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Regulation of Inner Ear Secretion and Transport Mechanism

Cetinkaya EA and Chong Y[2]*

[1]*Antalya Ataturk State Hospital, ENT Department,Antalya,Turkey*

[2]*ENT Department, Tan Tock Seng Hospital, Singpaore*

Abstract

The endocochlear potential is a positive voltage in the cochlear endolymphatic spaces. The maintence of the endocochlear potential is dependent on ions diffusion and the electrical barrier in the stria vascularis .The regulation of inner-ear fluid ionic concentration is essential for maintence ofthe endocochlear potential. This involves ion transportation, concentration, osmolarity , volume and pressure differnece. This is a complex process. The stria vascularis and vestibular dark cells are responsible for this regulation.Any impairments to the proper functioning of these 2 structures willconsequently affect the endocochlear potential and thus affect hearing. In this review,the function of inner ear secretionand its relationship to inner-ear diseases are briefly presented.

Keywords: Inner Ear; Stria Vascularis; Vestibular dark cells; Homeostasis

Introduction

The endocochlear potential depends on ions diffusion and the electrical barrier in the stria vascularis. This is a complex process and requires the the norming regulation of inner ear secretion and ionic transportation.The stria vascularis secretory epithelia, the vestibular dark cells, the endolymphatic sac and the planum semilunatum are intriguelyinvolved with inner-ear fluid creation. In addition, the endolymphatic duct and sac, Reissner's membrane sulcus cells, Deiter's cells, Boettcher cells, Hensen cells and spiral limbus cells are also involved with the regulation of inner-ear fluids. Histological similarities between strial marginal cells and vestibuler dark cell have long been known. However, functionally they are different, the marginal cells were believed to be directly involve with the generation of endocochlear potential.The endocochlear potential is essential for hearing and depends on an electrically isolated space [1,2]. Strial marginal and vestibular dark cells have similar ion transportation characteristic, transepithelial resistence and voltage. Many distinct precursor and hormones are involved with the regulation of the stria vascularis and the dark cells. This reflects, both the requirements for delicate regulation as well as the fact that a large sequence of responses to eventuallygeneration of endocochlear potential [3].

Recently advances in understanding of the physiology and pathology of inner made it possible to target new and noval approaches to therapy. In this review we represent the current understanding ofregulation of inner ear secretion and transport mechanism, namely, inner-ear homeostasis and its influence on related inner-ear diseases.

Homeostasis and Related Diseases

The chart below shows the function of strial marginal and vestibular dark listed according to recepters and effects: (Table 1).

The stress hormones plays major role in homeostasis.Noradrenaline appears to stimulatepotassium secretion in marginal cells and potassium cycling in the inner ear [4,5].

β1 Adrenergic receptors are the predominant subordinate type in the stria vascularis and the vestibular dark cells.This receptors are located in the baso-lateral plasma membrane and their stimulation results in increased Na/K—ATPase activity and subsequent potassium secretion. The lateral wall contains non-strial tissues which extract β2-receptors. By contrast, the semicircular canal duct secretes chloride under the control of β2-adrenergic receptors. The potassium secretion is under the inhibitory control of muscarinic receptors. In addition β2-adrenergic receptors,muscarinic receptors are also located in the basolateral plasma membrane.Trans-epithelial sodium and potassium transportation is regulated by cyclic adenosine mono-phosphate as a second precursor.

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***Correspondence:**
Erdem Atalay Cetinkay, Antalya Ataturk State Hospital, ENT Department,Antalya,Turkey.
E-mail: *drerdemcetinkaya@gmail.com*

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Factor	Effect
Adrenergic reseptors	β1 : K secretion ↑, Isk(K) ↑, metabolism ↑, Na/K-ATPase activity ↑ β2 : Cl secretion ↓
Muscarinic receptors	M3, M4 : K secretion ↓
Purinergic receptors , ATP, UTP	K secretion ↓, Isk(K) ↓
Vasopressin	AQP2 ↑, V2 ↑, cAMP ↑ ,K secretion ↑ , Adenylate cyclase ↑
Atrial natriuretic peptide	endolymph volume ↓
Glucocorticosteroids	Na absorption ↑, Isk(K) ↑, AQP1 ↑, AQP3 ↑, Vasopressin ↑
Mineralocorticosteroids	Secretion ↓, Isk(K) ↓, Na/K-ATPase activity ↑

Table 1: Regulation of endolymphtic content.

The stria vascularis demonstrates the maximum adenylate cyclase activity of the whole inner ear [6,7].

