Kidney-Ear Axis

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Key words: kidney, ear, claudins, tight junction, toxicity

IMAJ 2007;9:814–818

There is an intriguing connection between renal diseases and hearing disorders. The incidence of sensorineural hearing loss among patients with chronic renal failure is considerably higher than in the general population. The incidence is about 46–77% according to different studies, ranging from mild to severe hearing loss [1,2]. The etiology of this phenomenon is not fully known. The present review summarizes new developments in the understanding of the mechanisms underlying the link between hearing loss and renal disorders.

Claudins (tight junction proteins)

For cells to become functional they need good and efficient interactions with their neighboring cells. These interactions could be achieved by means of solutes passing through these cells, known as the trans-cellular pathway, or passing between cells, which would then be called the para-cellular pathway. For the latter pathway to work efficiently, these cells need potent tight junctions. Tight junctions are one mode of cell-cell adhesion in epithelial and endothelial cellular sheets. They have three principal functions: they are responsible for regulation of the para-cellular pathway, maintaining cell polarity, and a platform for trafficking and signaling protein complexes [3-5].

It was recently shown that tight junctions play an important role in other processes, including cell division and differentiation, wound healing, immune reactions, medications transport, and cancer [6-9].

Claudins are tight junction proteins that play an important role in the para-cellular transport of ions. The claudin super-family consists of at least 24 homologous proteins in humans. These proteins have both structural and functional roles in tight junctions. Both claudins and occludins are principal tight junctional constituents that have similar topologies with four alpha-helical trans-membrane segments, and all exhibit well-conserved extracytoplasmic cysteines that either are known to, or can potentially form, disulfide bridges [10]. Claudins are located in both epithelial and endothelial cells in all tight junction-bearing tissues. In addition to claudins, occludins and ZO proteins, several other proteins can be found associated with tight junctions. Treatment of an epithelium with the protease trypsin destroys the tight junctions, supporting the notion that proteins are essential structural components of these junctions. Each tight junction sealing strand is composed of a long row of trans-membrane adhesion proteins embedded in each of the two interacting plasma membranes. The extracellular domains of these proteins join directly to one another to occlude the intercellular space [Figure 1].

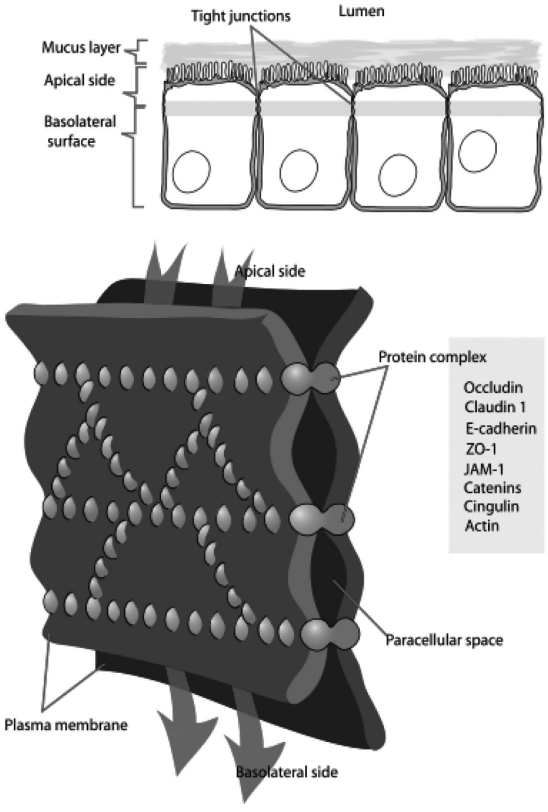

Figure 1. Current model of a tight junction. This drawing shows how the sealing strands hold adjacent plasma membranes together. The strands are composed of transmembrane protein complexes that make contact across the intercellular space and create a seal.

Defects in claudins are causatively associated with a variety

of human diseases, demonstrating that claudins play important roles in human physiology [Table 1]. In conditions where the cell adhesion function contributed by tight junctions is essential, as in altered para-cellular transport, in proliferative diseases and during morphogenesis, the claudin superfamily of homologous proteins provides the molecular basis for the uniqueness of tight junctions and emerges as a new target for intervention [11]. Several claudins are found in kidney epithelial cells in the nephron [Figure 2]. For example, claudin-16 is required for Mg2+ to be reabsorbed from the urine into the blood. A mutation in the gene encoding this claudin results in excessive loss of Mg2+ in the urine [Table 1]. In the inner ear, tight junctions are directly involved in maintaining the electrochemical potential gradient between the endolymph and perilymph.

