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Ion Homeostasis in the Ear: Mechanisms, Maladies, and Management

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Abstract

Purpose of Review—Describe ion and water homeostatic mechanisms in the inner ear, how they are compromised in hearing disorders, and what treatments are employed to restore auditory function.

Recent Findings—The ion and water transport functions in the inner ear help maintain the proper endolymph K^+ concentration required for hair cell function. Gene defects and idiopathic alterations in these transport functions cause hearing loss, but often the underlying cause is unknown. Current therapies largely involve glucocorticoid treatment, although the mechanisms of restoration are often undeterminable. Recent studies of these ion homeostatic functions in the ear are characterizing their cellular and molecular control. It is anticipated that future management of these hearing disorders will be more targeted to the cellular processes involved and improve the likelihood of hearing recovery.

Summary—A better understanding of the ion homeostatic processes in the ear will permit more effective management of their associated hearing disorders. Sufficient insight into many homeostatic hearing disorders has now been attained to usher in a new era of better therapies and improved clinical outcomes.

Keywords

Ion homeostasis; Meniere's disease; hearing loss; inflammation; middle ear; inner ear; endolymph

I. Introduction

Many recent studies are providing a clearer picture of ion and water transport **mechanisms** in the ear required to maintain the critical high K^+ levels of endolymph. Numerous hearing **maladies** result from disruption of these homeostatic processes. Many cases are spontaneously or therapeutically reversible, suggesting **management** is possible. Unfortunately many are due to genetic defects and irresolvable. The focus of this review will be to evaluate the latest research into the ion homeostatic processes of the ear, their associated hearing disorders, and what therapeutic approaches have been successful in their management.

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II. Ion Homeostasis in Ear

The inner ear is an ion transport organ. The hair cell depolarizes following transduction of some motion, releases neurotransmitter, and elicits nerve conduction signals to the brain. All of these processes require a unique environment of endolymph (high K^+) surrounding the hair cell stereocilia and perilymph (high Na^+) around the hair cell body. K^+ enters the hair cell as part of the transduction process, is recycled back to the lateral wall via a series of gap junctions and other transport mechanisms, and is secreted back into the endolymph by the stria vascularis (Fig. 1). Thus, the ion homeostasis mechanisms are simply the life support system for the hair cell. An extensive description of these channels and transporters is beyond the scope of this paper and one is referred to recent reviews of hair cell function [1–2], inner ear ion channels and transporters [3–6], and the genetic disorders that impact them [7–8].

The various cell layers of the stria vascularis have unique ion channels for moving K^+ into the endolymph (Fig. 2). The basal cells and marginal cells are sealed by tight junctions to control movement of ions and other substances. The capillary endothelial cells, also sealed by tight junctions, make up the blood labyrinth barrier. The spiral ligament also has an extensive vascular network and is occupied largely by fibrocytes. The fibrocytes in the spiral ligament, the basal and intermediate cells of the stria, and the endothelial cells of the strial vessels are all joined by gap junctions that mediate K^+ transport. This extensive syncytium reflects the significant control of ion homeostasis in the ear, as well as the potential for transport dysfunction that can occur.

III. Disorders of Homeostasis

There are numerous hearing disorders that are the direct result of disrupted ion homeostasis. While the initial cause may be something else (inflammation, ototoxicity, noise, etc.), the ultimate impact on the ear is the interference of some ion or water transport mechanism. Thus, impaired ion homeostasis is essentially the final common pathway for many inner ear diseases.

A. Ear vasculature/homeostasis processes

The endothelial cell monitors its environment and responds accordingly when stimulated by bacteria, virus, trauma, circulating antibodies, and immune complexes [9–11].

Mechanisms—The endothelial cell is not a victim of inflammation, but rather a major player in the local inflammatory response. It produces cytokines and other pro-inflammatory factors, such as adhesion molecules that bind leukocytes, monocytes, and macrophages, to move them across intercellular junctions into the tissue for host defense [12–14]. These inflammatory response processes in the brain involve microglia, astrocytes, and endothelial cells, leading to disruption of the blood brain barrier [15–17]. Debate still is ongoing as to whether such inflammation is protective, destructive, or both, but the ultimate goal is to protect the host from the pathogen or other inflammatory attack [16,18]. Inner ear studies show a similar role played by the cochlear vasculature. The lateral wall vasculature is a complex of endothelial cells, pericytes, and resident perivascular macrophages [19–21], all the components needed for the vascular inflammatory response to occur in the inner ear.

