Published in final edited form as:
Ear Hear. 2010 April ; 31(2): 156–165. doi:10.1097/AUD.0b013e3181c351f2.

Drug Delivery for Treatment of Inner Ear Disease: Current State of Knowledge

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Abstract

Delivery of medications to the inner ear has been an area of considerable growth in both the research and clinical realms over the past several decades. Systemic delivery of medication destined for treatment of the inner ear is the foundation upon which newer delivery techniques have been developed. Due to systemic side effects, investigators and clinicians have begun developing and utilizing techniques to deliver therapeutic agents locally. Alongside the now commonplace use of intratympanic gentamicin for Meniere's disease and the emerging use of intratympanic steroids for sudden sensorineural hearing loss, novel technologies, such as hydrogels and nanoparticles, are being explored. At the horizon of inner ear drug delivery techniques, intracochlear devices that leverage recent advances in microsystems technology are being developed to apply medications directly into the inner ear. Potential uses for such devices include neurotrophic factor and steroid delivery with cochlear implantation, RNA interference technologies, and stem cell therapy. The historical, current, and future delivery techniques and uses of drug delivery for treatment of inner ear disease serve as the basis for this review.

Introduction

Numerous disease processes cause inner ear dysfunction and represent an opportunity for therapeutic intervention. Hearing loss is the common endpoint of many inner ear disorders including presbycusis, sudden sensorineural hearing loss, genetic diseases, trauma, exposure to noise and ototoxic medications, and autoimmune inner ear disease. Inner ear disorders causing balance dysfunction include Meniere's disease, benign positional vertigo, and labyrinthitis. Therapeutic strategies to treat inner ear diseases include delivery of medications (systemically and locally), surgical intervention, sound amplification (with hearing aids), and physical therapy. This paper will focus on the pharmacologic management of inner ear disease and specifically will focus on the strategies used to deliver drugs for treatment of inner ear

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disease. The intent of this paper is not to perform an exhaustive review of the pharmacologic management of all forms of inner ear disease; rather, specific diseases and therapeutics will be used as examples to highlight the approaches and devices utilized to deliver drugs to the inner ear. The goals of the paper are to review the historical basis for management of inner ear disease using drug delivery techniques, to review the past and present strategies used to delivery drugs to the inner ear, to highlight the potential strengths and weaknesses of drug delivery techniques for treatment of inner ear disease, and to provide insight into novel and innovative strategies to achieve delivery of drugs directly into the inner ear. The overarching purpose of this paper is to review the current status of knowledge on drug delivery for treatment of inner ear disease and to provide insight into the potential future of the field.

Therapeutic management of inner ear disease is undergoing a paradigm shift. The first treatments for control of inner ear disease, including aminoglycosides for bilateral Meniere's disease and steroids for sudden sensorineural hearing loss, were delivered systemically. The systemic route for delivery of medication is accompanied by some troubling drawbacks, including variable penetration into the inner ear due to the presence of a blood-cochlea barrier and the potential for undesirable systemic side effects. Intratympanic drug delivery for inner ear therapy avoids some of the problems associated with systemic delivery and has now become a routine strategy for treating inner ear disease. The development of adjunctive devices and carrier mechanisms are active areas of research focused on improving drug delivery via the intratympanic route. Potential drawbacks of intratympanic drug delivery include anatomic barriers to absorption at the round window membrane, loss of drug down the Eustachian tube, and variable or unknown pharmacokinetic profiles of medications currently delivered via this route. Most recently, approaches to drug delivery have focused on bypassing the middle ear altogether and delivering medications directly to the inner ear. Direct therapy to the inner ear could have applications ranging from delivery of currently available drugs with undesirable systemic side effects to delivery of steroids or neurotrophins with cochlear implantation to novel gene- or stem cell-based therapies. Recent technological advancements in emerging fields such as microfluidics and microsystems technologies permit the development of drug delivery systems designed to deliver drugs directly to the inner ear over a sustained period of time. To understand the contemporary focus on local strategies for management of inner ear disease, one must understand the systemic therapeutic route and its drawbacks.

