**A Brief Conceptual Approach to Inner Ear Drug Delivery System**

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**INTRODUCTION**

The factors like environmental pollution, highly aging population, maximum exposure to harsh noise in the youth mass and vulnerability to ototoxic life caring compounds such as antibiotics, amino glycosides and certain chemotherapy treatments e.g. platinum chemotherapy, amplifying the concealing disability occurred due to loss of hearing. The inner ear drug delivery system(IEDDS) had been a matter of concern to physicians as well as to researchers in the diagnosis of inner ear complications. In the last few decades, novel biomaterials and advanced drug delivery applications has been developed for the loss of hearing ability. Previously two decades, huge progress had been achieved in perception and verifying the mechanisms of loss of hearing at its molecular and cellular level. Multiple favourable attempts have been made towards restoration of hearing loss; focusing in sustaining rejuvenation of the concerned cells and various cochlear nerve endings. The objective of the current chapter is to deliver a futuristic general recapitulation of IEDD and discussing their potential in recent advances in biomaterials, bio-technological methods and delivery technologies.



 Fig.1: Anatomy of Inner Ear

**Routes of administration for inner ear drug delivery**

1. **Systemic route:** Usually, many otic drugs are delivered to the inner ear through the systemic route, however only few drugs may reach to site of target at its therapeutic concentrations due to the presence of Blood Labyrinth Barrier(BLB) which is a significant barrier separating the inner ear from systemic circulation with its highly tight junctions, made from endothelial capillary cells which lines beneath the blood vessels located in the *stria vascularis*. In order to attain the therapeutic concentrations of drugs in the inner ear requires high systemic doses, which has been often combined with infelicity side effects. This type of systemic related toxicities and side effects may range from minor problem to feasible life- threatening conditions. In spite of these side effects, systemic medication through intravenous, intramuscular and oral routes are still regarded as the most convenient route of drug targeting to the inner ear and is currently conceded as the primary line avenue in the diagnosis of inner ear disorders.
2. **Intra-tympanic route:** Specifically the subject of diagnosing inner-ear disorders by local drug delivery system attracts the attention of research. Intra tympanic drug delivery to the inner ear was executed through the perfusion or injection of the medicament to the middle ear with the target of drug diffusion via Round Window Membrane; which is a soft tissue barrier dividing the middle ear from the inner ear. This kind of drug targeting introduced half a century ago for the treatment of Meniere’s disease (it is a type of disorder of the inner ear that can lead to dizzy spells and hearing loss) with local anaesthetics and antibiotics has been popularly used in clinics since 90s. This type of prospective technique possesses benefits over systemic drug delivery as this local drug delivery method can bypass the Blood Labyrinth Barrier and therefore result in higher drug concentrations in the inner ear fluids and can avoid undesired systemic exposures. Effective drug targetting to the inner ear through the intra-tympanic route also based on the contact time of the drug solution with the Round Window Membrane. But woefully, a large portions of the drugs administered are usually eliminated through the Eustachian tube which follows intra tympanic drug delivery. Hence, efforts have made to edge out these limitations during the development of devices and controlled-release drug delivery systems.
3. **Intra-cochlear route:** Corresponding to intra-tympanic delivery, the intra-cochlear delivery approach also gives an option to systemic drug delivery towards inner ear. The direct intra-cochlear drug delivery may detour the middle ear and permit the drugs to get to their expected sites directly. It may generally enhance drug’s bioavailability in the inner ear and having the higher efficiency among the inner ear targeting methods comprehended in this chapter. Miscellaneous intra-cochlear delivery technologies are now developed to enhance the efficiency of drug delivery to the inner ear. It includes parenteral preparations, osmotic mini-pumps, cochlear implants as well as reciprocating perfusions.

