Journal of Otology 17 (2022) 54–58

Contents lists available at ScienceDirect

Journal of Otology

journal homepage: www.journals.elsevier.com/journal-of-otology/

Review

Molecular mechanisms and roles of inflammatory responses on low-frequency residual hearing after cochlear implantation

Juanjuan Gao, Haijin Yi*

Department of Otolaryngology, Head & Neck Surgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, 102218, China

ARTICLE INFO

Article history:
Received 23 December 2020
Received in revised form
25 February 2021
Accepted 2 March 2021

Keywords:
Low-frequency residual hearing loss
Cochlear implantation
Electro-acoustic stimulation (EAS)
Inflammatory response
Blood labyrinth barrier (BLB)

ABSTRACT

Preservation of low-frequency residual hearing is very important for combined electro-acoustic stimulation after cochlear implantation. However, in clinical practice, loss of low-frequency residual hearing often occurs after cochlear implantation and its mechanisms remain unclear. Factors affecting low-frequency residual hearing after cochlear implantation are one of the hot spots in current research. Inflammation induced by injury associated with cochlear implantation is deemed to be significant, as it may give rise to low-frequency residual hearing loss by interfering with the blood labyrinth barrier and neural synapses. Pathological changes along the pathway for low-frequency auditory signals transmission may include latent factors such as damage to neuroepithelial structures, synapses, stria vascularis and other ultrastructures. In this review, current research on mechanisms of low-frequency residual hearing loss after cochlear implantation and possible roles of inflammatory responses are summarized.

Contents

1. Introduction 55
2. Current research on mechanisms of low-frequency residual hearing loss after cochlear implantation 55
   2.1. Inflammation induced by cochlear implantation stimulates fibrosis and ossification of endocochlear tissue and increases acoustic energy conduction impedance 55
   2.2. Injury to the stria vascularis and blood-labyrinth barrier after cochlear implantation in low-frequency residual hearing loss 55
   2.3. Synaptic injury caused by electrical stimulation may influence residual hearing 55
3. The role and possible mechanisms of inflammatory response in low-frequency residual hearing loss 56
   3.1. Rationale behind inflammatory response affecting low-frequency residual hearing 56
   3.2. EIT-induced inflammation destroying the BLB and interfering with ion balance is a possible mechanism of low-frequency residual hearing loss 56
      3.2.1. Structural features of the BLB and hearing protection 56
      3.2.2. Inflammation destroying the integrity of the BLB and disturbing EP and ion balance may be a mechanism of low-frequency residual hearing loss 56
   3.3. EIT-induced inflammation injuring synapses may be a possible mechanism of low-frequency residual hearing loss 56
      3.3.1. Structure and function of synapses and hearing protection 56
      3.3.2. Inflammatory stimulation may injure synaptic function and cause low-frequency residual hearing loss 56
      3.3.3. Correlation between inflammatory response and electrical stimulation in inner ear injury 57
4. Conclusion 57
   Statement of ethics 57
   Funding sources 57
   Author contributions 57

* Corresponding author. No.168 Litang Road, Changping District, Beijing, 102218, China.
E-mail address: dl7599@163.com (H. Yi).
Peer review under responsibility of PLA General Hospital Department of Otolaryngology Head and Neck Surgery.

https://doi.org/10.1016/j.joto.2021.03.001

Declaration of competing interest . . . 57
Acknowledgement . . . 57
References . . . 57

1. Introduction

Cochlear implantation technology enables patients to regain sound perception by bypassing damaged hair cells and stimulating the spiral ganglion through implanted electrodes, which is of great benefit to patients with severe to profound hearing impairment, often affecting higher frequencies. With advancements in technology, electro-acoustic stimulation (EAS) for patients with residual low-frequency hearing has become the focus of future development. Through combined use of cochlear implants for medium- and high-frequency hearing and acoustic stimulation to take advantage of residual low-frequency hearing (Gantz and Turner, 2003; Kiefer et al., 2005; Turner et al., 2008; von Ilberg et al., 1999; von Ilberg et al., 2011), speech perception and music appreciation can be substantially improved (Baumann and Helbig, 2009; de Carvalho et al., 2013; Mertens et al., 2014), with outcomes significantly superior to using cochlear implants alone. Preservation of residual low-frequency hearing is essential to take full advantage of EAS. However, in clinical practice, low-frequency residual hearing is often lost after cochlear implantation. Gstoettner et al. studied residual hearing changes in 23 patients on EAS, and found 5 (21.7%) had delayed hearing loss (Gstoettner et al., 2009). In a multicenter study conducted by the FDA, 75% of the patients had delayed low-frequency hearing loss, and 10% had complete low-frequency hearing loss after cochlear implantation (Yao et al., 2006; Woodson et al., 2010). Gantz also pointed out that nearly a third of EAS users experienced delayed, progressive or fluctuating residual hearing loss over weeks to months after operation (Gstoettner et al., 2009; Gantz et al., 2009, 2016; Santa Maria et al., 2013). As mechanisms of low-frequency residual hearing loss following cochlear implantation remain unclear, identification of factors affecting low-frequency residual hearing after cochlear implantation is a subject of great interest to researchers.

