REVIEW

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Genetic disorders of transporters/channels in the inner ear and their relation to the kidney

Abstract Inner ear physiology is reviewed with emphasis on features common to renal physiology. Genetic disorders in transporters/channels for chloride (ClC-K), bicarbonate (Cl$^-$/HCO$_3^-$ exchanger), protons (H$^+$-ATPase), sodium (ENaC, NKKC1, NBC3, NHE3), potassium (KCNQ1/KCNE1, Kcc4), and water (AQP4) in the inner ear and their relation to the kidney are discussed. Based on data from human disorders (with or without mouse counterparts) and mouse models (without human counterparts) this article focuses on the involvement of these transporters/channels in hearing loss.

Keywords Deafness · Endolymph · Hereditary · Inner ear · Transport disorders

Introduction

As the inner ear and the renal tubules share several common transporters/channels, disturbances in the function of the inner ear and renal tubules may occur at the same time. The number of disturbed transporters/channels in both organs is increasing. Both pediatric nephrologists and otologists should be aware of this and that linkage of some clinical consequences is possible.

The aim of this review is to give an overview of combined renal and inner ear transporter/channel defects. First, basic information on inner ear anatomy and physiology is provided, followed by a description of the different genetic disorders in transporters/channels in the inner ear in relation to the kidney. The cochlear part of the inner ear is the main focus of this review. Additional genetic causes of inner ear diseases are well covered in recent reviews [1, 2, 3].

Inner ear physiology

The inner ear or labyrinth is situated in the petrous part of the temporal bone. Within the otic capsule or bony labyrinth, lies the membranous labyrinth composed of the cochlea, vestibular system, and endolymphatic sac (Fig. 1).
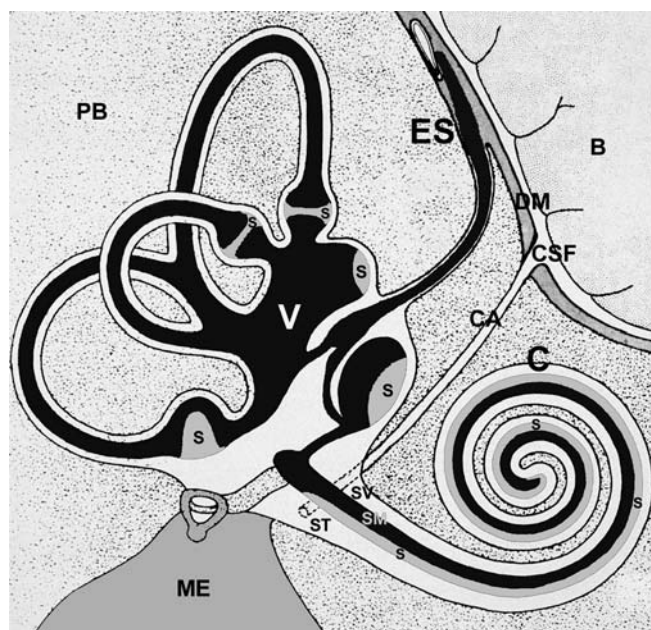

Fig. 1 Schematic anatomy of the various compartments of the membranous labyrinth. The inner ear spaces filled with endolymph are *black* and those filled with perilymph are *white*. [*B* brain, *C* cochlea, *CA* cochlear aqueduct (not so widely patent as depicted here), *CSF* cerebrospinal fluid, *DM* dura mater, *ES* endolymphatic sac, *ME* middle ear, *PB* petrous bone, *S* sensory organ, *SM* scala media, *ST* scala tympani, *SV* scala vestibuli, *V* vestibular system]

