^-$,K^+ cotransporter NKCC2 (SLC12A1), which is strongly expressed in the luminal membrane of the thick ascending limb (40)(Fig. 3B), is responsible for most of the NaCl reabsorption in that segment and is a prerequisite for the ability of the kidney to dilute and concentrate the urine. Accordingly, genetic defects of SLC12A1 lead to isosthenuria and severe renal salt loss (80; 204; 238; 287). SLC12A1 is not expressed in the inner ear and lack of functional SLC12A1 does not lead to hearing loss. Conversely, SLC12A2 deficiency, as discussed above, leads to deafness without leading to overt renal salt wasting (43; 57). Importantly, both SLC12A1 and SLC12A2 are inhibited by loop diuretics such as furosemide

and thus inhibition of the $Na^+,2Cl^-,K^+$ cotransport in the inner ear during excessive doses of loop diuretics leads to an accumulation of K^+ in the intrastrial space, which abolishes the endocochlear potential (129) and leads to hearing loss (81; 96; 322). Much lower doses are sufficient to inhibit the luminal SLC12A1 in the thick ascending limb, since the drug accumulates in the tubular fluid as a consequence of efficient secretion into proximal tubular fluid and fluid reabsorption along the tubule. Thus, natriuretic and diuretic actions can be achieved without hearing loss.

Cl^- channels

The Cl^- channel CLCNKA/BSND (ClC-Ka/barttin) is expressed in the basolateral membrane of thin ascending limbs (not shown) whereas the Cl^- channel CLCNKB/BSND (ClC-Kb/barttin) is expressed in the basolateral membrane of thick ascending limbs of Henle´s Loop (53; 297) (see Fig. 3B). In the mouse, ClC-K1 (the rodent orthologue of CLCNKA) is also expressed in the thin ascending limb. Knockout of ClC-K1 in mice results in nephrogenic diabetes insipidus establishing that ClC-K1 has a role in urine concentration, and that the countercurrent system in the inner medulla is involved in the generation and maintenance of a hypertonic medullary interstitium (171). In the thick ascending limb, basolateral CLCNKB /BSND contributes to transcellular NaCl reabsorption. Defects of CLCNKB lead to renal salt wasting of classical Bartter syndrome without hearing impairment (119; 237). The phenotype of patients suffering from defective CLCNKB (119; 237), however, is less severe than the phenotype of patients suffering from antenatal Bartter syndrome due to defective SLC12A1 (238) or apical K^+ channel ROMK (239). Genetic defects of BSND lead to renal salt wasting together with deafness (14) (Table 2).

Voltage clamp experiments disclosed that a common (prevalence 20 % in Caucasians, and 40 % in Africans) variant of the CLCNKB gene leading to the replacement of threonine by serine at the amino acid position 481 of the ClC-Kb protein (ClC-KbT481S), dramatically increases ClC-Kb chloride channel activity (100). Expression of the mutated channels should decrease cytosolic Cl^- concentration and thus enhance the driving force and transport rate of $Na^+,2Cl^-,K^+$ cotransport. As a result, the gene variant may lead to enhanced transport in inner ear and kidney. The gene variant was associated with increased blood pressure in one study on a population of largely young, healthy individuals (101), but not in two others on more elderly populations (117; 244). The same gain of function mutation was associated with a slight but significant delay of hearing loss in female humans, while no significant differences were observed between male carriers and noncarriers of the mutation (60).

Thus, whereas CLCNKA/BSDN and CLCNKB/BSDN serve the recycling of Cl^- across the basolateral membrane of marginal cells of the inner ear in order to maintain the uptake of K^+ via SLC12A2, in the kidney the two channels serve the very different function of basolateral net transport of Cl^- along the ascending thin and thick limb.

KCl cotransport

The K^+/Cl^- cotransporter KCC4 (SLC12A7) is found along the basolateral cell membrane in several nephron segments (289) (see Fig. 3A, E). KCC4 is colocalized with KCC3 (SLC12A6) in basolateral cell membranes of the proximal tubule (15; 47) (Fig 3A), where it may contribute to proximal tubular cell volume regulation. This cotransporter is also important for Cl^- recycling in type A intercalated cells (Fig. 3E). In accordance with a crucial role of SLC12A7 for KCl release in K^+ buffering and volume regulation in both the kidney and inner ear, mice lacking KCC4 suffer from renal tubular acidosis (15; 102; 196) and deafness (15; 16)(Table 2). Whether KCC4 is of similar pathophysiological significance in man, remained elusive.