2. Current research on mechanisms of low-frequency residual hearing loss after cochlear implantation

Low-frequency residual hearing loss after cochlear implantation is related to injury associated with the operation (O'Leary et al., 2013; Nakagawa et al., 2014; Kopelovich et al., 2015; Eshraghi et al., 2013), but the specific mechanism remains unknown. Recent studies have confirmed that it may be caused by the following mechanisms: fibrosis caused by electrode-insertion trauma (EIT), stimulation or new bone formation resulting in changes in cochlear mechanical sound transmission; post-EIT inflammation or immunogenicity (O'Leary et al., 2013); delayed intrastriatal microvascular injury (Nakagawa et al., 2014); or chronic electrical stimulation injury (Kopelovich et al., 2015; Eshraghi et al., 2013). However, the topic is still controversial.

2.1. Inflammation induced by cochlear implantation stimulates fibrosis and ossification of endocochlear tissue and increases acoustic energy conduction impedance

EIT can induce chronic inflammation, which can lead to hyperplasia and fibrosis of extracellular matrix and fibrocytes proliferation, resulting in low-frequency hearing loss (O'Leary et al., 2013; Ueha et al., 2012; James et al., 2008; Bas et al., 2016; Seyyedi and Nadol, 2014). By analyzing temporal bone tissue sections from patients with cochlear implants, Quesnel and Scheperle et al. found that low-frequency hearing loss may be related to increase of impedance and decrease of acoustic energy transmitted to the apical turn caused by fibrosis in the scala tympani. However, they also pointed out that not all low-frequency hearing loss is related to this factor (Quesnel et al., 2016; Scheperle et al., 2017).

2.2. Injury to the stria vascularis and blood-labyrinth barrier after cochlear implantation in low-frequency residual hearing loss

The stria vascularis and blood-labyrinth barrier (BLB) play a crucial role in maintaining endocochlear homeostasis, which produces endocochlear potential (EP), endolymph formation, and secretion and circulation of K^+(Shi, 2016; Zhang et al., 2012). EIT can cause injury to the stria vascularis in the lateral cochlear wall and induce inflammation, thus affecting auditory function (Wright and Roland, 2013). In a study in 2014, Tanaka revealed that cochlear implantation can lead to a decrease in vascular density in the stria vascularis and result in high-frequency hearing loss (Tanaka et al., 2014). However, there is a lack of experimental evidence supporting the theory that injury to the stria vascularis and BLB is correlated with low-frequency residual hearing loss (Zhang et al., 2015a, 2015b). Further research is needed in this area.

2.3. Synaptic injury caused by electrical stimulation may influence residual hearing

Inner hair cells form synaptic connections with type I afferent fibers and play a major role in the afferent pathway along the auditory nerve. Injury to apical turn synaptic structures may lead to low-frequency residual hearing loss. Based on animal experiments, hearing loss at 1 kHz occurs in normal or (noise-induced) deaf guinea pigs after chronic electrical stimulation with cochlear electrodes (Tanaka et al., 2014; Reiss et al., 2015). Histological studies showed that hearing loss was not correlated with the number of hair cells or spiral neurons, but significantly correlated with a decrease in the number of ribbon synapses and postsynaptic receptors on inner hair cells (Reiss et al., 2015); hence, synaptic injury caused by electrical stimulation may be one of the factors behind low-frequency residual hearing loss. Shen et al. indicated that the mechanism of synaptic injury caused by electrical stimulation may be related to abnormal opening of calcium channels (Shen et al., 2016). Reiss, on the other hand, believed that the synaptic structure was more likely to be affected by electrical stimulation due to the impact of inflammation (Reiss et al., 2015), but there is a lack of experimental evidence to support this theory. EIT-induced inflammation may spread to synapses, so it is necessary to study the effect and mechanism of inflammation on synapses.

