Ion Channelopathies in Auditory Dysfunction

Essay Submitted For full Fulfilment of Master Degree in Audiology

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Content

ABTRACT

All fundamental physiological processes are based on the ability of cells to receive, process, and transmit signals. Homeostatic regulation of ion gradients is critical for most functions. They play essential roles in the physiology and pathophysiology of all cells and it is therefore not very surprising that an ever increasing number of human and animal diseases have been found to be caused by defective ion channel function. A variety of hearing and vestibular disorders result from disruption of ion homeostasis.

KEY WORDS:

Ion channel, ion homeostasis, ion channelopathies

List of abbreviation

ABR	Auditory brain stem response testing
APEX	Arrayed primer extension
AQP 0-12	Aquaporin 0-12
ASSR	Auditory steady-state response testing
ATP	Adenosine TriPhosphate,
ATP1A1	ATPase, Na+/K+ transporting, alpha 1
ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide.
ATP1B2	ATPase, Na+/K+ transporting, beta 2 polypeptide.
ATP6V1B1	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit.
ATPV0A4	ATPase, H+ transporting, lysosomal V0 subunit a4.
BDNF	Brain-derived neurotrophic factor
BOA	Behavioral observation audiometry
ClCNKA	Chloride channel Ka CLCNKA, is a member of the CLC family of voltage-gated chloride channels.
ClCNKB	Chloride channel Kb (CLCNKB), is a member of the CLC family of voltage-gated chloride channels
CMV	Cytomegalovirus
CNS	Central nervous system
CT	Computed Tomography
CVS	Chorionic villus sampling
Cx26	Connexin 26

Cx30	Connexin 30
Cx43, 45, 29	Connexin 43, 45, 29
ECG	Electro-cardiography
EM	Electron microscopy
EOAEs	Evoked otoacoustic emissions
EP	Endocochlear potential
FISH	fluorescent in situ hybridization
GDNF	Glial cell-derived neurotrophic factor
GJ	Gap Junction
GJA1, A7	Gap Junction A1, A7
GJB2	Gap junction B2
GJB6	Gap junction B6
GJE1	Gap junction E1
Hath1	human atonal homologue 1
HIOMT	Hydroxyindole-O-methyl transferase
IHC	Inner hair cells
JLNS	Jervell and Lange-Nielsen Syndrome
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1.
KCNJ10	Potassium inwardly-rectifying channel, subfamily J, member 10.
KCNMA1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNN2	Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2.
KCNQ1	a potassium channel protein coded for by the gene KCNQ1
KCNQ4	Potassium voltage-gated channel, KQT-like subfamily, member 4.

KID	Keratitis-ichthyosis-deafness syndrome
Math1	Mouse atonal homologue1
MRI	Magnetic Resonance Imaging
NBHS	Newborn Hearing Screening
NIHL	Noise-induced hearing loss
NF-κB	Nuclear factor κB
NT-3	Neurotrophins
OAEs	Oto-acoustic Emissions
OHC	Outer hair cells
P2X	P2X receptors are a family of cation-permeable ligand gated ion channels
P2Y4	Pyrimidinergic receptor P2Y, G-protein coupled, 4.
ROS	reactive oxygen species
SGC	Spiral Ganglion Cell Survival
SLC12A2	Na-K-Cl Co-transporter
SLC26A4	Pendrin also known as solute carrier family 26, member 4.
SNHL	Sensorineural hearing loss
TRPV5 and TRPV6	Transient receptor potential V5 and V6
TSH	Thyroid stimulated hormones
VRA	visual reinforcement audiometry

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Introduction

Understanding how the cochlea works as a system has become increasingly important. We should know this before integrating new information from genetic, physiological and clinical sources. All fundamental physiological processes are based on the ability of cells to receive, process, and transmit signals ***(Ashmore, 2008).***

Sensory hair cells convert mechanical stimulation into electrical signals. The sound waves deflect the stereocilia on top of the hair cells**.** Deflection of these stereocilia opens mechano-sensitive potassium ion channels that convert the mechanical signal into an electrical signal. Calcium ions then enter the cell through voltage gated channels and depolarize the cell. This influx of calcium ions causes neurotransmitters to be released across the cell terminal membrane and an action potential is generated ***(Stauffer & Holt 2007)***.