Systemic administration of medications directed to the inner ear

The modern era of local delivery of medication for effect within the inner ear evolved from the prior use of systemic medications delivered for the same effect; this progression was principally driven by efficacy and safety limitations experienced in systemic therapy. Systemic therapy consists of dosing medication via the oral, intravenous, or intramuscular route with the intention of altering inner ear function. Two examples of systemic medications delivered for the control of inner ear disease include systemic streptomycin for vertigo control and systemic steroids for sudden sensorineural hearing loss (SSNHL).

Systemic streptomycin for vertigo

One of the first medications to be delivered systemically for treatment of inner ear disease was streptomycin. Soon after the drug's discovery, systemically delivered streptomycin was found to be ototoxic. As early as 1948, the ototoxic effect of systemic streptomycin was recognized to have potential as a therapeutic agent when given to patients for control of vertigo (Fowler 1948). Since that time, the indications for systemic streptomycin have been refined; today, the most common indication for streptomycin therapy is severe bilateral Meniere's disease (Graham and Kemink 1984, Sataloff et al. 1996, Berryhill and Graham 2002). In these cases, streptomycin is dosed via the intramuscular route, and titration is based on clinical effect. Treatment is halted if the patient experiences a rapid decline in vestibular function, develops

hearing loss, or manifests oscillopsia (Graham and Kemink 1984, Berryhill and Graham 2002).

Systemic steroids for sudden sensorineural hearing loss (SSNHL)

SSNHL is defined as hearing loss occurring over no longer than three days, with a drop of 30dB at three or more frequencies (NIDCD 2003). Systemic steroids remain a widely utilized form of therapy for treatment of SSNHL in the United States. Wilson et al. reported a double blind study performed at two institutions, wherein patients were given systemic steroids or placebo, and noted an overall statistically significant recovery rate of hearing in 61% of patients treated with steroids versus 32% with placebo (Wilson et al. 1980). Subsequent investigations have compared the efficacy of systemic steroids with combination therapies (e.g. systemic steroids plus antiviral therapy) for SSNHL (Stokroos et al. 1998, Tucci et al. 2002, Uri et al. 2003, Westerlaken et al. 2003). However, the efficacy of systemic steroids for the treatment of SSNHL has been called into question by several investigators, primarily on the basis of methodological flaws detected within prior studies and lack of a well-designed randomized controlled clinical trial with adequate power (Wei et al. 2006, Conlin and Parnes 2007). Nevertheless, systemic steroid therapy for SSNHL remains a common form of treatment and the standard of practice in North America.

Other systemic treatments for inner ear disease

In addition to systemic aminoglycosides for bilateral Meniere's disease and systemic steroids for SSNHL, multiple other drugs have also been delivered systemically to target the inner ear. For example, the inner ear has been the proposed site of action of systemic diuretics in controlling Meniere's disease (Coelho and Lalwani 2008). Additionally, systemic bisphosphonates have been proposed as a therapeutic option for otosclerosis (Kennedy et al. 1993, Brookler and Tanyeri 1997).

Drawbacks of systemic therapy

Concerns exist regarding the clinical efficacy of many systemic medications currently in use for the treatment of inner ear disorders. Despite this fact, the primary concern regarding their usage has been the potential side effects associated with delivery via the systemic route. These side effects can range from minor nuisances to potentially life threatening effects. For example, systemic steroid therapy has long been associated with many side effects including hyperglycemia, hypertension, hypokalemia, peptic ulcer disease, osteoporosis, immunosuppression, and, if given over a sustained period of time, adrenal suppression (Chrousos 2007). Other medications given systemically for inner ear disease similarly have side effects associated with their use. These side effects can lead patients to curtail usage of a therapeutic medication or to switch to a less efficacious alternative. Worse yet, the side effects associated with the systemic delivery of medications could potentially lead to rare events including serious organ damage or even death.