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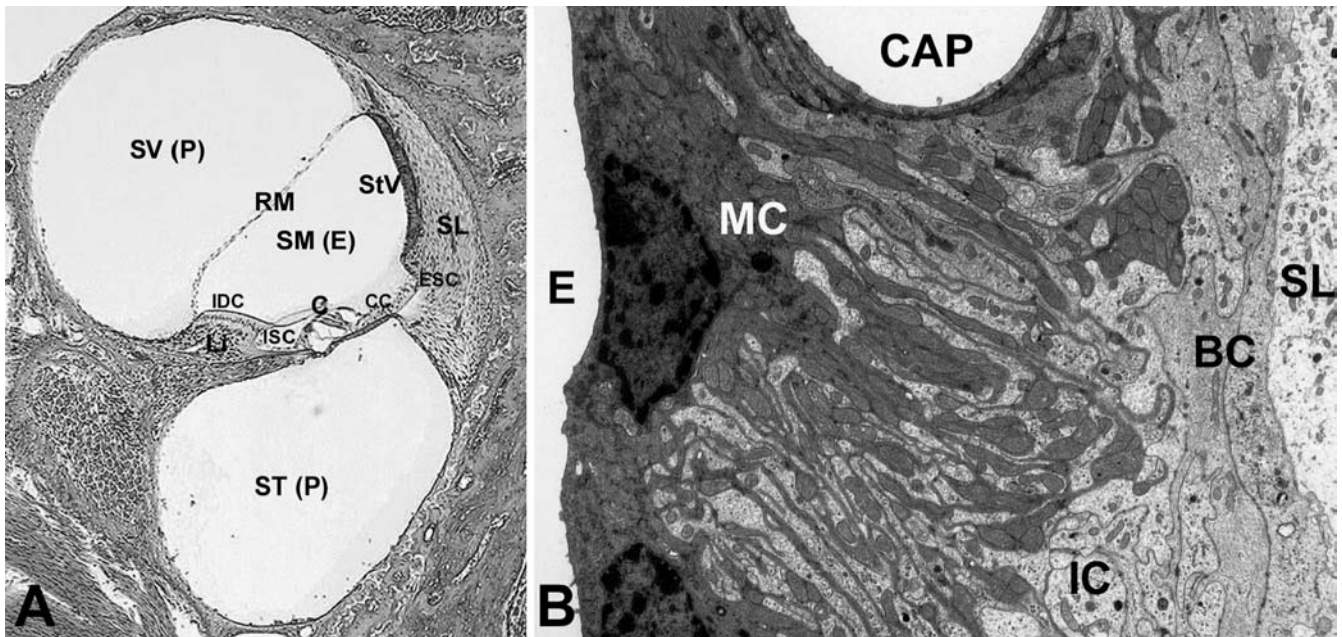Philips van Leydenlaan 15, 6525 EX Nijmegen, The Netherlands

Fig. 2 A Cross-section of one turn of the cochlea depicting the organ of Corti (*C*) composed of sensory hair cells and supporting cells, Claudius cells (*CC*), external sulcus cells (*ESC*), internal sulcus cells (*ISC*), limbus spiralis (*Li*), interdental cells (*IDC*), Reissner's membrane (*RM*), and stria vascularis (*StV*) adjacent to the fibrous spiral ligament (*SL*) (*E* endolymph, *P* perilymph). **B** High magnification of the stria vascularis composed of marginal cells (MC) facing the endolymph (*E*), intermediate cells (*IC*), and basal cells (*BC*) adjacent to the spiral ligament (*SL*) (*CAP* capillary)

Table 1 Composition, osmolarity, and pH of cochlear endolymph and perilymph with respect to plasma (*SM* scala media, *ST* scala tympani, *SV* scala vestibuli)

| | Endolymph | Perilymph | Perilymph | Plasma |
	SM	ST	SV	
Potassium (K$^+$)[a]	170	3	4	5
Sodium (Na$^+$)[a]	1	140	140	140
Chloride (Cl$^-$)[a]	145	120	120	105
Bicarbonate (HCO$_3^-$)[a]	30	23	24	26
Calcium (Ca^{2+})[a]	0.02	0.68	0.64	2.5
Magnesium (Mg^{2+})[a]	0.01	0.76	–	1.0
Protein[b]	0.6	1.4	1.6	65
Osmolarity[c]	330	290	290	290
pH	7.4	7.4	7.4	7.4