The vasopressin derivative stimulate Potassium secretion in the strial marginal cells. Glucocorticosteroids increase potassium secretion which is dose-dependent. Mineralocorticosteroids eg aldosterone demonstrate an opposite effect.All serumand glucocorticoid-inducible kinases as well as protein B kinase, stimulate an voltage gated potassium channel. Na(+) transport is controlled by natural and therapeutic glucocorticoids. Different glucocorticoid reseptors is present in differentsections of the inner ear and thesesectionscan be a direct therapeutic target of glucocorticoids in the inner ear diseases such as Meniere's disease [8-10].

Natriuretic peptides play an important role in maintaining the homeostasis of endolymph via interaction with atrial natriuretic peptide receptor. Atrial natriuretic peptide act in the central and peripheral regulation of body water and electrolytes. This peptid is mainly extracted in dark cells, intermediate cells and marginal cells. In animal study atrial natriuretic peptide reduces the endolymph volume of the inner ear [11,12].

Aquaporins are found to be profusely distributed in many sections in the vestibular end organs, vestibular dark cells, vestibular sensory and supporting cells, vestibular ganglion cells, as well as the endolymphatic sac epithelial cells. Regulation of water transportation in the inner ear requires the collective activities of several types of aquaporins.There is an extremely extracted and non-extend distribution form for the several aquaporin subtypes. Aquaporin one (AQP1) is express in the intermediate cells. These cells profusely extract ion transporters, with a proposerole in water regulation related with potent ion transport in the stria vascularis. Corticosteroid usage increases aquaporins 1 and 3. Aquaporin 2 is mainly extracted in the endolymph surrounding tissues. Vasopressin usage increases aquaporin two (AQP2) and antidiuretic hormone 2 (V2) receptors along the cochlear duct. In addition, aquaporins 5 and 7 have been found in the lateral wall and vestibular epithelia [13-15].

Purinergic receptors are plasma membrane molecules that are found in almost all tissues. There are three known receptors (P1, P2X, and P2Y receptors). P2Y receptors are G protein-coupled receptors composed and have eight subgroups. Regulation of potassium secretion across strial marginal cells happen by P2Y4 receptors. Adenosine triphosphate (ATP) and uridine triphosphate (UTP) intervened potassium secretion in the stria vascularis and the dark cells.Sound exposure leads to ATP secretion into the endolymph from the stria vascularis, and this creates preventive mechanisms. Adenosine triphosphate and uridine triphosphate inhibit potassium secretion by the basolaterally expressed P2Y2 and the apically located P2Y4 purinergic receptors. It activate reabsorptive path by P2X receptors [16,17].

There are five sections in the lateral wall of the inner ear, each with a different ionic composition. The ionic composition of the spiral ligament, which resembles that of perilymph, represents the first section. The secondsection contains the basal cells and shows asudden change in ion concentration.On the other hand, the third section, which contains the extracellular space, has a low potassium concentration. The fourth section which contains the marginal cells, is similar to the fifth sections and the scala media in terms of sodium and potassium concentration, but has lower chloride levels instead. Na/K-ATPase in the basal cells main role is to establish a barrier between the spiral ligament and the stria vascularis and its deficiency leads to inner ear pathology [5,18].

Sensory transduction in the cochlea and the vestibular labyrinth depends on the cycling of Potassium . It forms the main charge transporter for transduction, because it is by far the most abundant ion in the cytosol. Potassium is optimum for this function. The significance of potassium regulation is emphasized by the fact that ampullar nerve discharge activity may be increased or decreased by potassium levels.An increase in potassium over a prolong time

may damage the outer hair cells motility. It's excretion is correlated with the potassium substance of the perilymph. The main track for potassium excretion is in the apical plasma membrane via the short circuit channel (IsK). The Isk channel is inhibited by alkalinisation and activated by acidification of the cytosol.Voltage-gated potassium channels are transmembrane channels specific for potassium and have various subgroups. KCNE belongs to β subgroup and KCNQ belongs to α subgroup.The Isk channel is formed by joining of KCNE1/KCNQ1.KCNE subunits work as molecular switches by modulating the pH sensitivity of human KCNQ1. Defects of the KCNQ1 or KCNE1 subunit consequence of failure of endolymph production and collapse of the endolymph spaces. Mutations of these subunits are associated with the autosomal recessive condition as well as Jervell and Lange-Nielsen syndrome.In spite of its association with Meniere disease and tinnitus, the role of KCNE3 is unexplained [19-21].

