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

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Factors such an increasingly aging population, overexposure to noise in the youth and in the military, and exposure to ototoxic but lifesaving drugs such as amino glycoside antibiotics and platinum-based chemotherapy, exacerbate 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 decade, new biomaterials and drug delivery technologies have been developed for inner ear delivery. Over the past two decades, tremendous progress in understanding the underlying mechanisms of hearing loss at the cellular and molecular level has been made, and a number of promising approaches toward hearing restoration are focusing in establishing regeneration of the hair cells and cochlear nerve endings. The goal of the present chapter is to provide an updated general overview of inner ear drug delivery and discussing their potential as a result of recent advances in biomaterials, delivery technologies, and bio-technological methods.

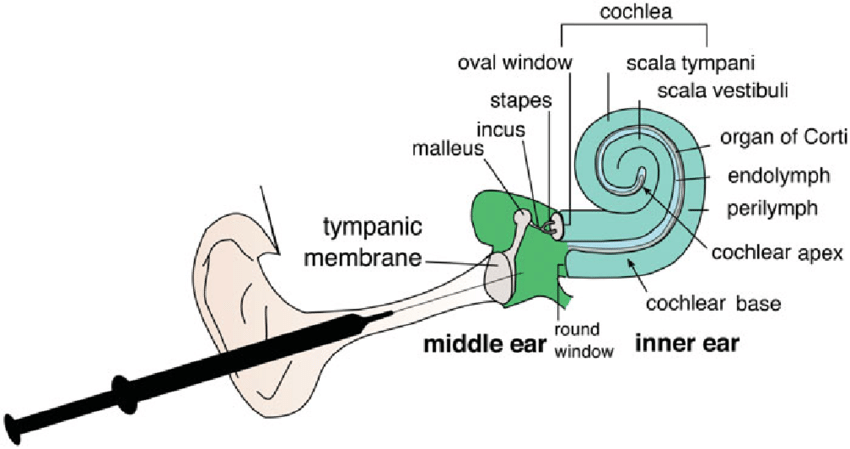


Fig.1 : Anatomy of Inner Ear

**Administration routes for inner ear drug delivery**

1. **Systemic route:** Generally, 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 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 levels of drugs in the inner ear high systemic doses are required, which are often associated with undesirable side effects. Such systemic toxicities and side effects can range from minor nuisances to potentially life- threatening situations. Despite these adverse effects, systemic delivery through oral, intravenous, and intramuscular routes is 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:** The topic of treating inner-ear disorders by local drug delivery has attracted considerable interest. Intra tympanic delivery to the inner ear was performed 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 was 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 1990s. This approach possesses several advantages 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 relies on the contact time of the drug solution (or drug delivery system) with the RWM. Unfortunately, large portions of the administered drugs are usually eliminated through the Eustachian tube following intra tympanic drug delivery. There have been efforts to overcome this limitation through the development of devices and sustained-release drug delivery systems.
3. **Intra-cochlear route:** Like intra-tympanic delivery, the intra-cochlear delivery approach provides an alternative to systemic drug delivery to the inner ear. Direct intra-cochlear drug delivery can bypass the middle ear and allow drugs to get to their intended sites directly. Intra-cochlear delivery can substantially increase drug bioavailability in the inner ear and has the highest efficiency among the inner ear delivery methods discussed in this review. Numerous intra-cochlear delivery technologies are being developed to improve the efficiency of drug delivery to the inner ear. They include direct injections, cochlear implants, osmotic mini-pumps, as well as reciprocating perfusion