[a] Ions in mM
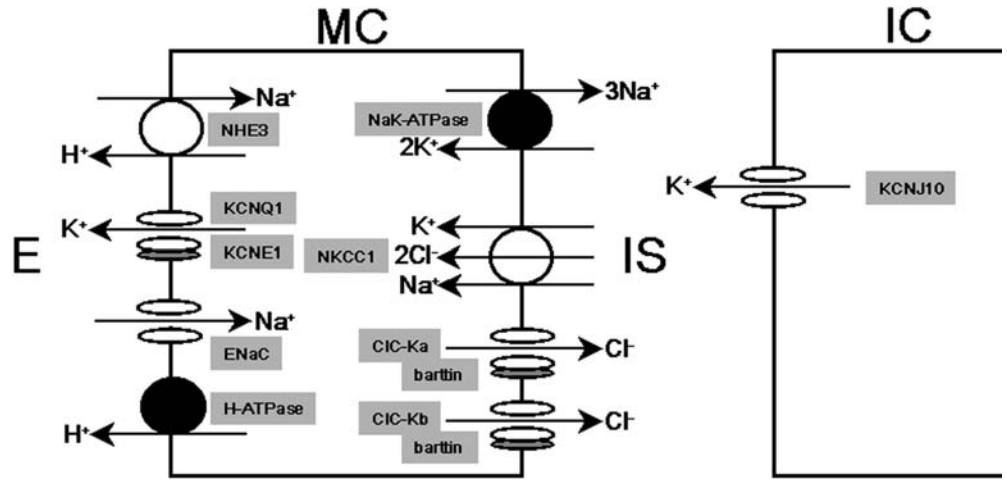[b] Protein in g/l
[c] Osmolarity in mosmol

The major function of the inner ear is the transformation of mechanical stimuli (sound, motion, and gravitational force) into electrical signals that enable the perception of sound and the vestibular sensation. For this conversion, which occurs in the sensory hair cells of the cochlea (Fig. 1) (i.e., the organ of Corti; Fig. 2A) and the vestibular system (Fig. 1), the availability of K$^+$ ions is essential.

The central lumen (scala media) of the membranous labyrinth is filled with endolymph (Fig. 1, black area), a K$^+$-rich/Na$^+$-poor, electrically positively charged fluid with a neutral pH (Table 1) [4]. The surrounding spaces (scala tympani, scala vestibuli) within the bony labyrinth are filled with perilymph (Fig. 1, white area; Table 1) [4]. The perilymph of scala vestibuli and scala tympani differs in origin. It is assumed that the origin of the scala ves-

tibuli perilymph is an ultrafiltrate from the capillary network in the inner ear. Tracer studies revealed that cerebrospinal fluid can account for 80% of the formation of the perilymph of the scala tympani via the cochlear aqueduct (Fig. 1). Perilymph rather than plasma should be considered as the precursor of the scala media endolymph. Homeostasis of the unique composition of the endolymph predominantly depends on secretion and/or absorption activities of specialized epithelial cells in the inner ear [5, 6].

It has become quite clear that in the inner ear the cochlear stria vascularis (Fig. 2A, B) plays an important role in endolymph homeostasis through large K$^+$ conductance capacities, which result in the generation of a positive transepithelial potential of cochlear endolymph (i.e., the

endocochlear potential) of +80 mV. The multilayered
stria vascularis is composed of three cell types: marginal
cells facing the endolymph, intermediate cells, and basal
cells adjacent to the fibrous spiral ligament (Fig. 2B) [7].

Tight junctions of marginal and basal cells separate
the endolymph from the perilymph-like fluid pervading
the spiral ligament. The marginal cells, secreting K^+ via
apical K^+ channels (KCNQ1/KCNE1 complex) into the
endolymph, take up K^+ basolaterally via distinct Na^+K^+-
ATPases ($\alpha1\beta2$ and $\alpha1\beta1$) and Na^+-K^+-$2Cl^-$ (NKCC1)
cotransporters [6, 8]. The localization of these and other
transporters/channels in the marginal and intermediate
cells are depicted in Fig. 3, which is a tentative but not
complete scheme. Future research is aimed at the com-
pletion of this scheme. The basolaterally extruded Na^+ by
the marginal cells provides the driving force for Na^+-K^+-
$2Cl^-$ cotransporters resulting in additional fluxes of K^+
into the cell. The Cl^- taken up is recycled back through
basolateral electroneutral chloride channels (ClC-Ka/
barttin and ClC-Kb/barttin) [9, 10]. Two sodium trans-
porters localized in the apical membrane of the marginal
cells, an amiloride-sensitive sodium channel (ENaC) and
a sodium hydrogen exchanger (NHE3), are involved in
the uptake of Na^+ from the endolymph [11, 12]. Fur-
thermore, an additional apical H^+-ATPase is involved in
the active secretion of H^+ [13]. The basal and interme-
diate cells are coupled via gap junctions. In the intrastrial
space between marginal and intermediate cells the po-
tential is +80 mV realized through specific K^+ channels
(KCNJ10) in the intermediate cell membrane [14]. The
marginal cell layer maintains a low K^+ concentration in
this space and apically secretes K^+ driven by a difference
in transmembrane potential between 0 and +10 mV. The
molecular mechanisms that generate the endocochlear
potential have recently been reviewed by Wangemann
[15].