Maladies—Inner ear homeostasis is susceptible to numerous insults that compromise the vasculature of the lateral wall (stria vascularis, spiral ligament) and modiolar artery. Unfortunately, the programmed endothelial cell response to open intercellular junctions to permit immune cell entry into the perivascular space will open the blood labyrinth barrier in the ear. Because integrity of the strial endothelial cell tight junction is critical for maintenance of the endolymph, such disruption will equilibrate ion potentials between the serum and endolymph to cancel the endocochlear potential. Thus, such an inflammatory response, while

generally protective of the host, is not compatible with hearing because of disrupted K^+ levels in the endolymph (Fig. 2).

Numerous insults to the inner ear have been shown to cause vascular inflammatory responses and potentially hearing loss. This may be a factor in sudden hearing loss, rapidly progressing hearing loss, immune-mediated hearing loss, autoimmune disease hearing loss, labyrinthitis, etc. Several recent studies have shown pro-inflammatory insults impact the vasculature and ion homeostatic processes of the lateral wall or endolymphatic sac:

- Circulating pathogens induce production of cytokines by endothelial cells [22].
- Circulating immune complexes and autoantibodies impact the ear [23–25].
- Noise trauma induces lateral wall inflammatory processes [19,26–30].
- Ototoxic drugs induce infiltrating lymphocytes [31].
- Hyperlipidemia occurs in Apo E null mice [32].
- Dysfunction of endolymphatic sac by inflammatory cytokine IFN-γ [33].

Management—The traditional glucocorticoid therapy (prednisone, dexamethasone, prednisolone) would be beneficial in suppressing vascular inflammatory processes and protecting/restoring hearing. However, one must be careful in interpreting whether the treatment affected the underlying inflammatory process or the disrupted inner ear homeostatic process. If inflammation disrupts stria vascularis ion homeostatic mechanisms, then therapies may treat the inflammation, the ion transport problem, or both. For example, autoimmune disease mice have significant hearing loss that develops due to elevated serum immune complexes that compromise stria vascularis ion transport [25]. The mineralocorticoid aldosterone upregulates the epithelial sodium channel (ENaC) and Na^+,K^+-ATPase, and is as effective as glucocorticoids in managing or preventing this hearing loss in mice. However, glucocorticoids also bind to the mineralocorticoid receptor, essentially upregulating genes related to both receptors' functions. Furthermore, recent studies have shown glucocorticoids in the ear may directly drive ENaC function via the glucocorticoid receptor also [34–35]. Thus, the line between glucocorticoid and mineralocorticoid driven processes is blurring. The recent characterization of *serum- and glucocorticoid kinase -1* (SGK-1), which is produced following binding by either steroid group, directly controls ENaC activation [36–37]. It also upregulates expression of numerous other ion transport channels, many of which are found in the inner ear [38]. How much SGK-1 impacts inner ear steroid treatment outcomes is currently uninvestigated.

Because one seldom can determine the exact cause of the hearing loss, it is often not clear whether the steroid given is suitable for the underlying homeostatic problem. This may be why recent meta-analyses debate whether steroids or vasodilators are beneficial [39–41]. Further compounding the confusion over outcomes is the fact the lateral wall will regenerate, causing recovery in 50–60% of sudden hearing loss cases. Unfortunately most reports have small sample sizes and power analyses suggest one would need 1,000 patients to effectively demonstrate a statistically significant improvement over this spontaneous recovery rate [41]. Until more effective diagnostic tools are available to determine the actual underlying ion homeostatic process involved in a patient's hearing loss, glucocorticoid therapy will continue to be the major therapy. Mineralocorticoid treatment (aldosterone, fludrocortisone) has shown some promise for treating human hearing loss, presumably by directly regulating ion transport functions via the mineralocorticoid receptor.