3. The role and possible mechanisms of inflammatory response in low-frequency residual hearing loss

3.1. Rationale behind inflammatory response affecting low-frequency residual hearing

It has been confirmed that inflammatory response plays a vital role in cochlear pathophysiology, and that an increase in inflammatory factors can damage the cochlear ultrastructure (Tan et al., 2016; Fuentes-Santamaria et al., 2017). Cochleitis caused by noise and ototoxic drugs is characterized by increased levels of cytokines and chemokines as well as leukocyte infiltration (Tan et al., 2016; Wood and Zuo, 2017), which can lead to aggravation of cochlear injury and hearing loss (Kalinec et al., 2017). Corticosteroids or nonsteroidal anti-inflammatory drugs are current treatment options. For instance, aspirin can inhibit overreaction and therefore reduce hearing loss, which further proves that cochleitis can result in hearing loss (Kalinec et al., 2017). Insertion trauma during cochlear implantation may also induce an inflammatory response and increase expression of inflammatory factors, including IL-1β, TNF-α or other proinflammatory cytokines(Jia et al., 2013), which may lead to low-frequency hearing loss. In 2016, Bas et al. claimed that by designing special cochlear implant electrodes that enable the long-term sustained release of corticosteroids to slow down inflammatory response, low-frequency residual hearing can be effectively protected (Bas et al., 2016). This study inversely proved that inflammation induced by cochlear implantation can give rise to low-frequency hearing loss, but the specific mechanism of injury remains unclear. Some researchers believe that inflammatory factors such as TNFa are involved in apoptosis of hair cells and supporting cells (Bas et al., 2012a, 2012b), thus damaging hearing; whereas Alicia and Rachel have suggested that there is no correlation between hearing loss after cochlear implantation and the numbers of hair cells and spiral neurons (Quesnel et al., 2016; Scheperle et al., 2017). The above conclusions are not completely consistent, and there is a lack of direct experimental data on low-frequency hearing loss caused by inflammatory injury to ultrastructures such as synapses.

3.2. EIT-induced inflammation destroying the BLB and interfering with ion balance is a possible mechanism of low-frequency residual hearing loss

3.2.1. Structural features of the BLB and hearing protection

As previously stated, the unique structures of the BLB play a crucial role in maintaining endocochlear homeostasis, important for EP, endolymph formation and K^+ secretion and circulation of (Zhang et al., 2012). These structures mainly include perivascular-resident macrophage-like melanocytes (PVM/Ms), tight junction proteins, and ion channel-associated proteins (Shi, 2016). PVM/Ms are cells in the middle layer of the cochlear stria vascularis that have properties of both macrophages and melanocytes, which have a similar function as that of astrocytes on the BLB. Loss of PVM/Ms results in destruction of tight junctions and tissue edema, affecting the establishment and maintenance of EP (Zhang et al., 2012). Tight junctions are the material basis for selective permeability by epithelial cells (Kitajiri et al., 2004). Together with various ion channel-associated proteins, including aquaporin water channels Aqp1 and Aqp3 and amiloride-sensitive sodium channel protein Scnn1 γ, tight junctions maintain ion concentration differences, high potassium concentration, and balance between endolymph and perilymph (Jeon et al., 2011). It has been proven that absence of claudin can greatly affect tight junctions in mice, leading to a failure to maintain normal EP (Liu et al., 2017). Additionally, matrix metalloproteinases (MMPs) are a class of zinc-dependent endopeptidases that can degrade extracellular matrix components. Under noise or other damage conditions, expression of MMPs is upregulated, which can downregulate expression of tight junction proteins to destroy BLB, making MMPs one of the markers of BLB injury (Hu et al., 2012; Wu et al., 2017).

