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Review

Inner ear drug delivery using liposomes

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Abstract: Dysfunction of inner ear can result in from several disease procedures and introduce a possibility for therapeutic intervention**.** The existence of a blood-cochlear obstacle and round window membrane restricts direct access into the inner ear and following inner ear drug, gene, protein and cell delivery**.** Several strategies have designed to increase drug delivery to the inner ear. One of main particles for inner ear drug delivery is liposome. Here we reviewed the application of liposomes in inner ear drug delivery.

Key words: Drug delivery; Liposome; Cochlea; Inner ear.

Introduction

Several disease procedures results in dysfunction of inner ear and introduce a possibility for therapeutic intervention (1, 2). The structure of the inner ear involve five vestibular appendages: the saccule, the cochlea, the utricle and three semicircular canals (3, 4).

In the majority of cases of ear disease, got or genetic hearing loss, and inner ear dysfunction, is hair cell damage and failure (5). By targeting hair cells, sustaining cells, or neurons, drug delivery is a way to change cellular phenotype for regeneration of hair cells and preservation (6).

Inner ear drug delivery has been a dispute to physicians in the cure of inner ear disorders because drug, gene, protein and cell delivery to the inner ear is restricted by the existence of a blood-cochlear obstacle and direct access into the inner ear is difficult because of the bony capsule (7). However, these isolation systems make inner ear diseases difficult to be treated (8). The inner ear provides a unique attractive target for local drug, gene, protein and cell delivery and therapy through the membranes inner ear has become usual in otologic practice and has introduced the possibility of treating disease of the inner ear or the auditory nerve and parity disorders (9). Therefore the inner ear is a particularly because for the vector can be with no trouble delivered to the localized structure of the inner ear (10).

The purpose of a drug delivery system is to deliver a drug to a specific site in a specific time and release pattern (6). Most of types of inner ear specific drug delivery system have been use the round window (11), sealing off one of two openings into the inner ear, as a method to deliver the agent into the inner ear, round window has an exceptional structure in the inner ear because is not covered with bone but sealed with a round window membrane (12). Intratympanic is a routine strategy for treating inner ear disease drug delivery for inner ear therapy whereas avoids some of the problems associated with systemic delivery (13). Several strategies have designed to increase drug delivery to the inner ear when drug is located within the middle ear are active areas and drug delivery to the inner ear effects can be altered by delivery into different regions of the cochlea as well as by different choices of vectors include nanoparticle carriers, micro catheter systems, liposome and hydrogel vehicles (14, 15). In order to improving delivery of vectors must alter the expression characteristics of the gene by changing the promoter that takes gene expression (16). One of main particles for inner ear drug delivery is liposome. Here we reviewed the application of liposomes in inner ear drug delivery.

Drug delivery for treatment of inner ear disease

In recent years, a paradigm shift is undergoing in therapeutic techniques of inner ear disease. There are three main strategies in inner ear drug delivery which have advantages and disadvantages (table 1).

The primary treatments of inner ear disease were delivered systemically, including steroids for sudden sensorineural hearing loss (18, 19), and aminoglycosides for bilateral Meniere's disease (20). This method for drug delivery have some disadvantages and troubling drawbacks, including the possible for unwanted systemic side effects and changeable infiltration into the inner ear owing to the existence of a blood-cochlea barrier (21).

The second drug delivery method for inner ear therapy is intratympanic drug delivery and aim to keeps

Table 1. Three main strategies in inner ear drug delivery (17).

Strategy	Safety	Efficiency
Systemic strategies	Low safety, side effects caused by high systemic doses over time	Low
Intratympanic strategies	High safety, minimally invasive procedure that can be performed in a physician's office	Moderate, produce variable outcome
Intracochlear strategies	Limited safety, precise surgery is needed and potential of serious complications	High

away from some of the disadvantages and troubling drawbacks associated with systemic delivery and has now undergoing to become a routine approach for inner ear disease therapy (22-25). Improving drug delivery via the intratympanic route is owing to the development of adjunctive devices and carrier mechanisms (26, 27). However this route currently delivered some potential disadvantages and troubling drawbacks of intratympanic drug delivery such as changeable or unknown pharmacokinetic profiles of drugs, loss of drug down the Eustachian tube, and anatomic barriers to absorption at the round window membrane (12, 28).