B. Middle ear processes

Although most research of otitis media has focused on the inflammatory cytokines, recent studies have begun characterizing the role of ion and water transport channels in the middle ear mucosa.

Mechanisms—Many of the ion transporters and aquaporins found in the inner ear also occur in the middle ear. These include several K^+ channels, ENaC, Na^+,K^+-ATPases, gap junctions, tight junction claudins, the sodium potassium chloride cotransporter (NKCC), and chloride channel (Clcnka) (42). These presumably are involved in the clearance of fluid to keep the middle ear clear [43–46].

Maladies—Inflammation in the middle ear suppresses gene expression of many of these ion channels and aquaporins [42–46], which possibly is responsible for failure of effusions to clear. If inflammation is to protect the host from pathogens, effusion formation may help kill bacteria by providing a concentrated pool of cytokines and inflammatory cells. Furthermore, inflammatory cytokines in the middle ear cause similar cytokine expression and pathology in the inner ear [47–52], leading to downregulation of these same ion and water transport channels (unpublished data). The sensorineural hearing loss accompanying otitis media may include inflammatory depression of these cochlear ion channels to decrease K^+ transport into the endolymph (Fig. 2).

Management—Because antibiotics are the only treatment for otitis media, little is known about the potential management of the ion homeostatic disruption in the middle ear. Recent efforts to manage these ion homeostasis channels in middle ear disease has focused on the glucocorticoids to suppress inflammation and mineralocorticoids to enhance K^+ and Na^+ exchange via ENaC and Na^+,K^+-ATPase to clear middle ear fluid [53–54]. However, it appears the glucocorticoid dexamethasone is also influential in driving middle ear ENaC function [55]. Future studies will undoubtedly clarify this role of ion and water transport in middle ear effusions and its control with therapeutics. Effusion control will reduce pain and discomfort in children, lower the risk to the inner ear, and potentially eliminate the need for many prescriptions of antibiotics that have limited effectiveness anyway.

C. Mineralocorticoid - Glucocorticoid processes

Several ion channels and transporters in the lateral wall are driven by natural and therapeutic steroid hormones.

Mechanisms—Several ion transport channels in the stria vascularis and spiral ligament are responsible for moving K^+ into the endolymph and Na^+ out (Fig. 2). These include the K^+ channels (KCNJ10, KCNE1, KCNQ1), ENaC, Na^+,K^+-ATPase, NKCC, gap junctions, aquaporins, TRPV4, purinergic receptors, and tight junction claudins. Mineralocorticoids and glucocorticoids are the hormone drivers for some of these [4–5,25,34–35,56], as well as arginine vasopressin, atrial natriuretic peptide, insulin, and endothelin [57]. However, the drivers of many of these channels are thus far undetermined.

Maladies—Gene defects affect many of these channels [7–8], the most common of which are the gap junction connexins [3–4,8,58]. These act primarily in the supporting cells and the interconnected fibrocytes in the spiral ligament. Although fibrocyte gap junctions move K^+, recent studies show they move other molecules relevant to cochlear homeostasis [58–60]. It is not clear if some forms of sudden and rapidly progressing hearing loss are the result of disruption of these pathways. Meniere's disease does not appear to involve these channels [61], instead involving those in the aquaporins-vasopressin complex (below). The vascular inflammatory diseases above also may directly impact the function of these channels. Aging

and noise damage can have a considerable effect on ion homeostasis. Noise exposure reduces purinergic signaling, potentially leading to reduction in K^+ secretion [62], while sound-induced expression of osmotic stress protein 94 in the lateral wall may help protect ion homeostasis [28]. Gene polymorphisms in these K^+ channels and heat shock proteins also appear to predispose individuals to noise-induced hearing loss [63–64]. Aging leads to degenerative changes in the lateral wall and decreased ion and water transport [65–66]. Loss of tight junction claudins leads to unregulated K^+ transport and hearing loss [67–68]. Loss of the pendrin function of anion exchange in the lateral wall impairs cochlear pH regulation, leading to hearing loss and enlarged vestibular aqueduct [69–70].

