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Hearing Research 165 (2002) 1–9

HEARING RESEARCH

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Review Article

K^+ cycling and the endocochlear potential

Philine Wangemann *

Cell Physiology Laboratory, Anatomy and Physiology Department, Kansas State University, 1600 Denison Avenue, Manhattan, KS 66506, USA

Received 9 July 2001; accepted 13 November 2001

Abstract

Sensory transduction in the cochlea and the vestibular labyrinth depends on the cycling of K^+. In the cochlea, endolymphatic K^+ flows into the sensory hair cells via the apical transduction channel and is released from the hair cells into perilymph via basolateral K^+ channels including KCNQ4. K^+ may be taken up by fibrocytes in the spiral ligament and transported from cell to cell via gap junctions into strial intermediate cells. Gap junctions may include GJB2, GJB3 and GJB6. K^+ is released from the intermediate cells into the intrastrial space via the KCNJ10 K^+ channel that generates the endocochlear potential. From the intrastrial space, K^+ is taken up across the basolateral membrane of strial marginal cells via the $Na^+/2Cl^-/K^+$ cotransporter SLC12A2 and the Na^+/K^+-ATPase ATP1A1/ATP1B2. Strial marginal cells secrete K^+ across the apical membrane into endolymph via the K^+ channel KCNQ1/KCNE1, which concludes the cochlear cycle. A similar K^+ cycle exists in the vestibular labyrinth. Endolymphatic K^+ flows into the sensory hair cells via the apical transduction channel and is released from the hair cells via basolateral K^+ channels including KCNQ4. Fibrocytes connected by gap junctions including GJB2 may be involved in delivering K^+ to vestibular dark cells. Extracellular K^+ is taken up into vestibular dark cells via SLC12A2 and ATP1A1/ATP1B2 and released into endolymph via KCNQ1/KCNE1, which concludes the vestibular cycle. The importance of K^+ cycling is underscored by the fact that mutations of KCNQ1, KCNE1, KCNQ4, GJB2, GJB3 and GJB6 lead to deafness in humans and that null mutations of KCNQ1, KCNE1, KCNJ10 and SLC12A2 lead to deafness in mouse models. © 2002 Elsevier Science B.V. All rights reserved.

Key words: KCNQ1; KCNE1; KCNJ10; Cochlea; Vestibular labyrinth

1. Introduction

The sensory hair cells of the cochlea and the vestibular labyrinth are part of a heterogeneous epithelium that encloses endolymph. Endolymph is an unusual extracellular fluid in that the major salt is KCl rather than NaCl. The presence of K^+ in endolymph is of great importance since K^+ provides the major charge carrier for the sensory transduction. The choice of K^+ as charge carrier over, for example, Na^+ has major advantages. An influx of K^+ ions into the sensory cells causes the least change in the cytosolic concentration compared to any other ion. This is because K^+ is by far the most abundant ion in the cytosol. Further, influx and extrusion of K^+ are energetically inexpensive for the sensory cell since both occur down an electrochemical gradient. Contributing to this electrochemical gradient is the membrane potential of the sensory cells that is mainly determined by K^+ selective channels in the basolateral membrane and by the mechanically gated K^+ permeable transduction channels in the stereocilia of the apical membrane.

The first step in the transduction of the mechanical stimuli into an electrical signal consists of a change in the conductivity of the mechanically gated ion channel (Dallos, 1996). Opening of this channel causes a depolarization of the membrane potential. This depolarization leads to the opening of voltage-gated Ca^{2+} permeable channels, an influx of Ca^{2+} and the release of neurotransmitter from the basal pole of the hair cell. Among the basolateral channels of hair cells are

* Tel.: +1 (785) 532-4863; Fax: +1 (785) 532-4557.
E-mail address: wange@vet.ksu.edu (P. Wangemann).

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PII: S0378-5955(02)00279-4

KCNQ4[1], KCNN2 (SK2 or small Ca^{2+} activated K^+ channels) and KCNMA1 (slo, BK or large conductance Ca^{2+}-activated) K^+ channels (Kros, 1996). The importance of KCNQ4 in humans is underlined by the finding that mutations of KCNQ4 cause an autosomal dominant form of progressive sensorineural hearing loss (Kubisch et al., 1999).

