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

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**INTRODUCTION**

The factors like environmental pollution , increasingly aging population, overexposure to noise in the youth and exposure to ototoxic but lifesaving drugs such as amino glycoside antibiotics and platinum-based chemotherapy, amplifying the spreading of hearing loss disability. Inner ear drug delivery has been a challenge to physicians in the treatment of inner ear disorders. In the past few decades, new biomaterials and drug delivery technologies have been developed for inner ear delivery. In last two decades, huge progress had been achieved in understanding and underlying mechanisms of hearing loss at the cellular and molecular level. A number of favourable attempts toward hearing restoration are focusing in establishing regeneration of the cells and cochlear nerve endings. The objective of the current chapter is to provide an updated general overview of inner ear drug delivery and discussing their potential in recent advances in biomaterials, bio-technological methods and delivery technologies.



 Fig.1: Anatomy of Inner Ear

**Administration routes for inner ear drug delivery**

1. **Systemic route:** Usually, drugs are delivered to the inner ear via the systemic route, but only a few drugs can reach the target site of action at therapeutic concentrations in the inner ear because of the presence of BLB (Blood Labyrinth Barrier) which is a major barrier separating the inner ear from systemic circulation with tight junctions, made up of capillary endothelial cells that line blood vessels located in the *stria vascularis*). In order to achieve therapeutic concentrations of drugs in the inner ear high systemic doses are required, which are often associated with infelicity side effects. Such systemic toxicities and side effects can range from minor problem to potentially life- threatening situations. Despite these adverse effects, systemic delivery through oral, intravenous, and intramuscular routes are still considered as the most convenient method of drug administration to the inner ear and is currently accepted as the first line approach in the treatment of inner ear disorders.
2. **Intra-tympanic route:** Specifically the subject of treating inner-ear disorders by local drug delivery has attracted considerable interest of research. Intra tympanic delivery to the inner ear was executed via the injection or perfusion of the drug to the middle ear with the aim of drug diffusion through the RWM (Round Window Membrane which is a soft tissue barrier separating the middle ear from the inner ear) into the inner ear. This route of drug delivery introduced more than half a century ago for the treatment of Meniere’s disease (it is a disorder of the inner ear that can lead to dizzy spells and hearing loss) with local anaesthetics and antibiotics and has been widely used in clinics since 90s. This prospective possesses benefits over systemic drug delivery as this local drug delivery method can bypass the BLB, and therefore result in higher drug concentrations in the inner ear fluids and avoid undesired systemic exposure. Effective drug delivery to the inner ear via the intra-tympanic route also based on the contact time of the drug solution with the RWM. But woefully, a large portions of the administered drugs are usually eliminated through the Eustachian tube which following intra tympanic drug delivery. There have been efforts to be made overcome this limitation through the development of devices and sustained-release drug delivery systems.
3. **Intra-cochlear route:** Corresponding to intra-tympanic delivery, the intra-cochlear delivery approach also provides an alternative to systemic drug delivery to the inner ear. Direct intra-cochlear drug delivery can detour the middle ear and allow drugs to get to their expected sites directly. It can substantially enhance drug bioavailability in the inner ear and has the highest efficiency among the inner ear delivery methods discussed in this chapter. Numerous intra-cochlear delivery technologies are being developed to improve the efficiency of drug delivery to the inner ear. It includes direct injections, osmotic mini-pumps, cochlear implants as well as reciprocating perfusion.

**Objectives of drug application in combination with drug- device combination**

* It should be by pass the blood–brain barrier (the target organ is directly reached)
* 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 loss of auditory neurons and spiral ganglion cells
* 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:** Several cannula-based delivery systems are available commercially for sustained delivery of drugs to the middle ear. These devices include Silverstein Microwick and Round Window Microcatheter. Potential problems and adverse effects of these devices include the persistent perforation of the tympanic membrane, risk of infection in the middle ear or external ear, and tissue growth in the middle ear either in the form of fibrosis or epithelial in growth leading 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% patints respectively. . In another study, Gelfoam infiltrated with brain-derived neurotrophic factor (BDNF)on to the RWM of deafened guinea pigs and evaluated the effect of this treatment by structural and functional measures. In the 2weeks of Gel- foams BDNF treatment ,survival of spiral ganglion neurons (SGNs) in the inner ear was observed in the low turn of the cochlea, but no significant improvement was observed in the apical turn of the cochlea, probably due to the small amount of drug reaching the apicalturn. This suggests that local delivery of BDNF using Gelfoams can protect the parts of the spiral ganglion neurons (SGNs) of cochlea.
3. **Stabilizing matrices:** The stabilizing matrices possesses 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, which is liquid at room temperature and a biodegradable gel at body temperature allows the drug to come in contact between the matrix and membrane of the inner eari.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 comparision 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 neurotrophic 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. Both spiral ganglion neurons and peripheral process re growth were enhanced with the treatment. The inclusion of fluidic channels within cochlear implant electrode provides the opportunity to chronically infuse neurotrophic factors and pharmacological agents to enhance efficacy of cochlear implants. Scientists describes a drug delivery system integrated into a scala tympani electrode which has designed for use in guinea pigs with demonstrated delivery of neomycin.
5. **Nano particles**: The delivery system of super paramagnetic iron oxide nano particles (SPIONs) through a three cellular layers RWM model in vitro showed that SPIONs distributed throughout the model membranes under an external magnetic field. In another study it has been investigated that the capability of ferro gel which consist of SPIONs and Pluronic with an imaging tag for the delivery of many therapeutic agents across the RWM 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 nanoparticle 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 suggested that the implantation of embriyonic stem cells, foetal root ganglions and otocyst cells in the inner ear to restore the damaged hair cells.

**CONCLUSIONS**

Loss of hearing represents one of the most widespread needs in all of medicine, and 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 safety and efficacy. Problems encountered by the physcians treating inner ear diseases are similar to the difficulties faced during preclinical drug development, and delivery remains the central barrier to progress. Current scenario of preclinical models needs large numbers of animals’ models due to significant variability and relatively small responses in hearing function. This factor is largely related to difficulties in delivery rather than limitations of the compounds themselves. Without reliable delivery systems capable of maintaining control over drug concentrations within the therapeutic window for extended periods is difficult to assess efficacy and functional assays for drug-treated groups.

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