Systemic side effects of medication for the inner ear are not the only concern regarding systemic delivery. Each medication is subject to a range of pharmacokinetic factors that influence the concentration of that particular drug in the inner ear. These factors include differing total body volumes of distribution, variability among different medications in their ability to cross the blood-labyrinth barrier, different drug metabolic pathways, and different routes of excretion (Paulson et al. 2008). Even for a single agent, variability in concentration in the inner ear is exacerbated by systemic variability, potentially leading to variable clinical outcomes. As a result of the variable pharmacokinetic profiles and systemic side effects, investigators have sought alternative means of delivering medications to the inner ear.

Medications applied to the middle ear for inner ear absorption

The clinical drive for safe and effective drug treatment for disorders of the inner ear has resulted in the development and implementation of various techniques for local drug delivery (Kujawa and Sewell 2006). A strategy that has gained widespread acceptance is intratympanic delivery of medication for local absorption into the inner ear. In addition, approaches designed to enhance medication delivery to the inner ear when drug is placed within the middle ear are active areas of research and include microcatheter systems, hydrogel vehicles, and nanoparticle carriers. Two types of medications currently in widespread use to treat inner ear disease include intratympanic gentamicin and intratympanic steroid therapy. These two medications will be reviewed in depth to provide an understanding of the current status of intratympanic therapy and to serve as a context for reviewing supplementary technologies that are designed to enhance the delivery of drugs to the inner ear when administered via the middle ear.

Intratympanic gentamicin

Intratympanic gentamicin application has become a commonplace strategy for the management of Meniere's disease. Prior to intratympanic gentamicin use, Schuknecht first described intratympanic aminoglycoside treatment with streptomycin in Meniere's disease (Schuknecht 1956). Intratympanic streptomycin delivery was accomplished by delivering the medication through a small plastic tube placed through the tympanic annulus into the middle ear. This form of intratympanic streptomycin was found to be efficacious for control of vertigo when treatment led to the elimination of cold caloric responses. However, this form of therapy also had the deleterious side effect of hearing loss (Schuknecht 1956). Interest returned to intratympanic aminoglycoside delivery in the late 1970s when investigators reported a significant decrease in hearing loss associated with a modification of this form of therapy (Lange 1977, Beck and Schmidt 1978). This decrease in hearing loss was attributed to a change in treatment philosophy; specifically, the endpoint of therapy was changed from complete vestibular ablation to arresting therapy once symptoms improved or a decline in hearing was noted. With this form of therapy, hearing loss associated with intratympanic aminoglycoside therapy decreased from 51% to 15% (Beck and Schmidt 1978).

Modern treatment for Meniere's disease includes intratympanic gentamicin as a standard form of therapy in the treatment armamentarium, usually reserved for patients experiencing continued vestibular symptoms despite conservative therapy with a low salt diet and/or diuretics (Chia et al. 2004, Sajjadi and Paparella 2008). The dosages and timing of therapy as well as endpoints selected to curtail therapy differ greatly among published reports (Youssef and Poe 1998, Minor 1999, Harner et al. 2001, Abou-Halawa and Poe 2002, Chia et al. 2004). In one series by Minor, 34 patients were evaluated in a protocol designed to determine clinical endpoints for cessation of intratympanic gentamicin therapy (Minor 1999). Intratympanic gentamicin was delivered on a weekly dosing schedule and the clinical endpoints selected for cessation of therapy included: a change from baseline of the presence of spontaneous nystagmus, head-shaking induced nystagmus, or head-thrust sign indicative of vestibular hypofunction on the treated side. With this treatment algorithm, 91% of patients achieved complete or substantial control of their vertigo (AAO-HNS classifications A and B) following completion of therapy, but in 32% of the patients, hearing was made worse as a result. An alternative strategy is based on delivering intratympanic gentamicin until vestibular symptoms cease. In a study designed to deliver gentamicin on a monthly basis until vertigo symptoms improved, 47 out of 56 patients required only one or two doses to abate vestibular symptoms (Harner et al. 2001). Long-term control utilizing this treatment strategy resulted in complete or substantial control in 82% of patients followed for greater than two years and 76% in patients followed for greater than four years. Given the long-term nature of follow up in this study, conclusions about treatment related hearing loss were difficult as the hearing loss could