3.2.2. Inflammation destroying the integrity of the BLB and disturbing EP and ion balance may be a mechanism of low-frequency residual hearing loss

The relationship between the BLB and low-frequency residual hearing is a hot spot in current research (Shi, 2016; Zhang et al., 2012, 2015a, 2015b; Wright and Roland, 2013; Tanaka et al., 2014). The high concentration of potassium ions in EP and endolymph is necessary for smooth hair cell electromechanical conversion. If the process is disrupted by inflammation, auditory function will be seriously affected. Experiments have proven that inflammation can destroy the integrity of stria vascularis and BLB while disturbing EP and ions balance. According to studies by Wright et al. and Zhang et al. published in 2013 and 2015, respectively, lipopolysaccharide-induced otitis media spreading to the inner ear through the oval window can downregulate expression of tight-junction proteins and increase permeability of the BLB (Wright and Roland, 2013; Zhang et al., 2015a). Zhang and Stark et al. conducted a study on hearing loss caused by EIT-induced inflammation destroying the BLB, in which the experiment data revealed that hearing in guinea pigs decreased rapidly after cochlear implantation (Zhang et al., 2015b). At different points in time, expression of cochlear inflammatory factor genes and ion homeostasis genes (Scnn1 γ, Aqp1 and Aqp3) dramatically increased, and tissue remodeling genes were upregulated (Zhang et al., 2015b). These findings indicate that an increase in MMP9 is related to high-frequency hearing loss. This experiment showed that EIT-induced inflammation could cause hearing loss by destroying the BLB and affecting EP and ion homeostasis. However, the study was limited in that the observation lasted only 2 weeks. Given that the impact of EIT-induced inflammation on low-frequency residual hearing is usually progressive and delayed (Gstoettner et al., 2009; Yao et al., 2006; Woodson et al., 2010; Gantz et al., 2016; Gantz et al., 2009; Santa Maria et al., 2013; O'Leary et al., 2013; Nakagawa et al., 2014; Kopelovich et al., 2015; Eshraghi et al., 2013), it is necessary to further study low-frequency residual hearing loss caused by inflammation impacting BLB.

3.3. EIT-induced inflammation injuring synapses may be a possible mechanism of low-frequency residual hearing loss

3.3.1. Structure and function of synapses and hearing protection

After depolarization of inner hair cells, opening of calcium channels on the presynaptic membrane causes a calcium influx (Frank et al., 2009), releases glutamate to activate glutamate receptors on the postsynaptic membrane, and generates excitatory conduction (Traynelis et al., 2010), marking the beginning of the excitatory conduction pathway of the auditory nerve. Recent studies indicate that noise-induced, age-related, and drug-induced deafness is related to synaptic injuries and abnormal expression of ribbon synapses. The intensity of synaptic transmission is determined by the release of neurotransmitters by synaptosomes and corresponding receptors on the postsynaptic membrane. Hearing loss may occur if inflammation disturbs the process and intensity of synaptic transmission (Reiss et al., 2015).

3.3.2. Inflammatory stimulation may injure synaptic function and cause low-frequency residual hearing loss

The relationship between synapses and hearing is a main focus of current research (Tanaka et al., 2014; Reiss et al., 2015; Shen et al.,

2016). Previous studies focused on the number of synapses injured by chronic electrical stimulation leading to hearing loss and showed that inflammatory response in the cochlea may cause synaptic injury. Studies on the Duffy antigen receptor for chemokines (DARC) have further verified that inflammation can damage synapses and cause low-frequency hearing loss. The DARC is a transmembrane protein expressed in vascular endothelium of various organs, red blood cells and some epithelial cells, which can mediate inflammatory response (Bao et al., 2009; Harrison et al., 2011; Karsten et al., 2018). Edderkaoui applied gene knockout techniques to create a DARC-deficient mouse model for studies on injury of hair cells and synapses by noise-induced inflammation (Edderkaoui et al., 2018). Their data demonstrated that injury of synapses by noise-induced inflammation could be inhibited in mice lacking DARC-mediated inflammatory response after knockout of the DARC gene, thus preventing low-frequency hearing loss (Edderkaoui et al., 2018). Hence, it is believed that cochlear inflammation can damage synapses and therefore affect low-frequency hearing. This is consistent with the results in the latest studies by Kujawa and Liberman (Kujawa and Liberman, 2009, 2015; Liberman and Kujawa, 2017), which verified that noise-induced cochlear inflammation can lead to synaptic injury and low-frequency hearing loss. EIT-induced inflammatory response may cause synaptic injury theoretically, thereby causing low-frequency residual hearing loss.