Management—The various therapeutic steroids have an impact on these channels, particularly ENaC, Na^+,K^+-ATPase, and some of the K^+ channels. Both glucocorticoids and mineralocorticoids upregulate KCNJ10, aquaporin 1, and gap junction connexin 26, with greater effect seen following intratympanic delivery (unpublished data). This supports the improved results seen with intratympanic steroid delivery clinically [71–74], although this is still debated [75]. Speculation regarding antioxidant therapy to prevent age-related degeneration of vascular and lateral wall functions raises an interesting possibility for the future [76].

D. Aquaporin-Vasopressin processes

Recent studies are beginning to clarify the role of certain aquaporins and vasopressin in the control of endolymph volume.

Mechanisms—Aquaporin 2 channels and vasopressin (anti-diuretic hormone) are responsible for moving K^+ and water into the endolymph. These channels are active in the stria vascularis [77–78], and endolymphatic sac [79]. Vasopressin supplementation will cause expression of numerous ion transport genes in the ear [80] and lead to hydrops [81–82]. The endolymphatic sac also contains purinergic receptors [83] and TRPV4 channels [84] that are proposed to control fluid balances, but whether they act in tandem with aquaporins and vasopressin is unknown.

Maladies—Meniere's disease is often associated with dysfunction of vasopressin and aquaporin 2 channels. Meniere's patients often have elevated levels of vasopressin during active disease [85]. It has been challenging to develop the causative relationship between elevated serum vasopressin and Meniere's disease since the symptoms are usually unilateral. Recently it was determined that mRNA of the vasopressin receptor is expressed at much higher levels in the endolymphatic sac of Meniere's patients [86–87]. This lead to the conclusion that it is the unilateral cochlear elevation of receptor expression, coupled with slightly higher serum levels, that causes unilateral Meniere's. Recent studies also have identified potential aquaporin gene polymorphisms in Meniere's patients that may impact water movement and hydrops formation [88]. Decreased aquaporin 4 expression has been suggested as a mechanism of aging related hearing loss as well [65].

Hydrops results from excess K^+ being moved into the endolymph, but it is not clear if this is always due to aquaporins 2 – vasopressin functions. For example, endogenous ouabain suppresses Na^+,K^+-ATPase, which is responsible for moving K^+ into the endolymph. Meniere's patients have low levels of endogenous ouabain [89], which may increase K^+ transport and cause hydrops. Also, a gene polymorphism in adducin, which increases Na^+,K^+-ATPase function, is increased in Meniere's patients [90]. ENac is also suppressed in the endolymphatic sac by inflammation [91], suggesting reduced movement of Na^+ out of the endolymph may increase hydrops. Salicylates downregulate cochlear aquaporin 6, which

suggests a link between the hearing loss and tinnitus seen with nonsteroidal anti-inflammatories [92].

Management—Steroids have been shown to be effective in many cases of Meniere's disease, but it is not clear why. They may be effective because of underlying inflammatory causes of vasopressin and receptor abnormalities, or those responding to steroids may not have aquaporins 2 – vasopressin issues at all. Dexamethasone does impact aquaporin 3 expression [79], but glucocorticoids also would help clear fluid buildup by restoring normal ion homeostasis. For example, we have shown that glucocorticoids upregulate cochlear gene expression of the K^+ channel KCNJ10, aquaporin 1, and gap junction connexin 26 (unpublished data). Diuretic treatments have been suggested for Meniere's disease, but it is not clear if they would operate on the vasopressin receptor to reduce water transport, act predominantly through the NKCC channel to suppress K^+ movement into the endolymph, or both.

Conclusion

Recent research on ion homeostatic mechanisms of the ear demonstrates the relevance of many channels to clinical hearing disorders. Basic research is gradually building the molecular profile of these channels and transporters that someday will make targeted therapies possible. Medical management of such disorders may eventually include genetic hearing loss by upregulating parallel transport systems to restore partial cochlear function. The molecular armamentarium available to researchers, coupled with the translational research mind set of our clinician scientists, set the stage for an exciting future.