either have been the result of therapy or the natural history of the disease. In a recent meta-analysis, therapeutic regimens of intratympanic gentamicin including multiple daily delivery, weekly delivery, low dose therapy, continuous delivery, and the titration method were compared (Chia et al. 2004). The authors demonstrated that the titration method had the best overall vertigo control and the multiple daily delivery method was associated with the highest rate of hearing loss at 34.7%.

Intratympanic steroids

In addition to intratympanic aminoglycosides, intratympanic steroids have been utilized as a therapeutic option for Meniere's disease. Intratympanic delivery of steroids for use in Meniere's disease was first described by Itoh, with 80% of treated patients experiencing improvement in vertigo (Itoh and Sakata 1991). Since that time, numerous investigators have described the use of intratympanic steroids in Meniere's disease (Silverstein et al. 1998, Garduno-Anaya et al. 2005, Boleas-Aguirre et al. 2008). A randomized controlled clinical trial comparing intratympanic dexamethasone to placebo for Meniere's disease demonstrated a statistically significant difference in complete vertigo control (Garduno-Anaya et al. 2005). Patients were treated with daily injections for five straight days with dexamethasone 4mg/mL or placebo; 82% of those receiving dexamethasone attained complete vertigo control compared with 57% of those receiving placebo. A retrospective review assessing long-term (over two year) vertigo control detailed a 91% success rate with intermittent intratympanic dexamethasone delivery (Boleas-Aguirre et al. 2008). A double-blind randomized crossover trial failed to show any improvement in other associated symptoms including hearing loss, tinnitus, or aural fullness when patients with advanced Meniere's disease were treated with intratympanic dexamethasone compared with placebo (Silverstein et al. 1998).

Intratympanic delivery of steroids is perhaps best known for therapeutic use in idiopathic SSNHL. Depending on numerous factors, including time from onset of hearing loss to initiation of intratympanic steroids, severity of hearing loss, and criteria selected to represent successful treatment/hearing recovery, success with intratympanic steroids for SSNHL has ranged from 0 to 100% (Haynes et al. 2007). As currently applied, intratympanic steroids are given most commonly as a form of salvage therapy after attempts to recovery hearing using systemic steroids have failed (Lefebvre and Staecker 2002, Slattery et al. 2005). In a report on six patients whose hearing did not respond to systemic therapy for SSNHL and were subsequently treated with continuous intratympanic methylprednisolone delivered via a microcatheter, all patients demonstrated improved pure tone thresholds and speech discrimination scores (Lefebvre and Staecker 2002). Another study examined intratympanic methylprednisolone in twenty patients after failed systemic therapy and found 55% of patients had a statistically significant improvement in pure tone average of 10dB or greater or speech discrimination of greater than 12% improvement (Slattery et al. 2005). Not all studies have utilized intratympanic steroids solely as a salvage therapy; some studies have evaluated their efficacy at presentation. In a study evaluating concurrent administration of systemic steroids and intratympanic dexamethasone for profound SSNHL, Battista concluded that there was no significant hearing recovery with the treatment regimen; however, they suggested the possibility of hearing improvement if treatment was initiated early (within 11 days of hearing loss) (Battista 2005). Similarly, a prospective, non-randomized study comparing patients who received systemic steroids with concurrent intratympanic methylprednisolone with another group of patients who received systemic steroids alone did not demonstrate a significant difference in hearing outcome (Lautermann et al. 2005). In an attempt to reconcile some of the controversy in therapy for SSNHL, a randomized clinical trial comparing primary systemic cortisteroids with primary intratympanic steroids is currently ongoing (Clinicaltrials.gov #NCT00097448) (Rauch 2008).