Stimulation of sensory transduction in the cochlea has been shown to result in an increased flux of K^+ from endolymph through the hair cells into perilymph (Johnstone et al., 1989). From perilymph K^+ is taken up and secreted back into endolymph. Thus, K^+ is cycling within the cochlea (Konishi et al., 1978; Salt and Ohyama, 1993; Sterkers et al., 1982). K^+ cycling, however, is not limited to the current loop through the sensory cells (Fig. 1). Part of the current that is generated by stria vascularis is carried through outer sulcus cells (Chiba and Marcus, 2000; Marcus and Chiba, 1999) and through Reissner's membrane (Konishi et al., 1978; Salt and Ohyama, 1993; Zidanic and Brownell, 1990).

Measurements of current loops suggested that K^+ released from the hair cells flows through scala tympani perilymph before it enters the spiral ligament (Zidanic and Brownell, 1990). In the spiral ligament, K^+ may be taken up by type 2 fibrocytes containing the Na^+/K^+-ATPase and the Na^+2Cl^-/K^+ cotransporter SLC12A2 (Crouch et al., 1997; Spicer and Schulte, 1996). These fibrocytes form a gap junction system involving GJB2 (connexin 26), GJB3 (connexin 31) and GJB6 (connexin 30) that includes strial basal and intermediate cells (Kikuchi et al., 1995; Xia et al., 1999, 2000, 2001). Interestingly, mutations of GJB2, GJB3 and GJB6 are associated with deafness (Grifa et al., 1999; Kelsell et al., 1997; Xia et al., 1998). K^+ is thought to enter stria vascularis via this gap junction system and to be released by intermediate cells into the intrastrial space from where it is taken up by strial marginal cells and secreted back into endolymph. Although the pathway of K^+ through stria vascularis and through the hair cells is well established, the path from the hair cells toward stria vascularis lacks definitive experimental evidence. Flux and current measurements support the concept that K^+ enters perilymph and flows through perilymph toward spiral ligament (Salt and Ohyama, 1993; Zidanic and Brownell, 1990). This concept is challenged by the hypothesis that K^+ released from the hair cells is taken up by adjacent supporting cells and flows from cell to cell via a gap junction system toward the spiral ligament thereby never entering the perilymph (Spicer and Schulte, 1996). Studies using mutant mice that lack GJB2 gap junctions between the supporting cells of the organ of Corti are under way and likely to yield interesting data.

K^+ cycling in the vestibular labyrinth bears many similarities to the cycling in the cochlea. Endolymphatic K^+ flows into the sensory hair cells via the apical transduction channel and is released from the hair cells via basolateral K^+ channels including KCNQ4. Stimulation of sensory transduction results in an increased flux of K^+ from endolymph through the hair cells into perilymph (Valli et al., 1990). Fibrocytes connected by gap junctions including GJB2 may be involved in delivering K^+ to the vestibular dark cells. Vestibular dark cells secrete K^+ back into endolymph using cellular mechanisms similar to those in strial marginal cells (Wangemann, 1995). Accordingly, vestibular dark cells take up K^+ via SLC12A2 and ATP1A1/ATP1B2 in their basolateral membrane and release K^+ into endolymph via KCNQ1/KCNE1. K^+ cycling in the vestibular labyrinth as in the cochlea does not appear to be limited to the current loop through the hair cells. Part of the current generated by vestibular dark cells appears to be carried through vestibular transitional cells (Lee et al., 2001).

2. Stria vascularis

Stria vascularis in the lateral wall of the cochlea is a multi-layered, highly vascularized epithelium that is

Table 1

Gene name[a]	Description and selection of alternative names
ATP1A1	α_1-subunit of Na^+/K^+-ATPase
ATP1B2	β_2-subunit of Na^+/K^+-ATPase
KCNE1	I_{sK} = slowly activating K^+ current minK = minimal K^+ channel
KCNQ1	K_VLQT1 = voltage-activated K^+ channel of long QT syndrome 1
KCNQ1/KCNE1	I_{sK}/KvLQT1 K^+ channel I_{sK} channel
KCNN2	SK2 Intermediate/small conductance Ca^{2+}-activated K^+ channel
KCNMA1	Large conductance Ca^{2+}-activated K^+ channel BK or big K^+ channel slo
KCNQ4	Voltage-gated K^+ channel, KQT-like subfamily, member 4
KCNJ10	Inward-rectifier K^+ channel, subfamily J, member 10 Kir4.1 = inward-rectifier K^+ channel 4.1
SLC12A2	Solute carrier, family 12, member 2 NKCC1 BSC2

[a] GDB™ Human Genome Database [database online]. Toronto (ON, Canada): The Hospital for Sick Children; Baltimore (MD, USA): Johns Hopkins University, 1990–2001. Available from Internet: URL http://www.gdb.org/.