K^+ flows from the endolymph through apical trans-
duction channels that are opened by movement of sensory
hair cells and leaves these cells via K^+ channels (e.g.,
KCNQ4). From the vicinity of the outer hair cells, K^+
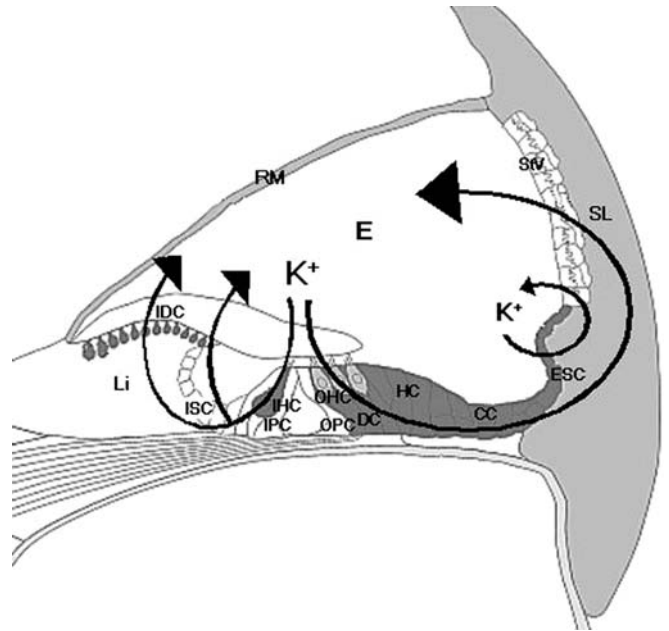diffuses back via gap junctions formed by connexins into

Fig. 4 Schematic representation of a cochlear turn with the most-
significant recycling pathways of K^+ ions illustrated by *arrows*.
Furthermore it depicts the organ of Corti composed of sensory inner
(*IHC*) and outer (*OHC*) hair cells and supporting cells [i.e., inner
(*IPC*) and outer pillar (*OPC*) cells, Deiters cells (*DC*), and Hensen
cells (*HC*)], Claudius cells (*CC*), external sulcus cells (*ESC*), in-
ternal sulcus cells (*ISC*), spiral limbus (*Li*), interdental cells (*IDC*),
Reissner's membrane (*RM*), and stria vascularis (*StV*) adjacent to
the fibrous spiral ligament (*SL*) (modified with permission of
Professor G. van Camp, University of Antwerp, Belgium)

the spiral ligament and further towards the stria vascularis
and is finally released into the endolymph. The most
significant recycling pathways of K^+ ions in the cochlea
are illustrated in Fig. 4. From the inner hair cells K^+ is
recycled back into the endolymph via internal sulcus cells
or via spiral limbus fibrocytes and interdental cells. In
addition external sulcus cells are also involved in the
recycling of K^+ [5, 6]. Knowledge of the components
involved in the pathways for K^+ recycling other than

Table 2 Defective transporters/channels in inner ear and/or kidney diseases

Protein	Gene	Disease
Barttin[a]	*BSND*	Deafness/Bartter type IV
Pendrin[a]	*SLC26A4*	Deafness/Pendred
H⁺-ATPase (B1, α4)[a]	*ATP6V1B1, ATP6V0A4*	Deafness/(distal) renal tubular acidosis
Transmembrane serine protease	*TMPRSS3*	Deafness
KCNQ1/KCNE1	*KCNQ1/KCNE1*	Deafness/Jervell and Lange-Nielsen
NKCC1	*Slc12a2*	Deafness/equilibrium disturbance
NBC3	*Slc4a7*	Deafness/blindness
NHE3	*Slc9a3*	(proximal) Renal tubular acidosis/diarrhea
Kcc4	*Slc12a7*	Deafness/(distal) renal tubular acidosis
AQP4	*Aqp4*	Deafness/urinary concentrating defect