3.3.3. Correlation between inflammatory response and electrical stimulation in inner ear injury

One of the important differences between cochlear inflammation caused by cochlear implantation and that caused by other factors is that there will be chronic continuous electrical stimulation after cochlear implantation. Yet, the correlation between inflammatory response and electrical stimulation in injury of inner ear ultrastructures remains unknown. It has been proven that electrical stimulation after cochlear implantation can give rise to a decrease in ribbon synapses and postsynaptic receptors (Tanaka et al., 2014; Reiss et al., 2015). Shen et al. revealed that electrical stimulation could cause abnormal opening of calcium channels (Shen et al., 2016). Reiss held that there was a correlation between inflammation and electrical stimulation and that inflammatory stimulation might make synapses more vulnerable to electrical stimulation (Reiss et al., 2015). No experimental evidence is available to support this, however, further studies are needed to confirm whether electrical stimulation can cause injury to ultrastructures of the BLB, such as PVM/Ms and ion channel proteins, and the role of inflammation.

4. Conclusion

In summary, there is a wide variety of factors influencing low-frequency residual hearing loss, and existing research cannot fully explain the mechanism of its occurrence. In theory, when sound waves reach the vestibular window, the basilar membrane of the apical turn (corresponding to the low-frequency hearing threshold) produces receptor potential by vibration. Pathological changes in any part along the low-frequency auditory transduction pathway, from synaptic release of neurotransmitters to the spiral ganglion, can impact low-frequency residual hearing. Inflammation induced by post-cochlear implantation injury is deemed to be significant, as it may give rise to low-frequency residual hearing loss by interfering with the BLB and synapses. Further research is needed to determine the specific mechanism involved.

Statement of ethics

Declared none.

Funding sources

Declared none.

Author contributions

Conception: Haijin Yi. Data collection and writing the article: Juanjuan Gao and Haijin Yi.

Declaration of competing interest

The authors confirm that this article content has no conflicts of interest.

Acknowledgement

Declared none.

References

Bao, P., Kodra, A., Tomic-Canic, M., et al., 2009. The role of vascular endothelial growth factor in wound healing. J. Surg. Res. 153 (2), 347–358.
Bas, E., Dinh, C.T., Garnham, C., et al., 2012a. Conservation of hearing and protection of hair cells in cochlear implant patients' with residual hearing. Anat. Rec. 295 (11), 1909–1927.
Bas, E., Gupta, C., Van De Water, T.R., 2012b. A novel organ of corti explant model for the study of cochlear implantation trauma. Anat. Rec. 295 (11), 1944–1956.
Bas, E., Bohorquez, J., Goncalves, S., et al., 2016. Electrode array-eluted dexamethasone protects against electrode insertion trauma induced hearing and hair cell losses, damage to neural elements, increases in impedance and fibrosis: a dose response study. Hear. Res. 337, 12–24.
Baumann, U., Helbig, S., 2009. Hearing with combined electric acoustic stimulation. Hno 57 (6), 542–550.
de Carvalho, G.M., Guimaraes, A.C., Duarte, A.S., et al., 2013. Hearing preservation after cochlear implantation: unicamp outcomes. Int. J. Otolaryngol. 2013, 107186.
Edderkaoui, B., Sargsyan, L., Hetrick, A., et al., 2018. Deficiency of duffy antigen receptor for chemokines ameliorated cochlear damage from noise exposure. Front. Mol. Neurosci. 11, 173.
Eshraghi, A.A., Gupta, C., Van De Water, T.R., et al., 2013. Molecular mechanisms involved in cochlear implantation trauma and the protection of hearing and auditory sensory cells by inhibition of C-Jun-N-terminal kinase signaling. Laryngoscope 123 (Suppl. 1), S1–S14.
Frank, T., Khimich, D., Neef, A., et al., 2009. Mechanisms contributing to synaptic Ca2+ signals and their heterogeneity in hair cells. Proc. Natl. Acad. Sci. U. S. A. 106 (11), 4483–4488.
Fuentes-Santamaria, V., Alvarado, J.C., Melgar-Rojas, P., et al., 2017. The role of glia in the peripheral and central auditory system following noise overexposure: contribution of Tnf-alpha and Il-1beta to the pathogenesis of hearing loss. Front. Neuroanat. 11 (9).
Gantz, B.J., Turner, C.W., 2003. Combining acoustic and electrical hearing. Laryngoscope 113 (10), 1726–1730.
Gantz, B.J., Hansen, M.R., Turner, C.W., et al., 2009. Hybrid 10 clinical trial: preliminary results. Audiol. Neuro. Otol. 14 (Suppl. 1), 32–38.
Gantz, B.J., Dunn, C., Oleson, J., et al., 2016. Multicenter clinical trial of the nucleus hybrid S8 cochlear implant: final outcomes. Laryngoscope 126 (4), 962–973.
Gstoettner, W., Helbig, S., Settevendemie, C., et al., 2009. A new electrode for residual hearing preservation in cochlear implantation: first clinical results. Acta Otolaryngol. 129 (4), 372–379.
Harrison, S.L., Vavken, P., Murray, M.M., 2011. Erythrocytes inhibit ligament fibroblast proliferation in a collagen scaffold. J. Orthop. Res. 29 (9), 1361–1366.
Hu, B.H., Cai, Q., Hu, Z., et al., 2012. Metalloproteinases and their associated genes contribute to the functional integrity and noise-induced damage in the cochlear sensory epithelium. J. Neurosci. 32 (43), 14927–14941.
von Ilberg, C., Kiefer, J., Tillein, J., et al., 1999. Electric-acoustic stimulation of the auditory system. New technology for severe hearing loss. ORL J. Otorhinolaryngol. Relat. Spec. 61 (6), 334–340.
von Ilberg, C.A., Baumann, U., Kiefer, J., et al., 2011. Electric-acoustic stimulation of the auditory system: a review of the first decade. Audiol. Neuro. Otol. 16 (Suppl. 2), 1–30.
James, D.P., Eastwood, H., Richardson, R.T., et al., 2008. Effects of round window