[1] Nomenclature is summarized in Table 1.

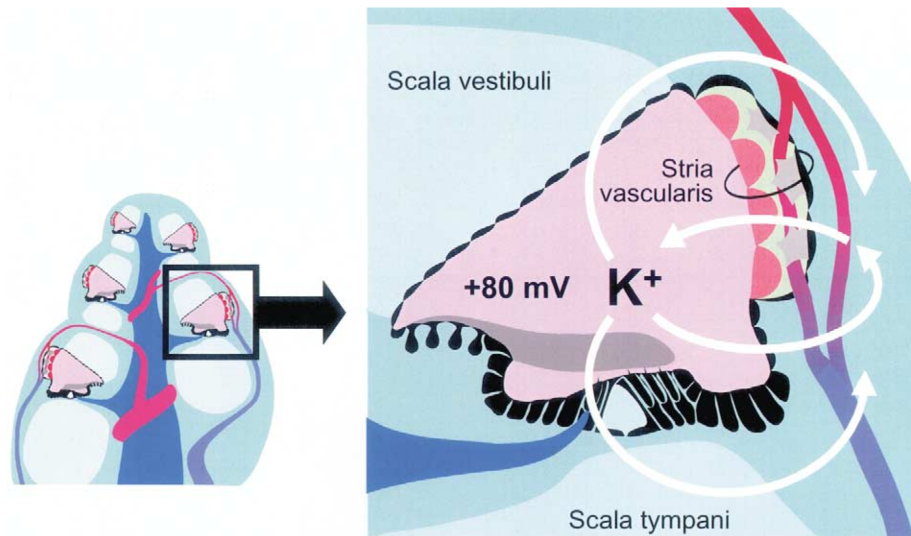

Fig. 1. Schematic cross-section through one turn of the cochlea. The lumen of the cochlea is filled with endolymph, which is an unusual extracellular fluid in that the major salt is KCl rather than NaCl. Sensory transduction depends on a current, which is driven by the endocochlear potential that is generated by stria vascularis. This current flows through the sensory hair cells and is mainly carried by K^+. Parts of this current flow through outer sulcus cells and through Reissner's membrane (Artwork by P. Wangemann (Marcus et al., 2000) reprinted with permission from the Physiological Society).

part of the epithelial barrier enclosing endolymph. Stria vascularis faces endolymph on the apical side and spiral ligament on the basal side (Figs. 1 and 2). Stria vascularis provides two electrochemical barriers consisting of epithelial cells joined together by tight junctions (Jahnke, 1975; Suzuki et al., 2001). The barrier between endolymph and the intrastrial fluid is comprised of strial marginal cells and the barrier toward spiral ligament is comprised of basal cells. Further, the barrier between intrastrial fluid and blood plasma is comprised of endothelial cells that do not form fenestrae but are joined together by tight junctions (Jahnke, 1975).

3. K^+ secretion by strial marginal cells and vestibular dark cells

Strial marginal cells and vestibular dark cells are highly developed epithelia that have many similarities (Wangemann, 1995). The major difference is that vestibular dark cells form single-layered epithelia in the vestibular labyrinth whereas strial marginal cells are part of the multi-layered stria vascularis in the lateral wall of the cochlea. Strial marginal cells and vestibular dark cells are responsible for K^+ secretion into cochlear and vestibular endolymph and thereby for the formation of endolymph. Both cell types take up K^+ across their basolateral membrane via a $Na^+/2Cl^-/K^+$ cotransporter and a Na^+/K^+-ATPase and secrete K^+ across the apical membrane via a K^+ channel (Fig. 2). Na^+ and Cl^- taken up via the $Na^+/2Cl^-/K^+$ cotransporter are recycled across the basolateral membrane via the Na^+/K^+-ATPase and Cl^- channels, respectively. The identities of these four main ion transport mechanisms in vestibular dark cells and strial marginal cells are now well established. Evidence is in most cases well rooted in a combination of functional, pharmacological, biochemical, molecular and morphological detection strategies. The malfunction of several of these transporters is associated with deafness in humans and mouse models.