ENaC

ENaC (Fig. 3D, SCNN1) is mainly expressed in the luminal membrane of the aldosterone-sensitive distal nephron, where about 1-3% of the filtered Na^+ is reabsorbed. ENaC is of critical importance for renal Na^+ reabsorption and secondary K^+ excretion and, thus, for salt and K^+ homeostasis and blood pressure regulation. Patients carrying loss of function mutations of ENaC ("dominant" pseudohypoaldosteronism type 1, PHA 1) as well as knockout mice for the ENaC subunits (SCNN1A, SCNN1B, SCNN1C) suffer from renal salt wasting (69; 90). As mutant mice die soon after birth it is still elusive whether the mutated gene would induce hearing loss. Patients with gain of function mutations of ENaC (Liddle´s syndrome) suffer from hypertension (19; 77; 145; 225; 319; 320) but are not known to suffer from deafness.

Gap junctional channels

The classic gap junction channels have been shown by freeze fracture studies in proximal tubule (125), and some of the ubiquitous connexin isoforms (GJA4 (CX37), GJA5 (CX40), GJA1 (CX43), and GJA7 (CX45)) have subsequently been identified in the kidney and localized to mainly vascular and glomerular components (8; 10). In the so-called juxtaglomerular apparatus, Cx40 and Cx43 have been implicated in the regulation of renin secretion (75; 296).

Moreover, GJB6 protein (CX30), probably in the form of luminal hemichannels, was found to be expressed in renal tubular epithelial cells (Fig. 3E) and inserted into the apical cell membrane particularly of intercalated cells (172). GJB6 proteins were upregulated by high salt diet in the distal nephron (172) (Fig. 3E). It has thus been speculated that GJB6 may function as an apical hemichannel allowing the passage of ATP and having a potential inhibitory role in the regulation of salt reabsorption in the distal nephron (172). Along those lines, a recent study showed that mice deficient for the ATP receptor $P2Y_2$ present a salt resistant form of arterial hypertension that is associated with facilitated renal Na^+ and fluid reabsorption (211). It would be interesting to learn whether renal electrolyte excretion and/or blood pressure are altered in patients with defective GJB6 or in GJB6 knockout mice.

Ca^{2+} homeostasis

Together with intestine and bone, the kidney is of primary importance for body Ca^{2+} homeostasis. Hormone-regulated renal Ca^{2+} reabsorption is mainly localized to the late distal convoluted tubule and the connecting tubule, where TRPV5 channels, expressed in the luminal membrane (Fig. 3C), accomplish Ca^{2+} uptake and Ca^{2+} ATPases (PMCA1B) (Fig. 3C) as well as Na^+/Ca^{2+} exchangers (NCX1) basolateral exit (85). Accordingly, TRPV5 deficient mice suffer from impaired Ca^{2+} reabsorption leading to renal Ca^{2+} loss (86; 209). Notably, TRPV6, which mediates Ca^{2+} reabsorption in the intestine, is also expressed in the luminal membrane of the collecting duct (i.e. downstream of the segments primarily expressing TRPV5) (Fig. 3D) and may contribute to renal tubular Ca^{2+} reabsorption. Accordingly, Ca^{2+} reabsorption in the collecting duct limits renal Ca^{2+} loss in mice lacking TRPV5 (86) and mice lacking TRPV6 also loose some Ca^{2+} into the urine (13).

Renal TRPV4 is expressed mainly in the basolateral cell membrane of thin and thick ascending limbs and distal convoluted tubule (28; 279) (Fig. 3B). TRPV4 channels were presumed to participate in the cellular response to alterations of extracellular osmolarity (195; 254). TRPV4 knockout mice tend to be hypercalcemic, which would indicate that TRPV4 rather decreases net renal Ca^{2+} reabsorption (63).