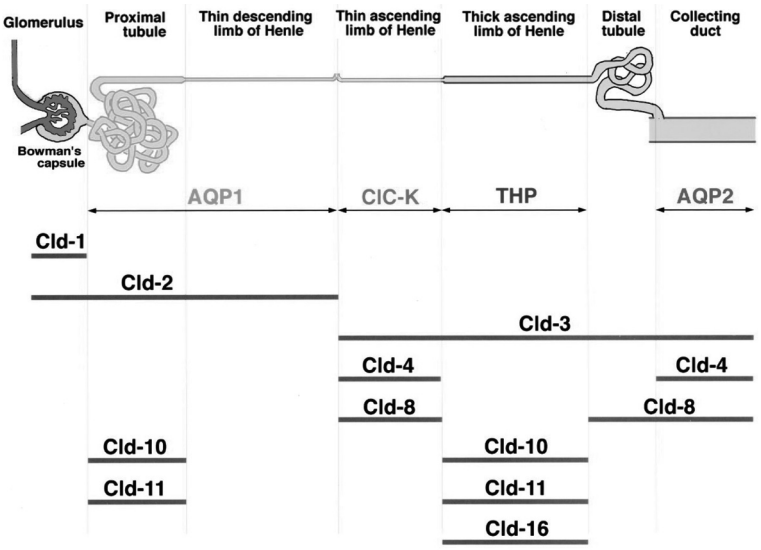

Figure 2. Expression of the different claudins along the nephron segments

Kidney-ear syndromes

Congenital ear and renal anomalies may occur as isolated malformations or one of several syndromes described in the literature. Clinical diagnosis is often difficult due to the broad clinical spectrum and overlap with other syndromes. Here we will discuss most known syndromes among them.

There is an intriguing connection between renal anomalies and deafness. For example, deletion of ATP6B, of pendrin, and of Kcc4, the K-Cl co-transporter present in intercalated cells, can cause deafness. One of the supporting cells of the sensory epithelium in the vestibular epithelium has many similarities to the intercalated cell, and it serves to control the acidic pH of the endolymph. Remarkably, deletion of Foxi1 depletes the epithelium of these cells, causing deafness [12].

Alport syndrome

Named after Dr. Cecil A. Alport in 1927, this is an inherited disorder of the basement membranes of the kidney, eye and ear. People who inherit defective genes for the "collagen" proteins in these basement membranes may develop progressive loss of renal function, deafness and abnormalities of the eye. It is characterized by hematuria (may be detectable by 1 year of age in about 15% of cases, and by 6 years of age in about 70% of cases), proteinuria, chronic progressive glomerulonephritis with gradual progression to end-stage renal disease, inner ear disorders (sensorineural hearing loss), and can also affect the eye (anterior lenticonus, posterior subcapsular cataract, posterior polymorphous dystrophy and retinal flecks).

Alport syndrome is caused by mutations in *COL4A3, COL4A4,* and *COL4A5,* collagen biosynthesis genes. Mutations in any of these genes prevent the proper production or assembly of the type IV collagen network, which is an important structural component of basement membranes in the kidney, inner ear, and eye. It is inherited by both X-linked and autosomal recessive patterns. About 85% of Alport syndrome cases have the classical X-linked pattern of inheritance [13].

Table 1. Genetic diseases of tight junction proteins

Gene	Disease	Pathology/Mechanism
Cldn-1	Ichthyosis and sclerosing cholangeitis	Affects skin and bile ducts
Cldn-14	Non-syndromic deafness. *DFNB29*	Cochlear hair cell degeneration
Cldn-16		
Human	HHNC	Defective renal Mg^{2+} reabsorption
Bovine	Interstitial nephritis	
PMP22	Peripheral polyneuropathies	Demyelination
	HNPP	Gene deletion
	Charcot-Marie-Tooth type 1A	Gene duplication
	Dejerine-Sottas syndrome	Mutations
ZO-2	Familial hypercholanemia	Defective PDZ-claudin binding

HHNC = hypomagnesemia hypercalciuria with nephrccalcinosis, HNPP = hereditary neuropathy with liability to pressure palsies.

Branchio-otorenal syndrome

BOR syndrome is an autosomal dominant disorder characterized by sensorineural, conductive or mixed hearing loss, structural defects of the outer, middle and inner ear, branchial fistulas or cysts, and renal abnormalities ranging from mild hypoplasia to complete absence. Reduced penetrance and variable expressivity has been observed. BOR syndrome results from mutations in the *EYA1* gene on chromosome 8 [14].