Non-selective calcium-activated cation channels in the apical membrane of vestibular dark cells and maxi K channels make a limited contribution to potassium excretion and sodium absorption. The main conductivity in the basolateral membrane of strial marginal cells and vestibular dark cells is via chloride conduction and it is down to themanaging for chloride cycle. This is principally represented by the type K chloride channel CLCKNA (C1C-K1) 104 and lesser by the chloride channels $CLCN_2$ and $CLCN_3$. Failure of the C_1C-K chloride channel in strial marginal cells and vestibular dark cells cause decrease endolymph volume, labyrinth collapse and may lead to hearing impairment. Mutations in the gene encoding the Barttin subunit destabilize channel structure, inducing ClC-K retention in the endoplasmic reticulum and accelerates channel degradationcausing the Bartter syndrome type IV [22,23].

The Sodium-Potassium-Chloride ($Na^+K^+Cl^+$) co-transporter $NKCC_1$ ($SLC1_2A_2$) has been found in the basolateral membrane of marginal cells and vestibular dark cells, in the spiral limbus, in spiral ligament fibrocytes and in tissues underlying the neurosensory epithelium. Marginal cells extract sodium basolaterally and supply the driving force for the Sodium-Potassium-Chloride (NaK_2Cl) co-transporter, resulting in extra flow of potassium into the cell.

Transmembrane serine protease (TMPRSS3) is an activator of the epithelial sodium channel and thus function as a regulator of sodium concentration in the cochlea. In cases of mutations in TMPRSS3, familial and sporadic cases of autosomal recessive sensorineural deafness (i.e. DFNB8/10) can be observed [24,25].

Sufficient Na/K—ATPase is necessary for the high potassium concentration of endolymph and for the endocochlear potential. This is neccesary for the sensory function of the inner ear. Extraction of Na/K—ATPase in the stria vascularis correlates with the endolymphatic potential reduction which observed towards the apex, reflecting the tonotopy of the cochlea. In addition, extracting of Na/K—ATPase is more pronounced in the ampullae than in the utricle. This difference leads to membrane infolding [26,27]. ATP is stored in the stria vascularis and is secreted in response to metabolic stresses such as noise and hypoxia. The binding sites of aldosterone are similar to the localisation of Na/K—ATPase, with highest extraction in the epithelial cells of the spiral prominence and the stria vascularis [28].

There is also mineralocorticoid receptor 1 in the stria vascularis. However, it appears that Na/K—ATPase activation cannot occur owing to mineralocorticoid receptor 1 only.In animal studies the isoforms of Na/K—ATPase in the stria vascularis, the cochlear nerve, the limbus spiralis and the spiral ganglion neuron are sensitive to thyroid hormone. In addition, the potassium-dependent phosphatase activity of the Na/K—ATPase complex is upregulated in the stria vascularis by noradrenaline, adrenaline and serotonin, while reserpine and dopamine decrease its activity [5,29].

The pH level of endolymph is similar that of blood or perilymph. The $H^+$is being secreted into endolymph against an electrochemical gradient.The chemical buffer in the endolymph consists of HCO_3^-/ CO_2 . These are produced metabolically in stria vascularis especially in strial marginal cells. Proteins play only a minor role because of their low concentration,. The importance of pH homeostasis in cochlear fluids is corralated to the general pH sensitivity of ion channels, metabolic enzymes and transporters. In animal studies, alkalinisation has a protective effect. Acidification of cochlear fluids on the other hand decreases the endocochlear potential and increases free radical stress thus causing hearing loss.The strial marginal and vestibular dark cells contains the Na^+-H^+ exchanger in the basolateral membrane. These functions to maintain intracellular pH levels. Blockage of this exchanger leads to cell acidification and transient stimulation of potassium secretion [30,31]. The Pendrin is an anion exchanger that contributes to the excretionof bicarbonate in the endolymph. The mutations of $SLC_{26}A_4$ which codes for pendrin cause the Pendred syndrome. This is a common non-syndromic hearing loss and is characterised by congenital deafness an enlarged vestibular aqueduct,a partial defect in iodide organification and goitre [32].

The glucose transporter is localised in the basal cells as well as the basolateral infoldings of the marginal cells. It is also founnd in the capillary walls of the strial marginal and vestibular dark cells. The importance of this transporter is in its contribution to glycogen storage [33].

The intrastrial space is electrically isolated from the extracellular fluids, perilymph, and endolymph. This isolation allows the intrastrial space to maintain its positive potential. Ion homeostasis is a fundamental cellular process especially significant in sensitive cell activities such as hearing. Numerous complex processes and interplay are required in regulation of inner ear secretion and transportation. Failure in any of these processes cause altered ion concentrations, osmolarity, volume and pressure in the inner ear which leads directly to hearing impairment.

We are still very much in the process of understanding the physiology and biochemistry of such complicated process. Additional research into the regulation and specific functions of these structures is essential in order to develop future surgical and clinical interventions.

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