Together these findings suggest that Ca^{2+} transport pathways that serve to stabilize the Ca^{2+} concentration of the endolymph in the inner ear, are involved in kidney function to regulate the Ca^{2+} homeostasis of the whole body.

pH homeostasis

The kidney is of pivotal importance for the regulation of the acid-base balance of the body. Renal regulation of acid base balance primarily involves the reabsorption, generation or excretion of HCO_3^- as well as the generation and excretion of NH_4^+. Vacuolar H^+-ATPase (ATP6V), H^+/K^+-ATPase (ATP4A), and the Cl^-/HCO_3^- exchangers pendrin (SLC26A4) and AE1 (SLC4A1) are all expressed in the kidney, where they contribute to acid-base balance. Gastric (and colonic) H^+/K^+-ATPase is expressed in the collecting duct (Fig. 3E). It is responsible for H^+ secretion and K^+ reabsorption under normal conditions and may be stimulated by acid-base perturbations and/or K^+ depletion. The regulation may be species specific (for review see (236)).

Vacuolar H^+-ATPase, H^+/K^+-ATPase, and the Cl^-/HCO_3^- exchangers SLC26A4 and SLC4A1 are all expressed in the intercalated cells of the kidney (Fig. 3E), which are critically involved in acid-base balance (for review see (4; 232; 299)). The localization of the H^+-ATPase in the apical or basolateral membrane can vary between cortical intercalated cells indicating that subpopulations of these cells have opposite polarities of an H^+-ATPase, consistent with the presence of both proton- and bicarbonate-secreting cells (17; 18). Along those lines, type A, type B or non-A, non-B intercalated cells are defined according to the presence or absence of the Cl^-/HCO_3^- exchanger SLC4A1, and the subcellular distribution of the H^+-ATPase (5; 111). Type A intercalated cells mediate net secretion of H^+ through an apical H^+-ATPase (ATP6V), which functions in series with basolateral SLC4A1 (51; 276; 321). Particularly during metabolic alkalosis, type B intercalated cells mediate secretion of HCO_3^- by employing the apical Cl^-/HCO_3^- exchanger, pendrin (SLC26A4), which functions in series with basolateral H^+-ATPase (5; 51; 62; 111; 112; 214; 243; 276; 300; 321). Non-A, non-B intercalated cells may be HCO_3^- or H^+ secreting cells or may interconvert between the two functions (111; 276). They express both pendrin as well as H^+-ATPase in the apical membrane (300).

Under basal unstimulated conditions, persons with genetic disruption of pendrin (SLC26A4; Pendred syndrome) and mice lacking SLC26A4 exhibit no change in arterial pH, renal function or fluid balance (213). Under conditions of dietary NaCl restriction or administration of mineralocorticoids, however, pendrin expression is increased in type B intercalated cells in rodents, and under these conditions mice lacking SLC26A4 show evidence for impaired renal HCO_3^- excretion as well as impaired Cl^- retention, which results in elevated arterial pH and serum HCO_3^- and lower blood pressure compared with wild-type mice (213; 293; 301). In contrast to the inner ear where SLC26A4 mutations lead to hearing loss in men and mice (Everett et al., 1999), in the kidney pendrin is essential for a normal response to low salt conditions (Table 2), indicating that pendrin may be a new target for antihypertensive therapy. In humans, loss of pendrin leads in addition to defective iodide uptake into thyroid glands and thus in later life to goiter (54). The latter is not found in mice and is in humans of much later onset than the hearing loss.

Autosomal-dominant and –recessive forms of distal tubular acidosis are caused by mutations in ion transporters of acid secreting type A intercalated cells (for review see (4)). These include at least two subunits of the apical H^+-ATPase (Fig. 3E, Table 2). Loss of function mutations of the genes encoding for the B1 subunit of the H^+-ATPase lead to recessive distal tubular acidosis with sensorineural hearing loss (105; 241). Bicarbonate therapy successfully treats systemic symptoms of distal renal tubular acidosis but fails to correct deafness suggesting that transepithelial acid secretion is required for normal cochlear development and hair cell survival. Mice lacking the B1 subunit (ATP6V1B1) have preserved hearing but exhibit impaired maximal urinary acidification (56). Although patients with distal renal tubular acidosis due to homozygous B1-subunit mutations typically present as infants with spontaneous metabolic acidosis and failure to thrive (105), mice lacking ATP6V1B1 raised on a standard rodent diet were healthy, grew normally, and did not develop metabolic acidosis (56). The phenotypic discrepancy may be related to dietary differences since a standard rodent diet provides a large net dietary alkali load whereas the typical Western human

diet, which has higher protein content, imposes a net acid load (56). On the other hand, apical expression of the alternative B-subunit isoform B2 is increased in the medulla of mice lacking ATP6V1B1 and may partially although not completely compensate for the loss of ATP6V1B1(56).