Most recently, a more invasive approach with the potential for bypassing the middle ear altogether and delivering medications directly to the inner ear is direct intracochlear delivery of therapeutic and curative agents (29). This technique reduces dependence on the round window membrane permeability and can make available improved separation of the target tissues to the delivered agent (29). This method of drugs or genes delivery has been effectively assessed in animal models by infusion or injection into the scala tympani (30-34), scala vestibuli (35, 36) and the perilymphatic space via the semicircular canals (37), injection into the endolymphatic sac (38), and endolymphatic space via the scala media (39) and finally injection through the round window membrane (40).

Liposome drug delivery in the ear therapy

Liposomes are a unique small bubble-shaped lipid molecules, and the most advanced and attractive candidate nanoparticles for delivering drugs and genes in vivo (41). Moreover, cationic liposomes vehicles have been explored as a means for gene therapy because they are composed of the same material as cell membranes (42). Cationic liposomes always used in contemporary medicine to transport and inject drugs and genes into different tissue areas of the body, because they can be combined with DNA for transfection of several cell types (43, 44). for examples types of cancer, for instance, are treated with liposome therapy (45). precise targeting of liposome therapy becomes possible with nanotechnology,these submicron particles have displayed increased biocompatibility, in vivo stability, target specificity, and cell/tissue uptake and internalization of the encapsulated healing means, principal to a decrease in the dose required and a decrease in side effects (46). Nano-sized liposomes would strangely improve the accuracy and value of drug and gene delivery (47). the most important problems to overcome before full clinical application is the improvement of precise delivery systems for drugs to the target sites and controlled statement in the inner ear nanoEar aims to deliver multifunctional nanoparticles for medical therapy (48). Today,scientists have an increasing attention in the treatment of inner ear ailments by current application of drugs to the inner ear. The application of a novel drug or gene therapy into the inner ear is hindered by a lack of vectors that are safe, efficacious and cell/tissue-selective, to treat the tissues of the inner ear, different efforts have been tried for example the use of bioimplantable drug reservoirs, implantable catheters with a drug reservoir, viral carriers for DNA and plasmids, and the recent development of synthetic vectors (49, 50). Including problems in the treatment of diseases of the inner ear is difficult to access by conformist systemic drug delivery due to difficult physiological and anatomic obstacles (9). In the inner ear, inside the cochlea, there are neurons called hair cells, injureis to which effect in hearing loss (51). Sanjeev Ranjan has studied the use of liposome nanoparticles with a new ultrasound method for assemblying liposome nanoparticles in the cure of inner ear disorders which can be delivered into the inner ear and inside the cochlea (48). They have schemed peptides with computer exhibiting and phage display and conjugated them to the liposome nanoparticles to be delivered into the cochlea,"The nanoparticles are presented to definite receptors in specific cells, and the encapsulated new gene will begin to explicit in the cells (52). The aims of their studied have the targeted delivery of liposomes encapsulated with Math1-genes, which aid hair cells to survive, design of an perfect multifunctional liposome with encapsulated drugs and genes, imaging agent, cell-probing agent and precise targeting moiety(figure 1) (53). This technique is very affordable and accessible in comparison to nanoliposomes ready with other currently available ultrasound techniques for examples, non-invasive, there is no lesion of materials, and it can be used in large scale these are all benefits (52).This distinctive blend of properties makes nanoparticles a novel delivery device, which achieves the requirements for inner ear application (54). In another study, Wareing and coworkers treated guinea pigs with either an osmotic pump delivery or injection of cationic liposomes holding DNA complexes, and tissue sections were assessed using PCR and immunohistochemistry analysis (43). They informed that 14 days of transgene expression was conversant with nonappearance of inflammatory or toxicity response. Beta-galactosidase was detected in almost all tissue types, and the spiral ligament had highest concentrations, which were confirmed with PCR-based assays. Durability of the transgene expression for 14 day was informed for both osmotic pump and microinjection infusion; though the osmotic pump delivery was related to inflammatory responses and local trauma (43).