Homeostatic regulation of ion gradients is critical for most functions. Due to their charge, the movement of ions across biological membranes necessarily involves facilitation by transport protein channels. Ion channels are integral membrane proteins that form a pore to allow the passage of specific ions and electrical charge. Plasma membrane channels are important for electrical excitability and trans-epithelial transport. There are hundreds of different ion channels and they are distinguished based upon their ion selectivity, gating mechanism, and sequence similarity. Ion channels can be voltage-gated, ligand-gated, pH-gated, or mechanically gated ***(Dubyak, 2004).***

Molecular biology provided the techniques to identify genes encoding ion channels, and as a result, a plethora of channels has been discovered to be critical to the physiological function of virtually every tissue, controlling such diverse functions as hearing. The combination of genetic identification of

multiple channel genes made it possible to extend understanding of the roles of molecular structures in the control of channel function. Diseases caused by mutations in genes that encode ion channel subunits or regulatory proteins are referred to as channelopathies, as might be expected based on the diverse roles of ion channels. The term channelopathy has been introduced to indicate that these syndromes and diseases share a common molecular defect and may therefore be viewed as similar pathophysiological entities ***(Bernard & Shevell 2008).***

During the past 50 years, understanding the roles and molecular structure of ion channels has grown at a rapid pace and has bridged fundamental basic research with advances in clinical medicine. The link between basic science and clinical medicine has been the discovery of human diseases linked to mutations in genes coding for ion channel subunits or proteins that regulate them **(*Kass 2005).***

The auditory system is a remarkable feat of engineering capable of detecting motion at the atomic level and transmitting this information to the brain with precise timing and fidelity, by using advanced electrophysiological, imaging, molecular and pharmacologic techniques to probe mechanisms of mechanotransduction and synaptic transmission at the auditory periphery ***(Ricci et al., 2005).***

Aim of the work

- To review selected disorders caused by mutations that result in defective ion channel function, regulation, or expression.

CHAPTER (1) Functional Anatomy of Inner Ear

Inner Ear is the sensory system for sound, motion, and gravity. It is housed within the temporal bone and consists of the cochlea, vestibular labyrinth, and endolymphatic sac (Fig. 1). The inner ear comprises an array of interconnected fluid compartments that are enclosed by a multitude of highly specialized epithelial cells ***(Highstein et al., 2004).***