Mutations in ATP6N1B, encoding a new kidney vacuolar H^+-ATPase subunit, which was also localized to the apical membrane of type A intercalated cells, cause recessive distal renal tubular acidosis with preserved hearing (241). Similarly, multiple mutations have been described for the Cl^-/HCO_3^- exchanger, SLC4A1, which are associated with distal renal tubular acidosis in the absence of deafness (for review see (4)).

In conclusion, many transport proteins that stabilize the pH of the endolymph of the inner ear are also involved in the renal transport of HCO_3^- and H^+ and, thus, contribute to the acid-base homeostasis of the body.

Water transport

The aquaporins AQP1 to AQP4 play a central role in water reabsorption of the kidney (for review see (183)). AQP1 is particularly expressed along the proximal tubule (Fig, 3A) and near-isosmolar fluid reabsorption, a hallmark of proximal tubular function, is dramatically impaired in mice lacking AQP1 indicating that proximal tubular fluid reabsorption is largely due to transcellular water movement through AQP1 (227; 285). AQP1 is the principal water channel in thin descending limbs of Henle's loop and is also expressed in outer medullary descending vasa recta, where it facilitates water transport and is thus an important component of the urinary concentrating mechanism (27; 153; 192; 291). Very recent studies provided evidence for the involvement of AQP1 in migration of proximal tubule cells and possibly in the response of the proximal tubule to injury (78). In comparison, AQP2 is exclusively expressed in the principal cells of the connecting tubule and collecting duct and is the predominant vasopressin-regulated water channel (Fig. 3D). AQP3 and AQP4 are both present in the basolateral plasma membrane of collecting duct principal cells (Fig. 3D) and represent exit pathways for water reabsorbed apically via AQP2. Studies in patients have demonstrated that AQP2 is essential for urinary concentration (183; 229; 290). Loss of function mutations of AQP2 cause nephrogenic diabetes insipidus (329). The inheritence is usually autosomal-recessive but may in some patients be autosomal-dominant (AD-NDI) (329), and could be related to a dominant-negative monomer that leads to a missorting of AQP2 to the basolateral instead of the apical plasma membrane of the collecting duct cells (242)(Table 2). Moreover, mice lacking AQP2, AQP3 or AQP4 suffer from various degrees of nephrogenic diabetes insipidus (292).

Conclusions

Epithelial transport in the inner ear and kidney is critical for the function of both organs. Many of the proteins accomplishing ion transport within inner ear and kidney are encoded by the same genes, as listed in Table 2. Most of the transporters are involved in K^+ cycling within the inner ear and simultaneously participate in renal tubular transport of Na^+ and K^+. Other transport systems are involved in regulating and stabilizing the Ca^{2+} concentration or the pH of the endolymph and in the regulation of renal tubular transport of Ca^{2+}, HCO_3^- and H^+ and thus participate in Ca^{2+} homeostasis and acid-base balance of the whole body. The different arrangement of the channel proteins may lead to completely different transport functions. For example, KCNQ1/KCNE1 K^+ channels serve to establish high K^+ concentrations in the endolymph of the inner ear, whereas in the proximal renal tubules, they stabilize the membrane potential across the apical cell membrane and thus contribute to the maintenance of the electrical driving force for Na^+ coupled electrogenic transport. The comparison of the transport

processes in the inner ear and kidney thus illustrates the amazing versatility of biology in the use of individual molecules. Moreover, the comparison leads to pathophysiological insight into syndromal genetic disease as well as into side effects of drugs targeting those channels and transporters and it may provide clues to new therapeutic approaches. Our knowledge, though, is still far from complete and many mechanisms are a matter of speculation. It is an aim of this brief synopsis to stimulate future interdisciplinary research in this exciting and clinically important area of physiology.