[a] It is proven that impairment of these proteins leads to defective transporters/channels in both inner ear and renal tubules in humans
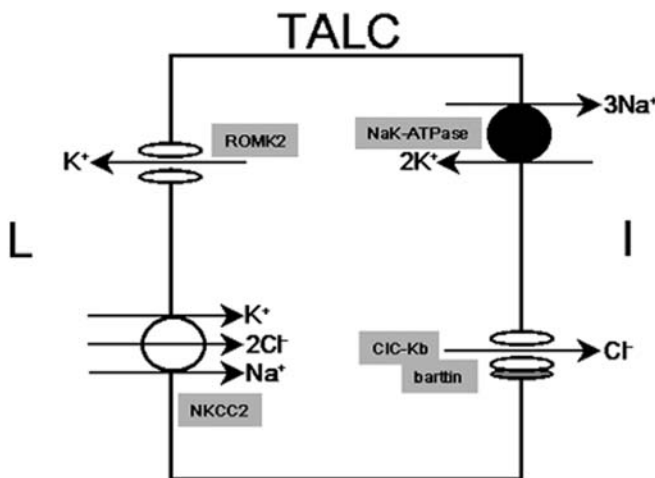

Fig. 5 Schematic localization of the transporters/channels in renal thick ascending limb cells (*TALC*) that can be affected in Bartter syndrome types I through IV, i.e., NKCC2 / type I, ROMK2 / type II, ClC-Kb / type III, and barttin / type IV (*I* interstitium, *L* luminal)

through the marginal cells is far from complete and needs to be pursued further.

Transport disorders

The composition of the endolymphatic fluid that bathes the sensory hair cells of Corti's organ (Fig. 2A) is strictly regulated to enable the transduction of sound into neural signals. Abnormalities in volume or composition of the endolymph will adversely affect hearing. Mutations in transporters or channels common to inner ear and/or kidney in humans and/or mouse models are presented in brief (Table 2).

Human disorders (with or without mouse counterparts)

Chloride channels in Bartter syndromes

Bartter syndrome is clinically characterized by salt wasting, hypokalemic alkalosis, hyperreninemia, hyperaldos-teronism with hyperplasia of the juxtaglomerular apparatus, and sensorineural hearing loss in some subtypes. Bartter syndrome types I through IV (autosomal recessive disorders), in which the thick ascending limb of Henle's loop is affected, result from mutations in genes encoding for different transporters/channels (schematically depicted in Fig. 5). Not only type K chloride channels (ClC-K, Bartter syndrome types III and IV) may be affected but also the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) and the ROMK2 potassium channel, causing Bartter syndrome type I and II, respectively. In contrast to ClC-K, the NKKC2 and ROMK2 are not detected in the cochlea. Functional ClC-K is composed of two subunits, i.e., barttin protein is associated with either human ClC-Ka or ClC-Kb (rodent orthologues ClC-K1 and ClC-K2, respectively). Enhanced expression of barttin (associated with either ClC-K1 or ClC-K2) studied in *Xenopus laevis* oocytes resulted in an increase in current amplitude, a difference in calcium sensitivity, and an enhanced ClC-K abundance in the cell membrane [16]. In the cochlea ClC-K1, ClC-K2 as well as barttin, is found in the basolateral membrane of marginal cells (Fig. 3) [10]. Mutations in the gene encoding the protein barttin (*BSND*) affect both chloride channels (ClC-Ka/barttin and ClC-Kb/barttin), causing the sensorineural hearing loss observed in Bartter syndrome type IV, while a defect in ClC-Kb alone (Bartter syndrome type III) does not cause deafness as ClC-Ka is still functioning. Knock-out of ClC-K1 (*Clcnk1⁻/⁻*), which is present in the thin ascending limb of Henle, leads to nephrogenic diabetes insipidus in mice [17]. In the absence of this chloride channel, a lower osmolality is observed in the inner medulla of mice, although no defect in humans has been observed yet. A remarkable digenic defect has recently been described by Schlingmann et al. [18]. They determined mutations in the genes encoding ClC-Ka (*CLCNKA*) as well as ClC-Kb (*CLCNKB*) within one patient. This patient displayed similar clinical symptoms to those seen in Bartter syndrome type IV.