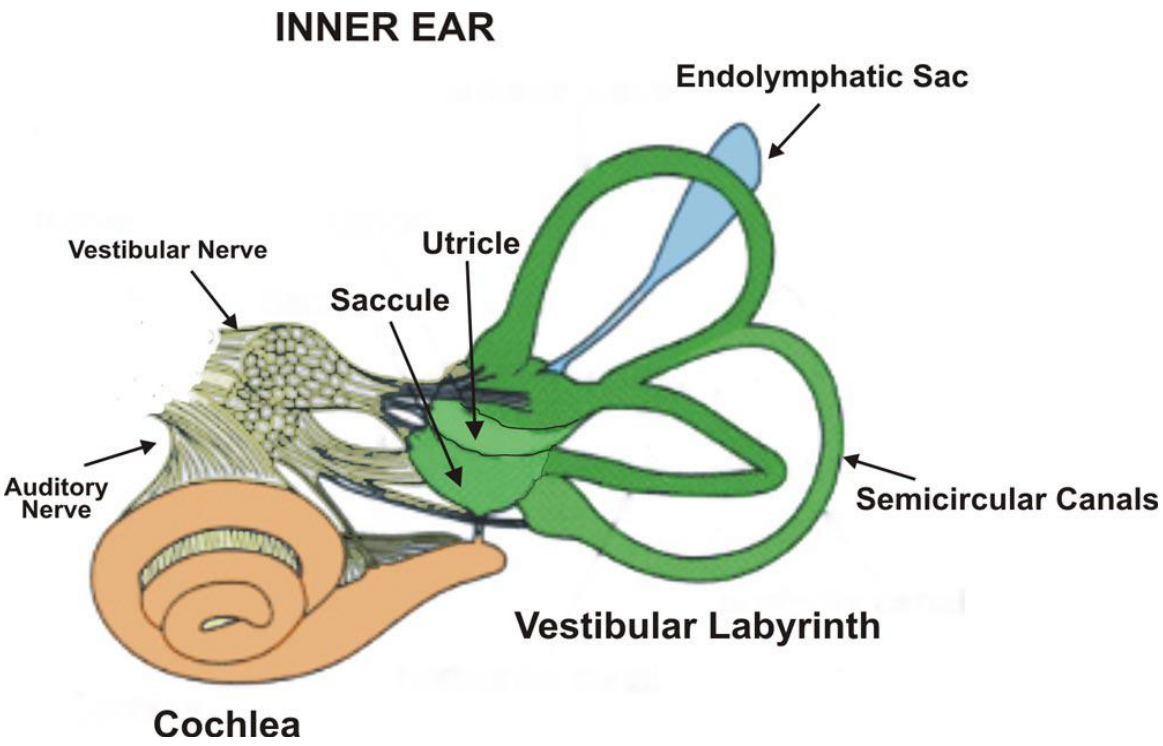

Figure (1): Inner ear compartment ***(Highstein et al., 2004).***

Inner Ear Fluids

Three extracellular fluids have been identified in the cochlea: endolymph, perilymph and intrastrial fluid (Table 1)**.** Endolymph fills scala media of the cochlea. Intrastrial fluid fills the small extracellular spaces within stria vascularis. Perilymph fills scala vestibuli and scala tympani and is continuous with all extracellular spaces of the cochlea except those that are filled with blood, endolymph or intrastrial fluid ***(Wangemann, 2006).***

Table (1): Composition of cochlear fluid:

Component	Unit	Endolymph scala media	Intrastrial fluid	Perilymph scala vestibule	Perilymph scala tympani	Plasma
Na^+	(mM)	1.3	85	141	148	145
K^+	(mM)	157	2	6.0	4.2	5.0
Ca^{2+}	(mM)	0.023	0.8	0.6	1.3	2.6
Cl^-	(mM)	132	55	121	119	106
HCO_3^-	(mM)	31	n.a.	18	21	18
Glucose	(mm)	0.6	n.a.	3.8	3.6	8.3
pH	(pH units)	7.4	n.a.	7.3	7.3	7.3
Protein	(mg / dl)	38	n.a.	242	178	4238

[Wangemann, 2006]

Endolymph is not only an unusual extracellular fluid for its high K^+ and low Na^+ concentration but also for its low Ca^{2+} concentration, high HCO_3^- concentration and low protein content. The significance of the high HCO_3^- concentration may be related to the need for pH buffering. The low Ca^{2+} concentration is critical for sensory transduction in the cochlea. Ca^{2+} enters the hair bundle together with K^+ and is necessary for the generation of the mechano-electrical transduction current as well as for adaptation of the transduction mechanism ***(Ricci & Fettiplace, 1998).***

Mechanism of Audition

The sensation of balance and hearing is initiated by the conversion of the movement of stereocilia on hair cells of the inner ear into electrical signals and release neurotransmitters to activate sensory neurons leading to the brain. This movement is driven by pressure waves that are generated by sound, head movement, or gravity, this transformation of energy occurs in very complex and delicate structures, where movements of atomic dimensions result in perception ***(Kharkovets et al., 2000).***