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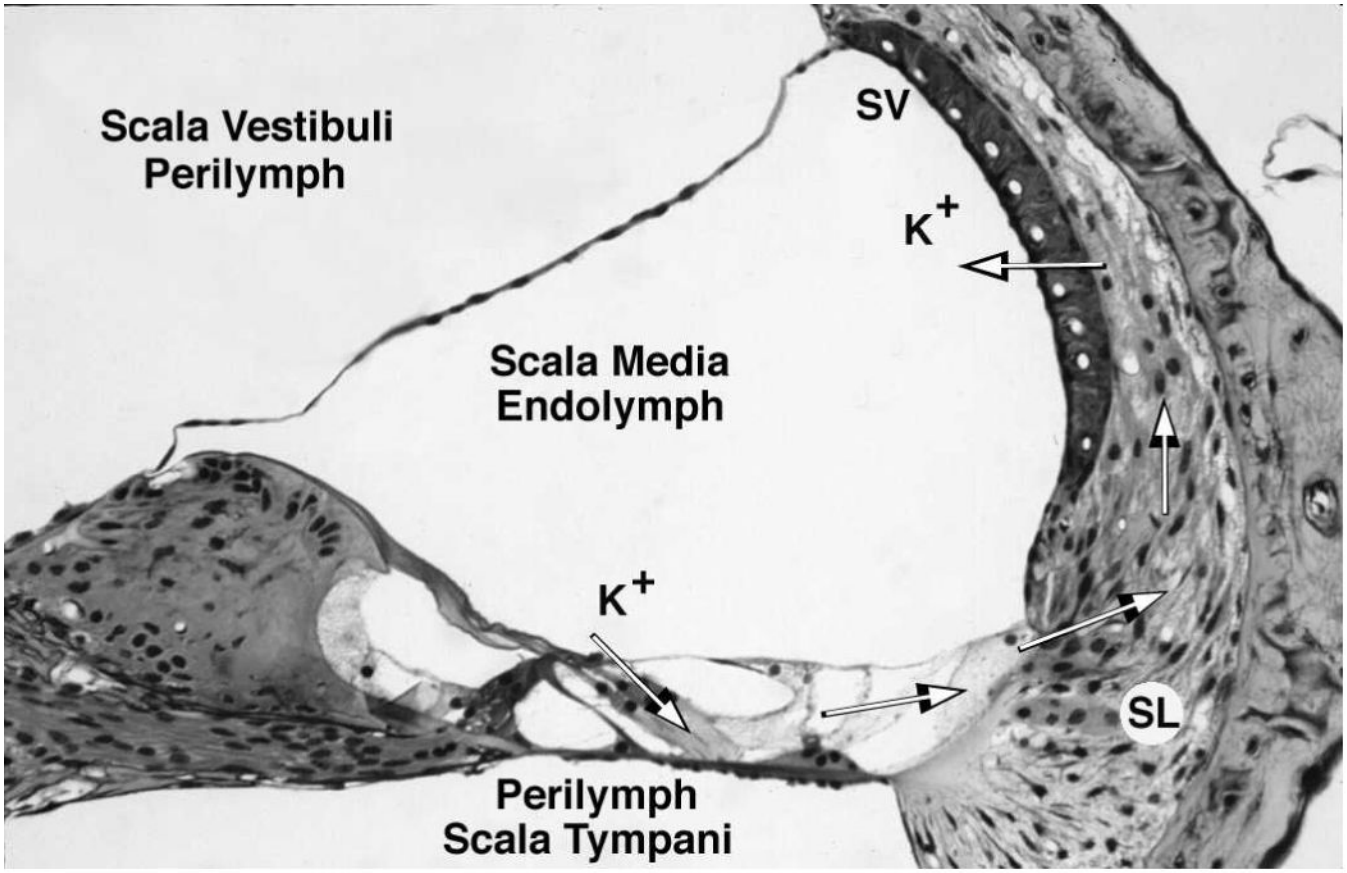

Fig. 1.
Movement of K^+ ions in the endolymph. Hair cell transduction causes movement of K^+ ions through the hair cell, after which they are transported along the supporting cells and spiral ligament (SL) to the stria vascularis (SV) for secretion back into the endolymph.