Chloride-bicarbonate exchangers in Pendred syndrome

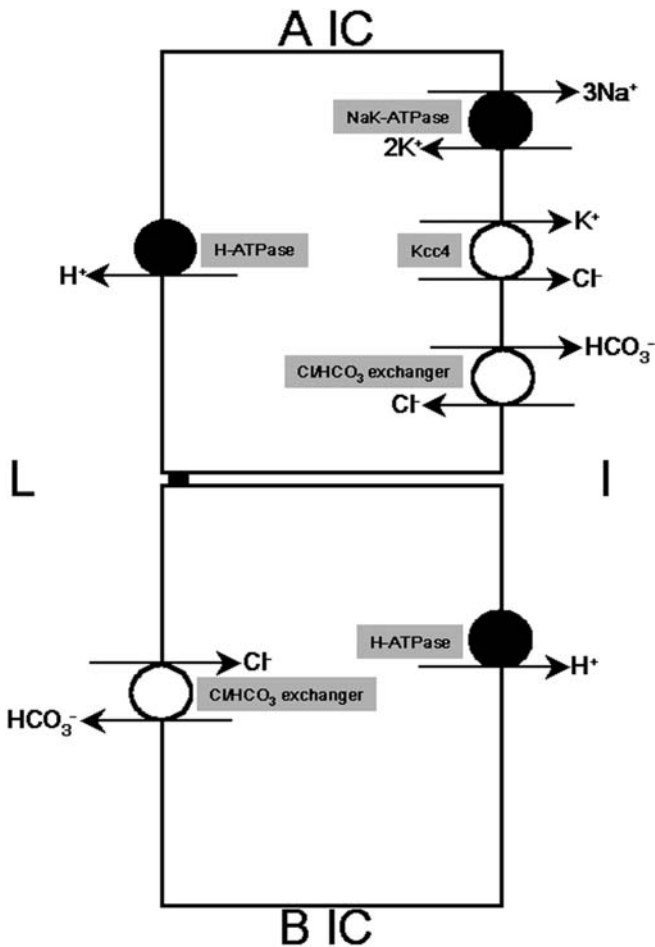Pendred syndrome, in which a mutation affects the pendrin gene *SLC26A4 (PDS)*, is an autosomal recessive

Fig. 6 Schematic localization of the transporters involved in acid/base homeostasis in renal A (*A IC*) and B (*B IC*) intercalated cells

disorder characterized by goiter and sensorineural deafness. The pendrin gene has a relatively restricted pattern of expression in the kidney, thyroid, and inner ear. In the kidney pendrin functions as an apically located Cl^-/HCO_3^- exchanger present in the type B intercalated cells of the distal nephron. In these cells H^+ is secreted into the interstitium, while HCO_3^- exits across the apical membrane into the lumen (Fig. 6) [19]. However, patients with Pendred syndrome do not display metabolic alkalosis [20]. In distinct thyroid follicular cells, pendrin is localized in the apical membrane where it functions as a Cl^-/I^- exchanger. In patients with Pendred syndrome impairment of this exchanger leads to a disturbed iodide organification as determined by a positive perchlorate discharge test [21]. In the inner ear pendrin gene expression is detected in distinct areas that are putatively critical in the regulation of endolymphatic fluid composition such as cochlear external sulcus cells (Fig. 2A), vestibular transitional cells, and endolymphatic sac cells (Fig. 1) [22]. Examination of the embryogenesis of pendrin knock-out mice (*Pds$^{-/-}$*) suggests a disturbance in endolymph resorption, resulting in an increased endolymphatic fluid volume at a critical developmental stage [23]. However,

the exact role of pendrin in the inner ear remains to be defined.

Proton pumps in renal tubular acidosis and sensorineural hearing loss

Renal tubular acidosis is a clinical syndrome in which an inherited renal tubular defect leads to a failure in secretion of H^+ and maintenance of a normal plasma HCO_3^- concentration (metabolic acidosis). The proton pump H^+-ATPase consists of two functional domains: the membrane-spanning V0 domain responsible for proton translocation and the V1 domain, composed of a hexamer of three A-subunits and three B-subunits and at least six other different subunits, functioning in ATP hydrolysis. Apically located renal proton pumps display tissue-specific isoforms, i.e., B1 of the V1 domain and α4 of the V0 domain. The genes encoding B1 (*ATP6V1B1*) and α4 (*ATP6V0A4*) are affected in the autosomal recessive form of distal renal tubular acidosis, which is characterized by a disturbance in the function of H^+-ATPase present at the apical surface of type A intercalated cells of the distal nephron [24, 25]. In these cells luminal H^+ secretion is linked to basolateral exchange of Cl^- and HCO_3^- (Fig. 6). Patients with a B1 mutation display sensorineural hearing loss with childhood onset in addition to distal renal tubular acidosis. During longer follow-up, it has become evident that mild and/or later-onset hearing loss can also be present in some patients with the α4 mutation [26]. In the cochlea the strongest immunoreactivity for H^+-ATPase is detected in the apical membrane and cytoplasm of marginal cells (Fig. 3). Apical staining is also observed in cochlear interdental cells (Fig. 2A) and endolymphatic sac cells (Fig. 1) [13, 25]. In the normal inner ear cochlear endolymph pH is maintained at 7.4, while in the endolymphatic sac it is 6.6. A fine regulation of the cochlear endolymph pH is apparently a prerequisite for adequate hearing. Remarkably mice lacking the B1-subunit of H^+-ATPase (*Atp6b1$^{-/-}$*) display a normal hearing [27].