3.1. The apical K^+ channel KCNQ1/KCNE1

The most prevalent conductive path in the apical membrane of vestibular dark cells and strial marginal cells is the K^+ channel KCNQ1/KCNE1 (formerly called I_{sK}, minK or KvLQT1/I_{sK} channel). KCNQ1 is the α-subunit consisting of six membrane-spanning regions and a pore-forming structure that confers K^+ permeability (Choe et al., 1999). Four α-subunits are thought to associate to form a channel together with an unknown number of the β-subunit KCNE1. This association is critical as it confers important properties to the channel including the single-channel conductance (Romey et al., 1997), overall channel activity (Romey et al., 1997), voltage dependence and activation time dependence (Chouabe et al., 1997; Kunzelmann et al., 2001; Melman et al., 2001), temperature and pH sensitivity (Unsold et al., 2000) and drug sensitivity (Abitbol et al., 1999; Barhanin et al., 1996; Unsold et al., 2000; Yang and Sigworth, 1998).

The KCNQ1/KCNE1 K^+ channel has been detected in the inner ear as functional channels and as message

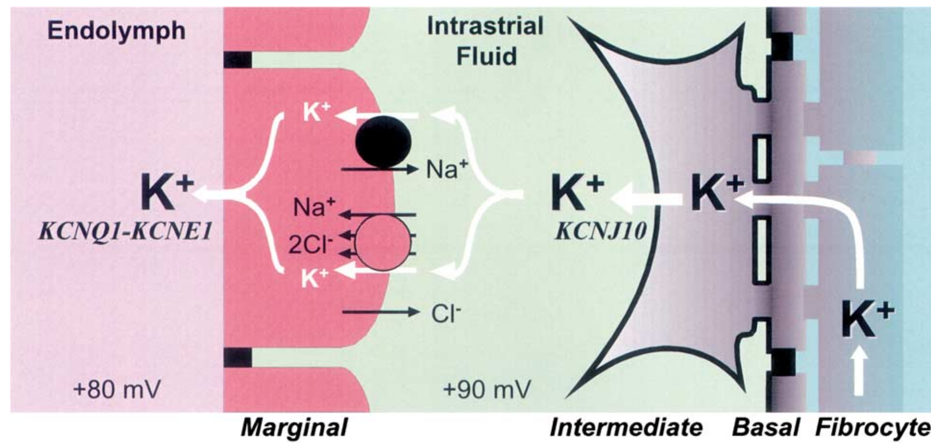

Fig. 2. Schematic cross-section through stria vascularis. Stria vascularis consists of two barriers comprised of cells that are joined by tight junctions. One barrier is comprised of marginal cells and the other of basal cells. Strial marginal cells secrete K^+ into endolymph. The endocochlear potential is generated across the basal cell barrier. Basal cells are joined by gap junctions to intermediate cells on the intrastrial side and to fibrocytes on the spiral ligament side. The molecular mechanism that generates the endocochlear potential is understood to be the KCNJ10 K^+ channel in the intermediate cells. The endocochlear potential is essentially a K^+ diffusion potential that is generated across the KCNJ10 K^+ channel by the very low K^+ concentration in the intrastrial fluid spaces and the high K^+ concentration in the cytosol of intermediate cells. Fibrocytes and strial marginal cells contribute indirectly to the generation of the endocochlear potential in that they ensure the low K^+ concentration in the intrastrial fluid spaces and the high K^+ concentration in the cytosol of intermediate cells (artwork by P. Wangemann (Marcus et al., 2000), reprinted with permission from the Physiological Society).