**Speculative approach of drug- device combination**

* It should have by pass the blood–brain barrier and can target organs directly.
* Appropriate drug concentration should reach into the inner ear
* Keeping away the first-pass effects
* Adverse systemic effects should be reduced
* Minimum drug doses are needed.
* Limiting the pain during insertion
* Reduced immune reaction
* Infection should be reduced
* Minimizing the damaging of spiral ganglion cells and auditory neurons
* It should decreases the chances of ossification and fibrosis
* Trimming of stimulation of non auditory neural structures
* Reduction of channel interaction

**Drug delivery technologies for inner ears**

1. **Cannula-based delivery systems:** Commercially various cannula-based drug delivery systems are available for sustained release of the drugs into to the middle ear. The devices for the above system include Microwick Silverstein and Round Window Micro catheter. The adverse effects of such devices includes persistent perforation of the tympanic membrane, risk of infection in the middle ear and there may be growth of the tissue i.e fibrosis in the middle ear or epithelial in growth which leads to cholesteatoma.
2. **Hydrogels:** The biodegradable gelatine polymer named Gelfoams was first introduced in the surgery of inner ear. The Gelfoams when soaked in gentamicin and placed on RWM proved to give improved outcome in the treatment Meniere’s disease as it is helpful to eliminate vertigo and tinnitus in 75% and 48% patients respectively. . In the second week of Gel- foams BDNF diagnosis the survival of spiral ganglion neurons (SGNs) in the inner ear was found to be in the low turn of the cochlea, but with having no specifically improvement was observed in the apical turn of the cochlea. This is probably due to the less amount of drug is reaching to the apical turn. This is recommended that local delivery of BDNF using Gelfoams can be able to protect the parts of the spiral ganglion neurons (SGNs) of cochlea.
3. **Stabilizing matrices:** The stabilizing matrices possess several benefits on middle ear perfusions. Unless using stabilizing matrices the drugs delivered to the middle ear got dispel out either by the absorption through the mucosal layer of middle ear or by drainage by the Eustachian tube. It’s a great matter of concern while using toxic agents for targeting them to the targeted tissues which allows superior control of dosing profiles, suggests future trans-tympanic delivery methodologies and gives focus on sustained release by using various techniques utilizing stabilizing gel matrices. A good example is Chitosan-glycerophosphate hydrogel is a novel example of a biodegradable gel which is liquid at room temperature and at body temperature it allows the drug to come in contact between the matrix and membrane of the inner ear i.e. round window membrane. The above material has successfully delivered dexamethasone to the inner ear through round widow membrane which has been proved by various studies carried out in mice.
4. **Cochlear Implants:** Intra-cochlear drug delivery has greater efficacy in comparison to cochlear implants in persons with deafness. Hearing can be restored by direct scala tympani delivery of dexamethasone for eight days which has loss due to insertion of electrode in the guinea pig basal turn, scala tympani with the brain-derived neuro trophic factor and fibroblast growth factor were infused into the guinea pig cochlea(basal turn, scala tympani) following deafening via a systemic amino glycoside and diuretic treatment. Scientists describe a drug targeting system integrated into a scala tympani electrode which has conspiracy for use in guinea pigs with demonstrated administration of neomycin.
5. **Nano particles**: The drug delivery system of Super Paramagnetic Iron Oxide Nano particles (SPIONs) via a three layered cellular Round Window Membrane model in vitro study showed SPIONs are sorted throughout the model membranes under an external magnetic field. In a different study it has been explored that the capability of ferro gel which consist of SPIONs and Pluronic with an illustrating tag for the delivery of many therapeutic substances across the Round Window Membrane of human temporal bones as well as in organo- typic explants cultures of rat’s inner ears. It has been found that the SPIONs were in the cytoplasmin organ which is suggesting that the nano particle system can be a suitable for cell targeted drug delivery system which prevents drug degradation in the cellendo lysosomal compartment. Some researchers has been showed that the cell targeting ability and toxicity of nerve growth factor-derived ligand functionalized with specific polymers and omenano- particles for specific cell targeting to SGNs in mouse cochlear organo typic culture and observed specific drug targeting various tissues.
6. **Stem Cell therapy:** The hearing loss can be restored by using the stem cell therapy, which has the potential to protect the hair cells and spiral ganglion neurons(SLNs).The stem cell therapy has been proved to be a prominent method to treat the inner ear disorders by replacing hair cells. It has been also recommended that the implantation of embryonic stem cells, foetal root ganglions and otocyst cells in the inner ear to restore the spoiled hair cells.