Sodium channels

Mutations in transmembrane serine protease (TMPRSS3), an activator of the epithelial sodium channel (ENaC), are observed in both familial and sporadic cases of autosomal recessive sensorineural deafness, i.e., DFNB8/10 [28, 29]. Studies in *Xenopus laevis* oocytes demonstrated that, after auto-catalytic processing, TMPRSS3 activates ENaC. In the cochlea ENaC is located apically in the marginal cells (Fig. 3) and plays a role in maintaining a low Na^+ concentration in the endolymph [11]. Mutations in the α, β, and γ subunits of ENaCs are found in patients with autosomal recessive pseudo-hypoaldosteronism type I [28]. This disease is characterized by tubular unresponsiveness to the action of aldosterone as manifested by salt-wasting and hyperkalemia. Studies of subtle hearing loss in this patient population are currently underway.

Potassium channels in Jervell and Lange-Nielsen syndrome

Long QT syndrome is a disorder with ventricular repolarization and a prolonged QT interval. This may result in syncope, seizures, and sudden death due to cardiac arrhythmias. The autosomal recessive form is the Jervell and Lange-Nielsen syndrome (JLNS), which is associated with profound bilateral sensorineural deafness [30]. Knock-out mice for KCNQ1 or KCNE1 encompass mouse models for JLNS ($Kcnq1^{-/-}$ and $Kcne1^{-/-}$) [31, 32]. Mutation in either gene is associated with JLNS in humans [33]. KCNE1 is essential for KCNQ1 membrane targeting and/or stability of KCNQ1 in the membrane. KCNE1 co-assembles with KCNQ1 and both are localized in the apical membrane of cochlear marginal cells (Fig. 3) and vestibular dark cells, realizing K^+ secretion into the endolymph [6]. In KCNE1 knock-out mice the proximal tubular function is disturbed, since the KCNQ1/KCNE1 complex is a luminal K^+ channel in proximal tubular cells, which generates the driving force for electrogenic Na^+ and substrate (glucose) reabsorption [32]. No information is yet available about the function of the proximal tubule in JLNS in humans.

Mouse models (without human counterparts)

Sodium-potassium-chloride cotransporters

The secretory Na^+-K^+-$2Cl^-$ cotransporter (isoform NKCC1) is localized in the basolateral membrane of cochlear marginal cells (Fig. 3) and is involved in the influx of Na^+, K^+, and Cl^- [6]. The other absorptive isoform NKKC2 is exclusively expressed in the kidney in the thick ascending limb of Henle (Fig. 5; affected in Bartter syndrome type I). Both isoforms display a difference in transcript size and share a relatively low overall amino acid homology and are products of different genes [34]. The absence of NKCC1 in knock-out mice ($Slc12a2^{-/-}$) results in a drastic decrease in secretion of K^+ into the endolymph and the collapse of the cochlear Reissner's membrane. The supply of Na^+ (effluxed by Na^+K^+-ATPase of the marginal cells; Fig. 3) is interrupted, consequently limiting the uptake of K^+. Both hearing and balance are affected in these mice [35]. In humans reversible hearing loss is observed after administration of high doses of furosemide, which inhibits NKKC1, temporarily disrupting the endocochlear potential [36]. Although NKCC1 is present in the basolateral membrane of the outer medullary collecting duct cells in the rat, its physiological role remains to be determined [37].

Sodium-bicarbonate cotransporters

The Na^+-HCO_3^- cotransporter NBC3 plays an important role in cochlear spiral ligament fibrocyte sodium bicarbonate transport, and subsequently preserves the function of the sensory inner and outer hair cells of Corti's organ (Fig. 2A) [38]. In the kidney NBC3 is localized in the collecting duct where it may modulate the activity of H^+-ATPase [39]. However, loss of NBC3 in knock-out mice ($Slc4a7^{-/-}$) causes hearing loss and blindness only due to the degeneration of sensory receptors. This indicates that the loss of NBC3 in the inner ear and eye cannot be compensated by other mechanisms in contrast to the kidney [38].