and protein of the subunits KCNQ1 and KCNE1 (Marcus et al., 1998; Neyroud et al., 1997; Nicolas et al., 2001; Sakagami et al., 1991). KCNQ1/KCNE1 K^+ currents were recorded and characterized by on-cell and whole-cell current measurements in vestibular dark cells (Marcus et al., 1997; Marcus and Shen, 1994; Sunose et al., 1997b; Wangemann et al., 1995b, 1996) and strial marginal cells (Marcus et al., 1998; Shen et al., 1997; Sunose et al., 1997a; Wangemann et al., 1995a). KCNQ1/KCNE1 forms a K^+ selective channel that activates very slowly (time constant of $\sim$1800 ms) at membrane potentials more positive than −40 mV and deactivates slowly (time constant of 100–400 ms) at membrane potentials more negative than −40 mV (Marcus et al., 1998). Once activated, the channel does not show any time-dependent inactivation (Shen et al., 1997). These properties make this channel an ideal carrier of K^+ secretion in vestibular dark cells and strial marginal cells since the membrane potential across the apical membrane in these cells is between 0 and +10 mV (Offner et al., 1987). Interestingly, the KCNQ1/KCNE1 K^+ channel is the sole mechanism that carries K^+ secretion across the apical membrane, which makes this channel an excellent pharmacologic target. Modulation of this channel could be of therapeutic value for the treatment of endolymphatic hydrops, a condition where endolymph secretion outweighs reabsorption resulting in a pathologic swelling of the endolymphatic compartment.

The importance of the KCNQ1/KCNE1 K^+ channel for K^+ secretion in the cochlea and the vestibular labyrinth was illustrated with striking clarity in mice that were engineered to lack either KCNE1 (Vetter et al., 1996) or KCNQ1 (Casimiro et al., 2001; Lee et al., 2000) or that harbor a spontaneous mutation in KCNE1 (Letts et al., 2000). Common to these mice is that their endolymphatic spaces develop normally until about postnatal day 3, which in mice is the onset of K^+ secretion (Anniko and Nordemar, 1980; Yamasaki et al., 2000). Later, the endolymphatic spaces appear to be collapsed due to the inability of vestibular dark cells and strial marginal cells to secrete K^+ and due to unimpeded reabsorptive processes that may have a similar onset in development (Vetter et al., 1996). Measurements of current densities in oocytes expressing KCNQ1 in the presence or absence of KCNE1 predict a dramatic reduction of K^+ secretion in KCNE1 knockout mice or patients lacking a functional KCNE1 (Barhanin et al., 1996; Kunzelmann et al., 2001; Sanguinetti et al., 1996). Interestingly, transcription of KCNQ1 has been shown at least in the heart to be independent of KCNE1 (Drici et al., 1998). It appears that KCNQ1 interacts at the translational or posttranslational level with KCNE1. Support for a posttranslational interaction comes from the observation that KCNQ1 in vestibular dark cells of mice lacking KCNE1 failed to concentrate in the apical membrane and appeared to remain in the cytoplasm rather than being trafficked to the apical membrane (Nicolas et al., 2001). Thus, KCNE1 may be necessary for trafficking of KCNQ1 to the apical membrane.

The KCNQ1/KCNE1 K^+ channel is not only respon-

sible for K^+ secretion and the formation of endolymph in the cochlear and vestibular labyrinth but carries in cardiac myocytes the slowly activating I_{Ks} current that plays a major role in the repolarization phase of the cardiac action potential (Barhanin et al., 1996; Sanguinetti et al., 1996; Varnum et al., 1993). More than 80 mutations in KCNQ1 and KCNE1 have so far been described (Splawski et al., 2000). Some mutations of KCNQ1 and KCNE1 cause a propensity for drug-acquired long-QT syndrome (Roden, 2001). Long-QT syndrome is a prolongation of the cardiac action potential that can be detected in surface electrocardiograms and that is associated with arrhythmias followed by syncope or sudden death in otherwise healthy individuals. More severe mutations of KCNQ1 or KCNE1 can lead to two forms of long-QT syndrome. The more common form is Romano–Ward syndrome, which is inherited as an autosomal dominant trait with variable penetrance and consists of long-QT syndrome without other abnormalities. The less common form is Jervell and Lange-Nielsen syndrome, which is inherited as an autosomal recessive trait and consists of long-QT syndrome combined with profound sensorineural deafness. Interestingly, the endolymphatic space of patients with Jervell and Lange-Nielsen syndrome is collapsed, as observed in mice lacking either KCNQ1 or KCNE1 (Friedmann et al., 1966). It is currently unclear why most heterozygous mutations of KCNQ1 and KCNE1 that cause cardiac abnormalities have no apparent effect on the inner ear and why homozygous mutations affect both the inner ear and the heart.