Townes-Brocks syndrome

First described in 1972 by Townes and Brocks, this syndrome is an autosomal dominant disorder. It is characterized by external ear anomalies (microtia or large ears, satyr ear, lop ear, pre-auricular tabs or pits, thickened superior helix, external auditory atresia), sensorineural hearing loss, pre-axial polydactyly and triphalangeal thumbs, imperforate anus, and renal and urogenital

BOR = bronchio-otoretinal

malformations (hypoplastic kidney, ureterovesical reflux, posterior urethral valve, meatal stenosis, hypospadias, bifid scrotum and rectovaginal fistula). The term REAR syndrome (renal-ear-anal-radial) has also been used to describe this condition. Intelligence is usually normal, although mild to moderate mental retardation has been reported. The gene for Townes-Brocks syndrome was mapped to 16q12.1 [15].

The kidney-ear axis has been poorly investigated and the etiology of this phenomenon is not fully known

Pendred syndrome

The syndrome is named after Dr. Vaughan Pendred (1869-1946), the English general practitioner who first described the syndrome in 1896. It is inherited as an autosomal recessive condition that consists of severe to profound bilateral congenital sensorineural deafness, abnormality of the bony labyrinth in the inner ear, and defective incorporation of iodine into thyroid hormone, resulting in goiter (enlargement of the thyroid gland). Pendred syndrome is the result of a defect in the production of the thyroid hormone. The systems affected are the inner ear (deafness at birth, defect in vestibular function, and malformation of the cochlea); hormonal (normal blood level of thyroid hormones due to compensated hypothyroidism); neck (swelling in the front of the neck due to goiter); intelligence (mental retardation due to the congenital thyroid defect); and cancer risk (possible increased risk of thyroid carcinoma).

Mutations in the solute carrier family 26, member 4 (*SLC26A4*) gene (also referred to as the *PDS* gene) cause Pendred syndrome [16]. The gene is located on the long arm of chromosome 7 (7q31). Mutations in the same gene also cause enlarged vestibular aqueduct syndrome, another congenital cause of deafness. The fact that SLC26A4 mutations are identified in only 50% of probands from multiplex families (i.e., more than one affected child) suspected on clinical findings of having Pendred syndrome/*DFNB4* suggests genetic heterogeneity for the condition. To date, no other genes or loci have been identified. The *SLC26A4* gene encodes a 780 amino acid protein called pendrin. This protein belongs to a superfamily of Cl-/anion exchangers and is expressed in the inner ear, the thyroid gland and the kidney. This protein transports negatively charged particles, particularly chloride and iodide, into and out of cells. Although the exact function of pendrin is not fully understood, it is important for the normal functions of the inner ear, thyroid and kidney. Recently pendrin was localized to the apical side of non-type A intercalated cells of the cortical collecting duct, and reduced bicarbonate secretion was demonstrated in a pendrin knockout mouse model. Mutations in the *SLC26A4* gene alter the structure or function of pendrin, which disrupts the transport of negatively charged particles.

Impaired pendrin activity in the thyroid and inner ear is responsible for the characteristic signs and symptoms of Pendred syndrome. Pendred syndrome accounts for as much as 10% of hereditary deafness. Approximately 75% of individuals with Pendred syndrome will develop a goiter in their lifetime. About 40% of individuals with Pendred syndrome will show some vestibular weakness when their balance system is tested.

Nephro- and ototoxicity

A number of drugs have been associated with nephro- and ototoxicity. The best known are listed in Table 2. Of these many drugs some are both nephrotoxic and ototoxic. There appears to be a hereditary predisposition to ototoxic reactions. Various medications may cause nephrotoxicity. The nephrotoxic effect of most drugs is more profound in patients who already have renal impairment. We will discuss here some of the drugs that are both nephro- and ototoxic.

Furosemide

Like other loop diuretics, furosemide acts by inhibiting the thick ascending loop of Henle apical Na-K-2Cl co-transporter, NKCC2. It causes profound natriuresis and calciuresis [17]. The Na-K-2Cl co-transport system also exists in the marginal and dark cells of the stria vascularis, which are responsible for endolymph

Table 2. List of nephro- and ototoxic drugs.