Sodium-hydrogen exchangers

Expression of the Na^+/H^+ exchanger type 3 (NHE3) in the cochlea is limited to the apical surface of marginal cells (Fig. 3) [12]. Impaired renal acid/base balance and disturbed Na^+ fluid volume homeostasis is observed in NHE3 knock-out mice ($Slc9a3^{-/-}$) [40]. It remains to be established whether this is associated with hearing problems.

Potassium-chloride cotransporters

K^+-Cl^- cotransporter Kcc4 in the cochlea is restricted to the supporting cells (Deiters cells) of the sensory outer hair cells of Corti's organ and plays a role in siphoning K^+, after its exit from these cells (Fig. 2A). Knock-out mice for Kcc4 ($Slc12a7^{-/-}$) display impaired hearing and distal renal tubular acidosis. The distal renal tubular acidosis is supposed to be due to an impairment of Cl^- recycling across the basolateral membrane of type A intercalated cells of the distal nephron (Fig. 6). The hearing loss may be a result of the disturbed K^+ integrity around the outer hair cells [41].

Water channels

Impaired hearing and a mild urinary concentrating defect is observed in knock-out mice lacking aquaporin 4 water channels ($Aqp4^{-/-}$). Aquaporin 4 is responsible for a substantial amount of the basolateral water movement in the inner medulla of the kidney. In the cochlea aquaporin 4 is expressed in the inner sulcus cells, supporting cells (Hensen cells) of the organ of Corti and in Claudius cells (Fig. 2A). It is assumed that aquaporin 4 facilitates rapid osmotic equilibration in cochlear cell types that are subject to large K^+ fluxes during signal transduction [42].

Miscellaneous

Mitochondrial diseases

Special attention should be given to the analysis of mitochondrial DNA because progressive hearing loss is frequently observed in patients with mitochondrial disease [43]. In the inner ear mitochondrial ATP production

is required for the active secretion of H^+ and K^+. The progressive nature of this hearing loss can probably be explained by heteroplasmy. When both normal and mutant mitochondrial DNA is present in mother cells, some daughter cells may drift towards more mutant DNA. The most common renal manifestations of mitochondrial disorders are Fanconi syndrome, focal glomerular sclerosis, and progressive tubulointerstitial nephropathy. Thus, these clinical manifestations in combination with hearing loss necessitate mitochondrial DNA screening.

Calcium/magnesium transporters/channels

Regulation of Ca^{2+} and Mg^{2+} transport in the endolymph is still an open area; the cochlear endolymph concentrations are extremely low with Ca^{2+} being 0.02 and Mg^{2+} 0.01 mmol/l (Table 1). However, calcium is required for an adequate functioning of sensory hair cells. A mutation in the gene encoding Ca^{2+}-ATPase, localized in the sensory hair cells, causes deafness and vestibular/motor disturbances in mice [44].

Water channels

Another interesting observation that needs to be further investigated is the extensive expression of aquaporin 2 in the epithelial lining of the cochlear Reissner's membrane [45] in relation to the difference in osmolarity between scala media endolymph and scala vestibuli perilymph (Table 1) [46]. Children with a defective aquaporin 2 system (nephrogenic diabetes insipidus) apparently display normal hearing.

Future perspectives

It is expected that the genetic basis for most if not all hereditary disorders causing hearing loss will eventually be known. Gene expression profiles through cDNA microarray analysis of inner ear tissues are a new promising tool [47, 48]. This will allow better genetic counseling.

Is there a prospective treatment of hereditary disorders causing hearing loss? In tubular transport disorders of the kidney, a defect in one segment of the tubule may sometimes be compensated by altered activity in other segments of the tubule. For example, amiloride treatment in Bartter syndrome type I, with a defect in the thick ascending limb of the loop of Henle, can considerably decrease the K^+ loss in the distal tubule and collecting duct. Elucidation of compensatory transport mechanisms in the inner ear (in particular in the endolymphatic sac [49, 50, 51]) may offer some new perspectives. The inner ear is also an attractive target for gene therapy, because the transgenes may be delivered locally [52, 53].

Synergy of research combining otological and nephrological expertise is a promising area. Within inner ear research it is expected that the increase in knowledge of electrolyte transport mechanisms and water movements will provide a more complete overview of the structures and processes involved in endolymph homeostasis, which may ultimately lead to the development of new preventive and therapeutic strategies for hereditary disorders causing hearing loss.

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