3.2. The basolateral $Na^+/2Cl^-/K^+$ cotransporter SLC12A2

SLC12A2 is the $Na^+/2Cl^-/K^+$ cotransporter in the basolateral membrane of vestibular dark cells and strial marginal cells as well as in a number of Cl^- secretory epithelia. SLC12A2 was previously called BSC2 or NKCC1 in contrast to another isoform, SLC12A1, that was previously called BSC1 or NKCC2 and that is expressed exclusively in the kidney in the apical membrane of the thick ascending limb of the loop of Henle (Haas and Forbush, 2000). Pharmacological studies first identified and linked SLC12A2 to K^+ secretion in vestibular dark cells and strial marginal cells (Marcus et al., 1987; Wangemann et al., 1995a; Wangemann and Marcus, 1990). Immunohistochemical studies confirmed the localization of SLC12A2 (Crouch et al., 1997; Goto et al., 1997; Mizuta et al., 1997). The importance of the SLC12A2 for K^+ secretion was illustrated with striking clarity in mice that were engineered to lack this $Na^+/2Cl^-/K^+$ cotransporter (Delpire et al., 1999; Dixon et al., 1999; Flagella et al., 1999; Pace et al., 2001). Common to these mice is that their endolymphatic spaces appear to be collapsed due to the inability of vestibular dark cells and strial marginal cells to secrete K^+ and apparently unimpeded reabsorptive processes.

3.3. The basolateral Cl^- channel CLCNKA

The most prevalent conductive path in the basolateral membrane of vestibular dark cells and strial marginal cells is a Cl^- conductance (Marcus et al., 1993; Takeuchi et al., 1997; Wangemann et al., 1995a; Wangemann and Marcus, 1992). Cl^- channels have been studied as whole-cell currents and single-channel currents and have been identified as CLCNKA (CLC-K1) (Ando and Takeuchi, 2000; Marcus et al., 1993; Takeuchi et al., 1995; Takeuchi and Irimajiri, 1996). Additional Cl^- channels, CLCN2 (CLC-2) and CLCN3 (CLC-3) that may be able to form hetero-oligomeric channels with each other or with CLCNKA, have been detected as message in the cochlear lateral wall (Oshima et al., 1997). Whether CLC-2 and CLC-3 are translated into protein is currently unclear. It would be of interest to study the importance of CLCNKA by using mutant mice that have recently been created (Matsumura et al., 1999).

3.4. The basolateral Na^+/K^+-ATPase ATP1A1/ATP1B2

Vestibular dark cells and strial marginal cells contain in their basolateral membrane a Na^+/K^+-ATPase for the uptake of K^+ (Konishi et al., 1978; Marcus and Marcus, 1987; Wangemann et al., 1995a). The Na^+/K^+-ATPase takes up two K^+ and extrudes three Na^+ during one cycle that is powered by the energy released from the hydrolysis of one ATP. The extrusion of Na^+ establishes a Na^+ gradient that energizes the $Na^+/2Cl^-/K^+$ cotransporter for further K^+ uptake. The extruded three Na^+ ions power three cycles of the $Na^+/2Cl^-/K^+$ cotransporter to transport three Na^+, six Cl^- and three K^+. It is noteworthy that the combination of the Na^+/K^+-ATPase and the $Na^+/2Cl^-/K^+$ cotransporter is very energy efficient in that a total of five K^+ ions are taken up per one ATP hydrolyzed.

The Na^+/K^+-ATPase has two obligatory subunits, α and β. Four α- (ATP1A1–4) and three β-subunits (ATP1B1–3) are currently known (Blanco and Mercer, 1998). Some Na^+/K^+-ATPases associate in addition with a γ-subunit (ATP1G1) (Beguin et al., 1997). Whether a Na^+/K^+-ATPase is normally a protomer containing one copy of each subunit or a dimer or a tetramer is currently a matter of controversy. The combination of different subunits confers specific properties to the Na^+/K^+-ATPase (Beguin et al., 1997; Blanco and Mercer, 1998; Crambert et al., 2000). Stria vascularis and vestibular dark cells express ATP1A1 and ATP1B2 (Fina and Ryan, 1994; McGuirt and Schulte,

1994; Peters et al., 2001; Schulte and Adams, 1989; ten Cate et al., 1994) as well as ATP1B1 (Fina and Ryan, 1994; Schulte and Steel, 1994). The Na^+/K^+-ATPase consisting of ATP1A1 and ATP1B1 or ATP1B2 has a very low affinity for Na^+ and K^+ compared to other subunit combinations (Blanco and Mercer, 1998; Crambert et al., 2000; Kuijpers, 1974) and is thereby perfectly suited to maintain a low K^+ concentration in the intrastrial spaces of stria vascularis.