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

* Bypassing of the blood–brain barrier (the target organ is directly reached)
* Higher drug concentration in the inner ear
* Avoiding “first-pass” effects
* Reduction of adverse systemic effects
* Lower drug doses are necessary
* General reduction of insertion trauma
* Reduction of immune reaction
* Reduction of infection
* Reduction of loss of auditory neurons and spiral ganglion cells
* Reduction of fibrosis and ossification
* Reduction 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 :** Gelfoams is a biodegradable gelatine polymer that was first introduced in middle ear surgery and recently used as a drug delivery system for the inner ear. A recent study has demonstrated improved outcome of Meniere’s disease treatment by the placement of Gelfoams soaked in gentamicin on the RWM, which eliminated vertigo and tinnitus in 75% and 48% of the patients, respectively. In another study, Gelfoams in filtrated 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 SGNsin parts of the cochlea.
3. **Stabilizing matrices:** The use of stabilizing matrices offers many potential benefits over middle ear perfusions. Medications delivered to the middle ear are ultimately dissipated by drainage down the Eustachian tube or absorption by middle ear mucosa unless a stabilizing matrix is used. For potentially toxic agents this raises significant concerns regarding isolation to target tissues. This, coupled with superior control of dosing profiles, suggests future trans-tympanic delivery methodologies are likely to focus on techniques utilizing stabilizing gel matrices for passive sustained release. Chitosan-glycerophosphate hydrogel, a liquid at room temperature and a biodegradable gel at body temperature, allows injection into the round window niche and facilitates close contact between the matrix and the round window membrane. This material has been used successfully in mouse studies to deliver dexamethasone to the inner ear through the round window membrane and has tunable delivery properties.
4. **Cochlear Implants:** Intra-cochlear drug delivery has the potential to greatly enhance efficacy of cochlear implants for the profoundly deaf. Researchers demonstrated conservation of hearing by direct scala tympani delivery of dexamethasone for 8 days following electrode insertion trauma induced hearing loss in the guinea pig . Some other novel experiments shows chronically infused the guinea pig cochlea (basal turn, scala tympani) with brain-derived neurotrophic factor and fibroblast growth factor following deafening via a systemic amino glycoside and diuretic treatment. Survival of spiral ganglion neurons and peripheral process re growth were both enhanced with the treatment. The inclusion of fluidic channels within cochlear implant electrode arrays provides the opportunity to chronically infuse neurotrophic factors and pharmacological agents which may enhance efficacy of cochlear implants. Scientists describes a drug delivery system integrated into a scala tympani electrode array designed for use in guinea pigs with demonstrated delivery of neomycin.
5. **Nano particles**: It has been tested a delivery system of super paramagnetic iron oxide nano particles (SPIONs)through a 3-cell layer RWM model in vitro. The results showed that SPIONs distributed throughout the model membrane under an external magnetic field. In another study it has been investigated the capability of ferro gel consisting of SPIONs and Pluronic with an imaging tag for the delivery of therapeutic agents across the RWM of cadaver human temporal bones as well as in organo- typic explants cultures of mouse inner ears. It was found that the SPIONs were in the cytoplasmin organ otypicexplant culture, suggesting that the nanoparticle system can be a suitable cell specific drug delivery vehicle that prevents drug degradation in the cellendo lysosomal compartment during drug delivery. Some experiment examined the cell targeting ability and toxicity of nerve growth factor-derived ligand functionalized polymers omenano- particles for specific cell targeting to SGNs in mouse cochlear organo typic culture and observed specific targeting to SGNs, Schwann cells and nerve fibres in the cochlear culture.
6. **Stem Cell therapy:** Stem cell therapy to treat hearing loss has recently received attention due to its potential to replace and/or protect hair cells and SGNs after deafness. The feasibility of stem cell therapy in the treatment of inner ear disorders to replace damaged hair cells has been previously reported. It was suggested that the implantation of embryonic stem cells, foetal dorsal root ganglion and otocyst cells in the inner ear could be used to restore damaged hair cells.

**CONCLUSIONS**

Hearing loss represents one of the most prevalent unmet needs in all of medicine, and bringing new treatments to market will require concerted advances along multiple fronts, due to the major challenges presented by the nature of the inner ear as a target for therapy. Challenges in achieving safety and efficacy faced by clinicians treating inner ear diseases are similar to the difficulties encountered during preclinical drug development, and delivery remains the central barrier to progress. Current preclinical models require very large numbers

of animals due to significant variability and relatively small responses in hearing function, and this 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, it is difficult to assess efficacy, and functional assays for drug-treated groups often fall short of expected results for this reason.

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