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Table 1: Fluid composition of cochlear endolymph and perilymph as well as endolymph of the endolymphatic sac and cerebrospinal fluid. Values are taken from a recent review (316) and amended by additional data (35; 93-95; 178; 281; 315).

		Cochlear Perilymph	Cochlear Endolymph	Sac Endolymph	Cerebro-spinal Fluid
Na^+	(mM)	148	1.3	129	149
K^+	(mM)	4.2	157	8-13	3.1
Cl^-	(mM)	119	132	124	129
HCO_3^-	(mM)	21	31	-	19
Ca^{2+}	(mM)	1.3	0.023	-	-
Protein	(mg/dl)	178	38	-	24
pH		7.3	7.5	6.7-7.1	7.3

Table 2: Channels, transporters and pumps expressed in both, inner ear and kidney

Gene Symbol	Aliases	Function		Consequences of loss of function	
		Inner ear	Kidney	Inner ear	Kidney
Channels and associated proteins					
KCNJ10	Kir4.1 or Kir1.2	formation of endocochlear potential	unknown	deafness[b]	unknown
KCNQ1/ KCNE1	KvLQT1 / mink or ISK	K^+ secretion into endolymph; endolymph formation	maintain PT brush border membrane potential[b]	deafness[a,b]	no (KCNQ1) or modest (KCNE1) urinary loss of Na^+ and glucose[b]
KCNMA1/ KCNMB1	BK channel, alpha 1 and beta 1	K^+ efflux from cochlear inner hair cells	(flow-dependent) K^+ secretion in CNT and CD[b]	progressive hearing loss (only KCNMA1)[b]	impaired flow-dependent renal K^+ excretion[b]
CLCNKA	chloride channel Ka	recycling of Cl^- in strial marginal cells and vestibular dark cells; endolymph formation	basolateral Cl^- reabsorption in thin (CLCNKA) or thick (CLCNKB) ascending limb or both (BSND)[b]	deafness when both CLCNKB and CLCNKA are defective[a]	nephrogenic diabetes insipidus[b]
CLCNKB	chloride channel Kb				Bartter syndrome[ab]
BSND	Barttin			deafness[a]	Bartter syndrome[ab]
SCNN1A, SCNN1B, SCNN1G	ENaC, alpha, beta & gamma	uptake of Na^+ into epithelial cells of Reissner's membrane and semicircular canal	Na^+ reabsorption and secondary K^+ excretion in CNT and CD[ab]	no known inner ear phenotype	pseudohypoaldosteronism type 1[ab]
GJA1	gap junction protein, CX43	metabolic coupling & glutamate buffering in the lateral and medial network; buffering of K^+ released from outer hair cells (GJA1, GJB6); endocochlear potential (GJB6)	regulation of renin secretion[b]	deafness	unknown
GJB6	gap junction protein, CX30		pathway for ATP release from intercalated cells?[b]	deafness	unknown
TRPV4		Ca^{2+} homeostasis of endolymph	cellular response to alterations of extracellular osmolarity?[b]	delayed-onset hearing loss & vulnerability to acoustic injury[b]	unknown
TRPV5	CaT2		Ca^{2+} reabsorption in late DCT & CNT (TRPV5) or CD (TRPV6)[b]	unknown	urinary Ca^{2+} loss[b]
TRPV6	CaT1				
AQP1	aquaporin 1, CHIP28	unknown	water transport in PT, TDL & OMDVR[b]	no overt phenotype[ab]	impaired near-isotonic reabsorption in PT and urine concentration[b]
AQP2	aquaporin 2	unknown	water reabsorption in CNT & CD (apical: AQP2;	unknown	urinary concentrating defect[b] (AQP2[a])
AQP3	aquaporin 3	unknown		no overt phenotype[b]	