4. Stria vascularis generates the endocochlear potential

The endocochlear potential is generally understood to be produced by stria vascularis (von Békésy, 1950) and to provide the main driving force for sensory transduction (Davis, 1953; Wangemann and Schacht, 1996). Remarkably, the molecular mechanism that generates this potential remained elusive until very recently. Early notions ascribed both K^+ secretion and the generation of the endocochlear potential to strial marginal cells. This constraint led to speculations about unusual ATPases, which became key elements in models that understood stria vascularis as a current source. Most recently it became clear that the endocochlear potential is generated by the KCNJ10 (Kir4.1) K^+ channel that is located in the intermediate cells of stria vascularis. It is understood that this channel generates the endocochlear potential in conjunction with a very low K^+ concentration in the intrastrial fluid spaces and a normal high K^+ concentration in the cytosol of intermediate cells. Thus, the endocochlear potential is essentially a K^+ diffusion potential.

Several lines of evidence have contributed significantly to the elucidation of this understanding. First, strial marginal cells that had been suspected of harboring the molecular mechanism for the endocochlear potential were found to secrete K^+ by a mechanism incompatible with generation of the endocochlear potential (Marcus and Shen, 1994; Wangemann et al., 1995a). Based on the similarity between strial marginal cells and vestibular dark cells, it became clear that strial marginal cells play an indirect role in the generation of the endocochlear potential in that they ensure the low K^+ concentration in the intrastrial spaces (Wangemann, 1995). Second, the endocochlear potential was found to be generated across the basal cell barrier rather than across the marginal cell barrier (Salt et al., 1987). Third, intermediate cells were found to be connected to basal cells via a high density of gap junctions such that the membranes of intermediate cells could functionally be a part of the basal cell barrier (Forge, 1984; Kikuchi et al., 1995; Reale et al., 1975). This finding opened the possibility that intermediate cells harbor the molecular mechanism that generates the endocochlear potential. Fourth, intermediate cells were found to play a significant role since the endocochlear potential was absent in mutant mice lacking these cells (Cable et al., 1992, 1994; Carlisle et al., 1990; Schrott and Spoendlin, 1987; Schulte and Steel, 1994). Fifth, the endocochlear potential was sensitive to K^+ channel blockers, suggesting that a K^+ channel contributes to its generation (Marcus et al., 1985; Takeuchi et al., 1996). A comparison of a drug sensitivity profile between the endocochlear potential and currents through KCNJ10 K^+ channels supported the hypothesis that this channel generates the endocochlear potential (Takeuchi et al., 2000; Takeuchi and Ando, 1998). The KCNJ10 K^+ channel was indeed found in stria vascularis to be solely localized in intermediate cells (Ando and Takeuchi, 1999), although another report that suffered from the difficulty of distinguishing marginal from intermediate cell membranes claimed localization in marginal cells (Hibino et al., 1997). The importance of the KCNJ10 K^+ channel in intermediate cells for the generation of the endocochlear potential was finally illustrated with striking clarity in mice that were engineered to lack this channel. The endocochlear potential was found to be absent in KCNJ10 knockout mice and the cochlear endolymphatic volume and K^+ concentration were partly reduced, whereas the vestibular endolymphatic space and K^+ concentration were normal (Marcus et al., 2002). Sixth and last, an evaluation of the Ba^{2+} sensitivity of the endocochlear potential suggested that the extracellular K^+ concentration in the intrastrial space is as low as 1–2 mM (Takeuchi et al., 2000), which in conjunction with a normal intracellular K^+ concentration and a high K^+ selectivity of intermediate cell membrane could account for a source voltage of up to 120 mV. This source voltage is most likely sufficient to generate an endocochlear potential of 80 mV. Taken together, this multitude of observations points toward the KCNJ10 K^+ channel as the molecular mechanism for the generation of the endocochlear potential. The channel provides an important but not essential route for cochlear K^+ cycling.

Acknowledgements

The support by Research Grant NIH-R01-DC01098 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health is gratefully acknowledged.

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