dexamethasone on residual hearing in a Guinea pig model of cochlear implantation. Audiol. Neuro. Otol. 13 (2), 86–96.
Jeon, J.H., Park, J.W., Lee, J.W., et al., 2011. Expression and immunohistochemical localization of tmem16a/anoctamin 1, a calcium-activated chloride channel in the mouse cochlea. Cell Tissue Res. 345 (2), 223–230.
Jia, H., Wang, J., Francois, F., et al., 2013. Molecular and cellular mechanisms of loss of residual hearing after cochlear implantation. Ann. Otol. Rhinol. Laryngol. 122 (1), 33–39.
Kalinec, G.M., Lomberk, G., Urrutia, R.A., et al., 2017. Resolution of cochlear inflammation: novel target for preventing or ameliorating drug-, noise- and age-related hearing loss. Front. Cell. Neurosci. 11, 192.
Karsten, E., Hill, C.J., Herbert, B.R., 2018. Red blood cells: the primary reservoir of macrophage migration inhibitory factor in whole blood. Cytokine 102, 34–40.
Kiefer, J., Pok, M., Adunka, O., et al., 2005. Combined electric and acoustic stimulation of the auditory system: results of a clinical study. Audiol. Neuro. Otol. 10 (3), 134–144.
Kitajiri, S.I., Furuse, M., Morita, K., et al., 2004. Expression patterns of claudins, tight junction adhesion molecules, in the inner ear. Hear. Res. 187 (1–2), 25–34.
Kopelovich, J.C., Reiss, L.A., Etler, C.P., et al., 2015. Hearing loss after activation of hearing preservation cochlear implants might Be related to afferent cochlear innervation injury. Otol. Neurotol. 36 (6), 1035–1044.
Kujawa, S.G., Liberman, M.C., 2009. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J. Neurosci. 29 (45), 14077–14085.
Kujawa, S.G., Liberman, M.C., 2015. Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. Hear. Res. 330 (Pt B), 191–199.
Liberman, M.C., Kujawa, S.G., 2017. Cochlear synaptopathy in acquired sensorineural hearing loss: manifestations and mechanisms. Hear. Res. 349, 138–147.
Liu, W., Schrott-Fischer, A., Glueckert, R., et al., 2017. The human "cochlear battery" - claudin-11 barrier and ion transport proteins in the lateral wall of the cochlea. Front. Mol. Neurosci. 10, 239.
Mertens, G., Punte, A.K., Cochet, E., et al., 2014. Long-term follow-up of hearing preservation in electric-acoustic stimulation patients. Otol. Neurotol. 35 (10), 1765–1772.
Nakagawa, T., Kumakawa, K., Usami, S., et al., 2014. A randomized controlled clinical trial of topical insulin-like growth factor-1 therapy for sudden deafness refractory to systemic corticosteroid treatment. BMC Med. 12, 219.
O'Leary, S.J., Monksfield, P., Kel, G., et al., 2013. Relations between cochlear histopathology and hearing loss in experimental cochlear implantation. Hear. Res. 298, 27–35.
Quesnel, A.M., Nakajima, H.H., Rosowski, J.J., et al., 2016. Delayed loss of hearing after hearing preservation cochlear implantation: human temporal bone pathology and implications for etiology. Hear. Res. 333, 225–234.
Reiss, L.A., Stark, G., Nguyen-Huynh, A.T., et al., 2015. Morphological correlates of hearing loss after cochlear implantation and electro-acoustic stimulation in a hearing-impaired Guinea pig model. Hear. Res. 327, 163–174.