AQP4	aquaporin 4	unknown	basolateral: AQP3,AQP4)[b]	minor hearing loss[b]	
Transporters					
SLC12A2	Na^+,2Cl^-,K^+ transporter, NKCC1	K^+ uptake into strial marginal cells and vestibular dark cells; endolymph formation	regulation of renin release[b]	deafness	hypotension[b]
SLC12A7	KCl transporter, KCC4	K^+ exit (or uptake) in Deiter's cells?	Cl^- recycling in type A intercalated cells[b]	deafness	distal renal tubular acidosis[b]
SLC26A4[a]	Cl^-/HCO_3^- exchanger, Pendrin	HCO_3^- secretion into endolymph	HCO_3^- secretion and Cl^- reabsorption in type B and non-A, non-B intercalated cells[b]	acidic endolymphatic pH; deafness	no basal phenotype[ab]; elevated arterial pH & serum HCO_3^- & lower blood pressure with NaCl restriction[b]
Pumps					
PMCA1B	Ca^{2+}-ATPase	Ca^{2+} homeostasis of endolymph	Ca^{2+} reabsorption in late DCT and CNT	unknown	unknown
ATP6V1B1, ATP6V0A4[a]	H^+-ATPase (B1, A4)	acidification of endolymph	acidification of urine[a]	deafness	distal renal tubular acidosis[a]

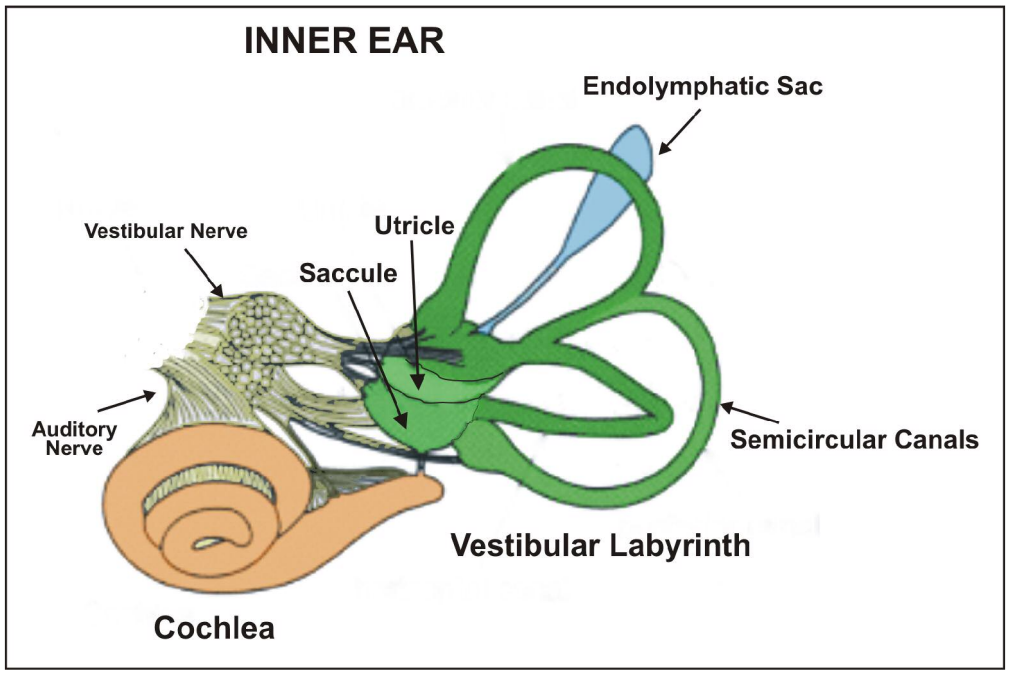
[a] observed in humans; [b] observed in mouse models; CD, collecting duct; CNT, connecting tubule; DCT, distal convolted tubule; OMDVR, outer medullary descending vasa recta; PT, proximal tubule; TDL, thin descending limb