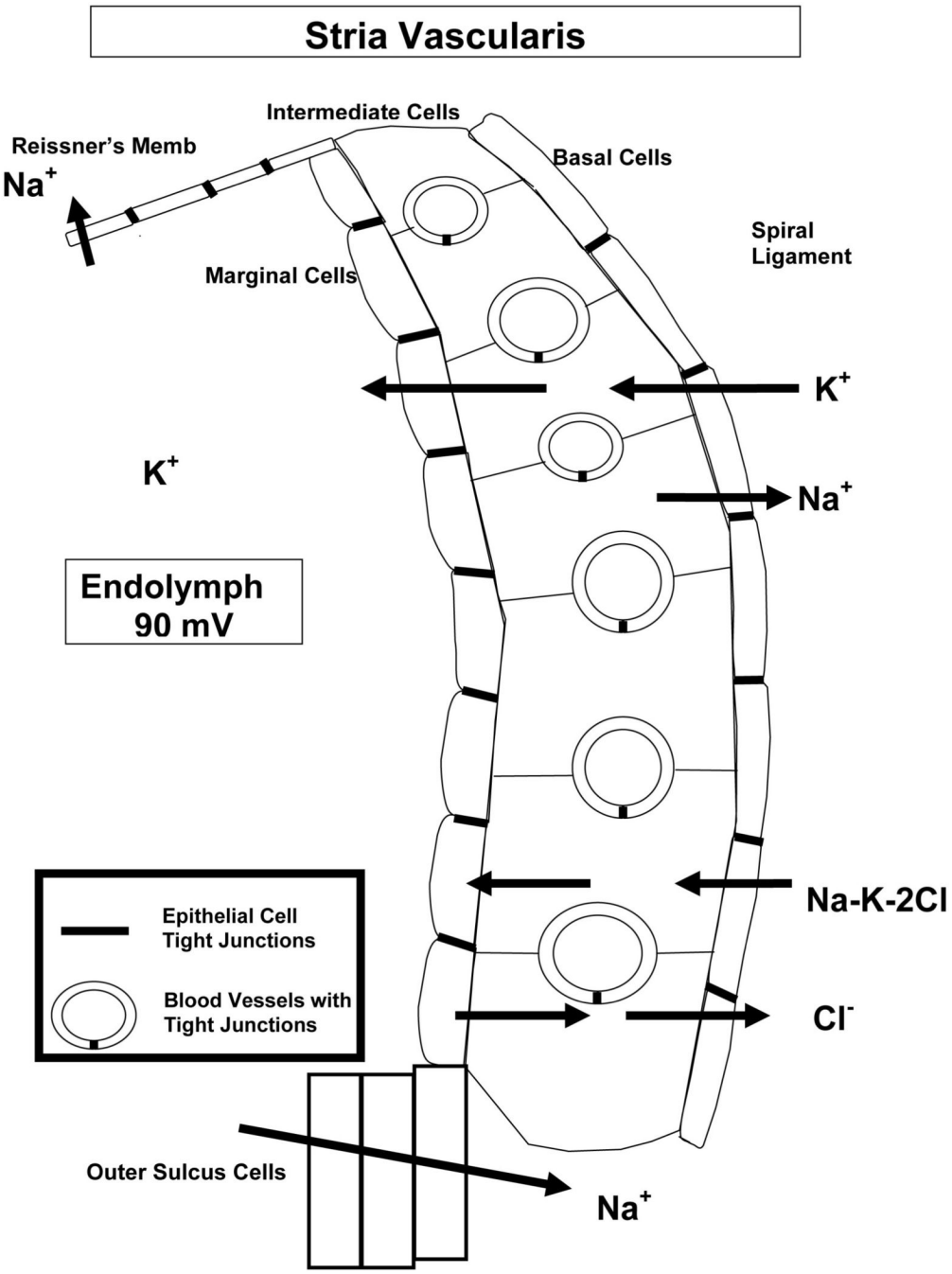

Fig. 2.

Schematic of the stria vascularis showing the general directional flow of ions through the stria vascularis. K^+ is moved into the endolymph through a series of channels in the various cell layers. Tight junctions occur between basal cells, marginal cells, and vascular endothelial cells, the latter making up the blood labyrinth barrier.