Santa Maria, P.L., Domville-Lewis, C., Sucher, C.M., et al., 2013. Hearing preservation surgery for cochlear implantation–hearing and quality of life after 2 years. Otol. Neurotol. 34 (3), 526–531.
Scheperle, R.A., Tejani, V.D., Omtvedt, J.K., et al., 2017. Delayed changes in auditory status in cochlear implant users with preserved acoustic hearing. Hear. Res. 350, 45–57.
Seyyedi, M., Nadol Jr., J.B., 2014. Intracochlear inflammatory response to cochlear implant electrodes in humans. Otol. Neurotol. 35 (9), 1545–1551.
Shen, N., Liang, Q., Liu, Y., et al., 2016. Charge-balanced biphasic electrical stimulation inhibits neurite extension of spiral ganglion neurons. Neurosci. Lett. 624, 92–99.
Shi, X., 2016. Pathophysiology of the cochlear intrastrial fluid-blood barrier (review). Hear. Res. 338, 52–63.
Tan, W.J., Thorne, P.R., Vlajkovic, S.M., 2016. Characterisation of cochlear inflammation in mice following acute and chronic noise exposure. Histochem. Cell Biol. 146 (2), 219–230.
Tanaka, C., Nguyen-Huynh, A., Loera, K., et al., 2014. Factors associated with hearing loss in a normal-hearing Guinea pig model of hybrid cochlear implants. Hear. Res. 316, 82–93.
Traynelis, S.F., Wollmuth, L.P., McBain, C.J., et al., 2010. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol. Rev. 62 (3), 405–496.
Turner, C., Gantz, B.J., Reiss, L., 2008. Integration of acoustic and electrical hearing. J. Rehabil. Res. Dev. 45 (5), 769–778.
Ueha, S., Shand, F.H., Matsushima, K., 2012. Cellular and molecular mechanisms of chronic inflammation-associated organ fibrosis. Front. Immunol. 3, 71.
Wood, M.B., Zuo, J., 2017. The contribution of immune infiltrates to ototoxicity and cochlear hair cell loss. Front. Cell. Neurosci. 11, 106.
Woodson, E.A., Reiss, L.A.J., Turner, C.W., et al., 2010. The hybrid cochlear implant: a review. Adv. Oto-Rhino-Laryngol. 67, 125–134.
Wright, C.G., Roland, P.S., 2013. Vascular trauma during cochlear implantation: a contributor to residual hearing loss? Otol. Neurotol. 34 (3), 402–407.
Wu, J., Han, W., Chen, X., et al., 2017. Matrix metalloproteinase-2 and -9 contribute to functional integrity and noiseinduced damage to the blood-labyrinth-barrier. Mol. Med. Rep. 16 (2), 1731–1738.
Yao, W.N., Turner, C.W., Gantz, B.J., 2006. Stability of low-frequency residual hearing in patients who are candidates for combined acoustic plus electric hearing. J. Speech Lang. Hear. Res. 49 (5), 1085–1090.
Zhang, W., Dai, M., Fridberger, A., et al., 2012. Perivascular-resident macrophage-like melanocytes in the inner ear are essential for the integrity of the intrastrial fluid-blood barrier. Proc. Natl. Acad. Sci. U. S. A. 109 (26), 10388–10393.
Zhang, J., Chen, S., Hou, Z., et al., 2015a. Lipopolysaccharide-induced middle ear inflammation disrupts the cochlear intra-strial fluid-blood barrier through down-regulation of tight junction proteins. PLoS One 10 (3), e0122572.
Zhang, H., Stark, G., Reiss, L., 2015b. Changes in gene expression and hearing thresholds after cochlear implantation. Otol. Neurotol. 36 (7), 1157–1165.