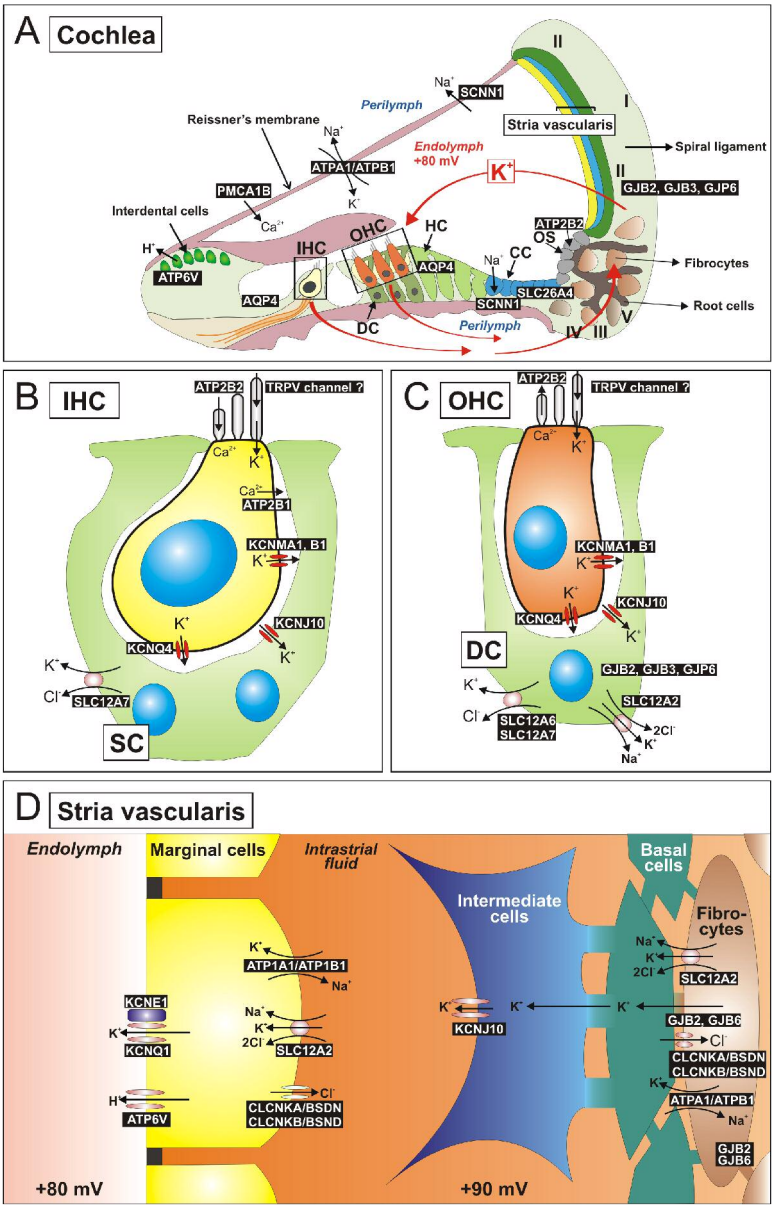
Figures

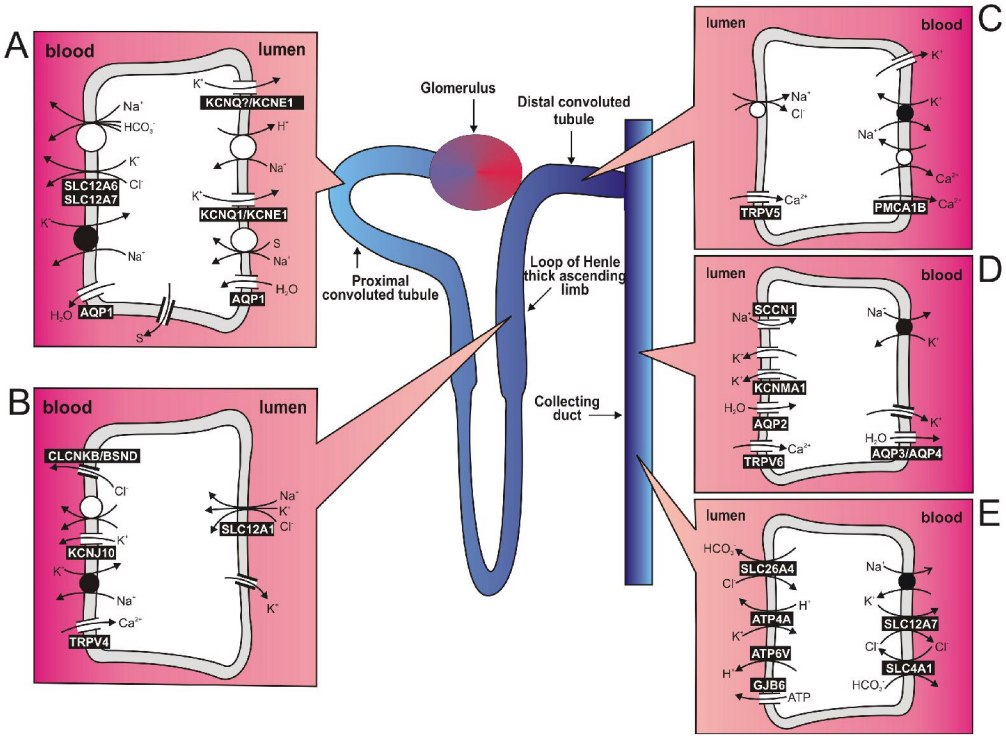
Fig. 1.
Most important compartments of the inner ear, including cochlea, vestibular system and endolymphatic sac.