Drug	Nephrotoxicity	Ototoxicity	Both
Furosemide	+	+	+
Cisplatin	+	+	+
Aminoglycoside antibiotics (e.g., gentamicin)	+	+	+
NSAIDs (e.g., aspirin, ibuprofen, diclofenac)	+	+	+
Erythromycin	+	+	+
Nicotine	-	+	–
Beta-blockers	+	–	–
Angiotensin-converting enzyme inhibitors	+	–	–
Ciclosporin	+	–	–
Amphotericin B	+	–	–
Radiocontrast media	+	–	–
Lithium salts	+	–	–
Cyclophosphamide	+	–	–
Sulphonamides	+	–	–
Methotrexate	+	–	–
Aciclovir	+	–	–
Polyethylene glycol	+	–	–
Beta-lactam antibiotics	+	–	–
Vancomycin	+	–	–
Rifampicin	+	–	–
Ciprofloxacin	+	–	–
Ranitidine	+	–	–
Cimetidine	+	–	–
Thiazides	+	–	–
Phenytoin	+	–	–
Fluoride	+	–	–
Demeclocycline	+	–	–
Foscarnet	+	–	–

secretion. Furosemide also has inhibitory activity on carbonic anhydrase. Used in the treatment of congestive heart failure and edema (associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndrome and hypertension). It is also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration. Although disputed, it is considered ototoxic usually with large parenteral doses and rapid administration and in renal impairment [18].

There seems to be a close connection between renal diseases and hearing disorders. This link might be explained by the presence of several proteins in both renal and ear tissues. Therefore, it is tempting to assume that genetic or acquired defects in these proteins concomitantly impair the function of both organs.

Cisplatin

Cis-dichlorodiaminoplatin (also known as CDDP) is a platinum-based chemotherapy drug used to treat various types of cancers, including sarcomas, some carcinomas (e.g., small cell lung cancer and ovarian cancer), lymphomas and germ cell tumors. It was the first member of its class, which now also includes carboplatin and oxaliplatin. Its use in these and other types of tumors is narrowed by onset of chemoresistance and severe undesired side effects, such as nephrotoxicity and ototoxicity, whose mechanisms of action are only partially understood. The dose of cisplatin must be reduced when the patient's creatinine clearance is reduced. Adequate hydration and diuresis is used to prevent renal damage. The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species and in animal models can be ameliorated by free-radical scavenging agents. This is a dose-limiting toxicity. Unfortunately, there is at present no effective treatment to prevent ototoxicity, which may be severe. Audiometric analysis may be necessary to assess the severity of the damage. The ototoxicity of cisplatin may be related to its ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species. Previati et al. [19] investigated the effects of cisplatin on a cell line (OC-k3) developed from organs of Corti of transgenic mice. They observed at 48 hours that cell death due to cisplatin was time and concentration dependent. The cell death displayed some morphological hallmarks of apoptosis, including nuclear fragmentation into several large nuclear fragments, surrounded by a rearranged and thickened actin cytoskeleton. No DNA laddering was detected, suggesting absence of endonuclease activity, or annexin V positivity, suggesting absence of phosphatidylserine externalization.

Aminoglycoside antibiotics

For aminoglycosides, the renal proximal tubule cell is susceptible due to high concentration achieved and slow clearance with direct effects on phosphoinositide binding and mitochondrial bioenergetics. Pathogenesis appears to involve iron-induced free-radical formation, since iron chelators prevent nephrotoxicity. Analogous effects of aminoglycosides on the inner and outer hair cells have been observed [20]. The ototoxicity of aminoglycosides, like in cisplatin, may be related to their ability to bind to melanin in the stria vascularis of the inner ear or the generation of reactive oxygen species.

Erythromycin

Erythromycin and some other macrolide antibiotics can induce temporary deafness, which resolves upon withdrawal of the drug. Erythromycin is known to exacerbate cyclosporine nephrotoxicity. This has been attributed to the potential of erythromycin to reduce the hepatic microsomal metabolism and clearance of cyclosporine. The decline in renal function observed in patients co-administered these drugs may be due in part to additive renovascular toxicity. Yet, it was shown that erythromycin alone may cause nephrotoxicity [21].

Conclusions

It seems that there is a close connection between renal diseases and hearing disorders. This link might be explained by the fact that several proteins exist in both renal and ear tissues. Therefore, it is tempting to assume that genetic or acquired defects in these proteins concomitantly impair the function of both organs.

Although we have summarized both established and newly described mechanisms underlying the pathology of kidney-ear disorders and syndromes, it seems that the nature of the kidney-ear axis is far from being understood and still needs further investigation. Today, a variety of new genetic techniques are available and might be of great benefit in mapping novel genes expressed exclusively in both tissues, and when mutated cause kidney-ear disorders. The data presented here suggest the importance of the clinical and basic evaluation of syndromes sharing both kidney and ear disorders due to genetic or pharmacological etiologies.

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