Reviews regarding the practicality of utilizing these transfer agents can be found in the literature (55). In this study, liposome drug delivery is a viable approach

for intratympanic delivery but the main purpose is the transfer by liposome to the inner ear. The aim of the study was to present the practicability of liposome drug delivering into the inner ear with liposomes (55). SHI Li and coworkers construct a eukaryotic expression plasmid pEGFP and transfect hair cells using fluorescent plasmid pEGFP as a reporter gene with SA liposome and introduce into the cochlea (56). Compared with the guinea pigs injected with single plasmid, the expression levels of guinea pig injected with the plasmid-cationic liposome complex was higher, and the expression period was longer. They show direct cochlea injection with recombinant expression plasmid or plasmid-cationic liposome complex is economical, modest, competent, and for foreign gene transfer and expression in experimental guinea pigs in vivo.

In another study, Deng Zhihong and coworker assessed the expression of cationic liposome medicated transgene expression in the guinea pig cochlea (57). The NT-3 cDNA gene were cloned and were constructed its eukaryotic expression vector (pIRES2-EGFP-NT3) with the reporter gene-EGFP. Then the liposome-plasmid complex was injected into the guinea pig cochlea, and were observed the expression of the reporter gene-EGFP and NT-3. Transgene expression of the guinea pig injected with the plasmid-cationic liposome complex was persistent up to 4ws. This study informs the effective use of cationic liposomes for cochlear gene transfer, thus providing an effective, rapid, and safe way in gene therapy for inner ear illnesses.

Biocompatibility to the inner ear using liposomes were confidently studied (58). Further liposomes have also confirmed efficient drug delivery and a following biological effect in the cochlea (52).

All these studies recommended that liposome delivery is a practical method for intratympanic delivery but that the means to carrying the liposomes to the cochlea is an important component of the approach and, the main problems are cytotoxicity and short-term expression of gene products.

Ear gene therapy using liposomes

The drug or gene construct can be presented into inner ear cell by packaging the drugs or genes in a liposome (55). In ear gene therapy using liposomes, liposomes comprises of a diversity of positively charged polymers or lipids that condense the DNA and permit it to cross the cell membrane (59, 60).

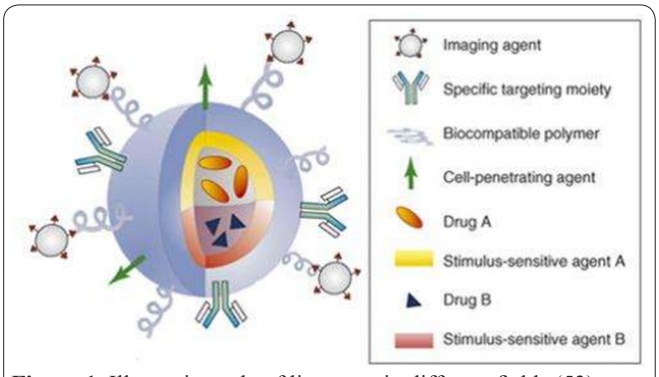

Figure 1. Illustration role of liposome in different fields (53).