Fig. 2
Compartments of the cochlea. (A) A cross section through the cochlear duct, (B) the inner hair cell, (C) the outer hair cell, and (D) the stria vascularis. Gene names of expressed ion channels and transporters are illustrated within the approximate position.
IHC, inner hair cell; OHC, outer hair cell; DC, Deiter`s cell; CC, Claudius Cell; HC, Hensen Cell; OS, outer sulcus cells; SC, supporting cell.

Fig. 3
Individual segments of the tubular and collecting duct system of the kidney. Positions within the nephron are indicated. Gene names of expressed ion channels and transporters are illustrated within the approximate position. S, Substrate for Na^+-coupled electrogenic transport.


INNER EAR
Endolymphatic Sac
Vestibular Nerve
Utricle
Saccule
Auditory Nerve
Semicircular Canals
Vestibular Labyrinth
Cochlea


A Cochlea
II
I
Na+
SCNN1
Perilymph
Reissner's membrane
Stria vascularis
Spiral ligament
Na+
Endolymph
+80 mV
ATPA1/ATPB1
K+
II
PMCA1B
GJB2, GJB3, GJP6
Interdental cells
Ca2+
OHC
HC
ATP2B2
H+
IHC
OS
CC
Fibrocytes
ATP6V
AQP4
Na+
AQP4
SLC26A4
SCNN1
Root cells
DC
Perilymph
IV
III
V
B IHC
ATP2B2
TRPV channel ?
Ca2+
K+
Ca2+
ATP2B1
KCNMA1, B1
K+
K+
KCNJ10
KCNQ4
K+
K+
Cl-
SLC12A7
SC
C OHC
ATP2B2
TRPV channel ?
Ca2+
K+
KCNMA1, B1
K+
K+
KCNQ4
KCNJ10
K+
DC
GJB2, GJB3, GJP6
K+
Cl-
SLC12A2
SLC12A6
SLC12A7
2Cl-
K+
Na+
D Stria vascularis
Endolymph
Marginal cells
Intrastrial fluid
Basal cells
Intermediate cells
Fibro-cytes
K+
ATP1A1/ATP1B1
Na+
Na+
K+
2Cl-
SLC12A2
KCNE1
K+
KCNQ1
Na+
K+
2Cl-
SLC12A2
K+
K+
K+
KCNJ10
GJB2, GJB6
Cl-
CLCNKA/BSDN
CLCNKB/BSND
H+
ATP6V
Cl-
CLCNKA/BSDN
CLCNKB/BSND
K+
ATPA1/ATPB1
Na+
GJB2
GJB6
+80 mV
+90 mV


A
blood
lumen
KCNQ7/KCNE1
SLC12A6
SLC12A7
KCNQ1/KCNE1
AQP1
AQP1
B
blood
lumen
CLCNKB/BSND
SLC12A1
KCNJ10
TRPV4
Glomerulus
Distal convoluted tubule
Proximal convoluted tubule
Loop of Henle thick ascending limb
Collecting duct
C
lumen
blood
TRPV5
PMCA1B
D
lumen
blood
SCCN1
KCNMA1
AQP2
TRPV6
AQP3/AQP4
E
lumen
blood
SLC26A4
ATP4A
ATP6V
GJB6
SLC12A7
SLC4A1
ATP