 **CONCLUSIONS**

Loss of hearing constitute one of the most ubiquitous requirements in all of medicine and research oriented topic which bringing new treatments to the field of medicine, which will require advances in therapies along with multiple fronts. The challenges required for the nature of the inner ear as a target for therapy which consequently achieving well being and efficacy. Problems encountered by the physicians treating inner ear diseases are almost similar to the difficulties faced during preclinical drug development, and delivery remains the central barrier to progress. The maintenance of control drug delivery cannot be possible without reliable command over the drug concentrations within the therapeutic window for longer periods of time, which is challenging to assess the efficacious and functionally assays for drug-treated various groups.

**References**

1. M. Peppia, A. Marieb, C. Bellineb and J. T. Borensteina. Intracochlear drug delivery systems: a novel approach whose time has come. Expert Opinion on Drug Delivery, 2018. VOL. 15, NO. 4, 319–324
2. Hongzhuo Liu, Jinsong Hao, KevinS.Li. Current strategies for drug delivery to the inner ear. Acta Pharmaceutica Sinica B. 2013;3(2):86–96
3. Ayoob AM, Borenstein JT. The role of intracochlear drug delivery devices in the management of inner ear disease. Expert Opin Drug Deliv. 2015;12(3):465–479.
4. Holley MC. Keynote review: the auditory system, hearing loss and potential targets for drug development. Drug Discov Today. 2005;10(19):1269–1282.
5. Plontke SK, Siedow N, Wegener R, et al. Cochlear pharmacokinetics with local inner ear drug delivery using a three-dimensional finiteelement computer model. Audiol Neurootol. 2007;12(1): 37–48.
6. Breglio AM, Rusheen AE, Shide ED, et al. Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nat Commun. 2017;8 (1):1654.
7. Crowson MG, Hertzano R, Tucci DL. Emerging therapies for sensorineural hearing loss. Otol Neurotol. 2017;38(6): 792–803.
8. Suckfuell M, Lisowska G, Domka W, et al. Efficacy and safety of AM-111 in the treatment of acute sensorineural hearing loss: a doubleblind, randomized, placebo-controlled phase II study. Otol Neurotol. 2014;35(8):1317–1326.
9. Oishi N, Schacht J. Emerging treatments for noise-induced hearing loss. Exp Opin Emerg Drugs. 2011;16(2): 235–245.
10. Mizutari K, Fujioka M, Hosoya M, et al. Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma. Neuron. 2013;77(1):58–69. PMCID: 3573859.
11. McLean WJ, Yin X, Lu L, et al. Clonal expansion of Lgr5-positive cells from mammalian cochlea and high-purity generation of sensory hair cells. Cell Rep. 2017;18(8):1917–1929.
12. Suzuki J, Corfas G, Liberman MC. Round-window delivery of neurotrophin 3 regenerates cochlear synapses after acoustic overexposure. Sci Rep. 2016;6: 24907.
13. Swan EE, MescherMJ, SewellWF,TaoSL,BorensteinJT. Inner ear drug delivery for auditory applications. Adv Drug Deliv Rev 2008;60:1583–99.
14. BorkholderDA. State-of-the-art mechanisms of intra cochlear drug delivery. Curr Opin Otolaryngol Head Neck Surg 2008;16:472–7.
15. Salt AN, PlontkeSK. Principles of local drug delivery to the inner ear. Audiol Neurootol 2009;14:350–60.
16. McCall AA, SwanEE, BorensteinJT, SewellWF, KujawaSG, McKenna MJ. Drug delivery for treatment of inner ear disease: current state of knowledge. Ear Hear 2010;31:156–65
17. Jackson LE, Silverstein H: Chemical perfusion of the inner ear. Otolaryngologic Clinics of North America 2002, 35:639–653
18. Light JP, Silverstein H: Trans tympanic perfusion: indications and limitations. Curr Opin Otolaryngol Head Neck Surg 2004, 12:378–83
19. Hoffer ME, Balough BJ, Gottshall KR: Delivery of drugs to the inner ear. Curr Opin Otolaryngol Head Neck Surg 2006, 14:329–331
20. Darlington CL, Smith PF: Drug treatments for tinnitus. Prog Brain Res 2007, 166:249–262
21. Plontke SKR, Wood AW, Salt AN: Analysis of gentamicin kinetics in fluids of the inner ear with round window administration. Otol Neurotol 2002, 23:967–974