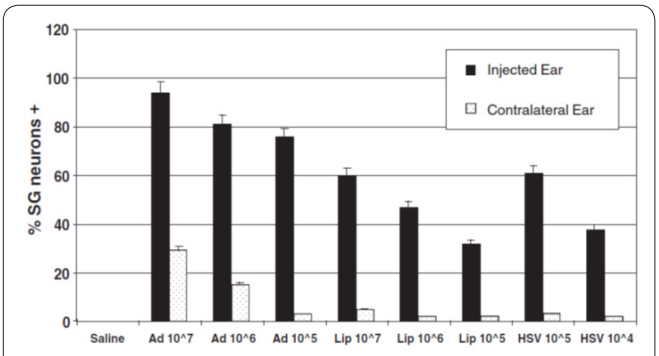

Figure 2. Comparison of different gene delivery strategies in the inner ear. Ad, adenovector; HSV, herpes simplex virus; Lip, liposomes (40).

Nonviral or liposomal gene delivery usages charged polymers or lipids to condense the DNA to be transferred cross the cell membrane (61, 62). At now, liposomal gene delivery is less efficient than viral gene transfer approaches (table 2). Existing essential fields of gene therapy investigation are vector retargeting, tissue-specific promoters and inducible promoters (63). Most efforts in ear gene therapy investigation purpose to improve the expression and localization properties of the transferred genes (64, 65).

Liposome- and AAV- packaged plasmids have also been efficiently transferred into the guinea pig cochlea in vivo following direct microinjection into the cochlea, and persistent up to 14 days in the neurosensory epithelia and surrounding tissue without toxicity and inflammation in the target organ (43). This study shows the successful use of the cationic liposomes as gene transfer vectors for the cochlea provides a rapid and safe substitute to the use of recombinant viral vectors for cochlear gene transfer studies.

Proficiency of cochlea gene transfer for diverse vectors has been reported by injecting equivalent particle numbers of a liposome construct carrying a plasmid containing gfp, a herpes virus vector carrying lacZ and an adenoviral vector carrying gfp and were delivered into the basal turn of the cochlea in a C57Bl6 mouse. Liposomal gene delivery was less efficient and the most efficient delivery was with adenoviral vectors, and HSV vectors were almost as efficient (40). The figure 2 shows the comparison of these three systems.

Conclusion

Hearing loss is a large problem distressing about 13% of the European population. New methods to reduce size drug carriers to nano-sizes and assign them with targeting moieties prove new occasions for effec-

Table 2. Advantages and disadvantages of commonly used vectors in the inner ear.

Vector	Advantages	Disadvantages
Liposome	Easy to make; Nonpathogenic Nonimmunogenic	Inefficient
Adenovirus	Easy to make; 10 kb insert	Immunogenic?
Adeno-associated virus	Noncytotoxic; Stable expression	Difficult to make; small insert
Herpes virus	Neurotropic; Stable expression	Difficult to achieve high titer

tive drug/gene delivery into the inner ear (66-69). Nanoparticle facilitated gene transfer is a smart methodology for of its easiness and reduced toxicity, and it holds potential in given that a major innovation for future therapy (70-74). Liposomes have broad potential in a variety of medical applications. The nano size gives some of its exciting properties to a multifunctional liposome (75-77). Liposomes are capable of carrying payloads which would not ordinarily cross the RWM or would cause morphological changes in the inner ear by doing so(78-81). The advance of technologies to induce specific drug delivery by liposome is outpacing the development of appropriate liposome drug delivery systems that are applicable to the inner ear. Today, Delivery of medication to the inner ear is a field undertaking rapid progress (82-84). In an attempt to alleviate some of the problems associated with systemic delivery, mostly the systemic post factors, researchers and clinicians have been studying application of medications topically to the middle ear to authorization dispersal through the round window membrane and into the inner ear (85-87). Current challenges for research is focused on the development of controlled drug delivery and administration without damaging the inner ear. Laboratory animals are a necessary instrument for the progress of these methods, which goal to decrease unpredictability in dosage and rise drug bioavailability. Developments in local drug management to the inner ear will advantage patients with hearing injurys by proposing better treatment options with reduced side effects, and hence, a better quality of life. In the process of optimising liposome-based drug delivery to the inner ear, it is essential to be able to trace the passage of liposomes through the cochlea.

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