Methods for Intratympanic Delivery

Interest in applying medications to the middle ear for inner ear absorption has led to the development of technologies to improve delivery. Current strategies in various stages of development and use include transtympanic injection, the Silverstein Microwick ®, microcatheter implantation, hydrogels, and nanoparticles; brief reviews of each follow.

Transtympanic injection or myringotomy

The simplest form of intratympanic medication delivery is via injection into the middle ear either directly with a needle or through a myringotomy with or without a tympanostomy tube. This form of delivery is quick, can be performed in the clinic setting, and is currently in widespread use. Transtympanic injection does require the need for repeat procedures should dosing of medication be necessary beyond a one-time application. Placement of a tympanostomy tube comes with a small, but real, risk of persistent perforation of the tympanic membrane upon extrusion of the tube, otorrhea associated with the presence of the tube, and the need to keep the ear dry to avoid a middle ear infection (Hochman et al. 2006, Licameli et al. 2008).

Silverstein MicroWick ®

The Silverstein MicroWick ® is a 1mm by 9mm wick that is composed of polyvinyl acetate (Silverstein et al. 2001). It is applied through a ventilation tube placed in a myringotomy in the tympanic membrane overlying the round window membrane. The MicroWick ® is utilized in an attempt to provide the inner ear with sustained release of medication over time. The patient then instills medication into the external auditory canal, usually several times a day for several weeks, which travels down the MicroWick ® to the round window membrane (Light and Silverstein 2004). Gentamicin has been delivered through this system to successfully manage the vertigo attacks in Meniere's disease in over seventy-six percent of patients in one study (Hill et al. 2006). The MicroWick ® has also been used to deliver methylprednisolone in the setting of sudden sensorineural hearing loss with a noted improvement in hearing in eight of twelve subjects studied (Van Wijck et al. 2007). Potential drawbacks to the use of the Silverstein MicroWick ® may include the development of a persistent perforation of the tympanic membrane (Van Wijck et al. 2007), infection of the middle or external ear, and the potential for tissue ingrowth into the middle ear either in the form of fibrosis or epithelial ingrowth leading to cholesteatoma. Despite these potential complications, in a series of sixty-nine Meniere's disease patients treated with gentamicin delivered through the Silverstein MicroWick ®, no long-term complications were noted (Hill et al. 2006).

Microcatheter implantation

An alternative method for delivering medications in a continuous fashion to the round window membrane is the implantable microcatheter. In this system, a microcatheter is placed in the round window niche, traverses a tunnel developed at the tympanic annulus and then through a well in the posterior external auditory canal, and emerges at the external auditory meatus. The advantage of this system is the ability to deliver medication to the middle ear continuously over a period of several weeks. This system has been used for human application in twenty-five patients for the delivery of steroid medications to treat SSNHL after failed systemic therapy (Plontke et al. 2005, Plontke et al. 2006). Complications associated with this delivery system included five catheter dislocations, two catheter obstructions, seven cases of minor granulation tissue development within the middle ear, and two tympanic membrane perforations healed with underlay grafts (Plontke et al. 2006). The catheter dislocations occurred as a result of the partially implantable nature of the device. The microcatheter system was brought externally near the helix to connect to the pump mechanism, and several catheters were accidentally removed secondary to activities such as hair brushing or wearing eyeglasses. Catheter

dislocations were eliminated by a change in technique which consisted of placement of a thin transparent adhesive over the external portion of the microcatheter for protection. This catheter system was used for intratympanic infusions of steroids for up to four weeks in patients with acute severe to profound sensorineural hearing loss that persisted despite treatment with intravenous steroids and vasodilators. A statistically significant pure tone average improvement was found in patients receiving catheter delivered steroids (19dB improvement over pretreatment levels) compared with historical controls (5dB improvement) (Plontke et al. 2005).

Hydrogel application

One vehicle designed to deliver consistent doses of medication to the inner ear is the hydrogel. The basic formulation of a hydrogel, when applied as a delivery vehicle, is a dissolvable matrix that can be mixed with medications prior to instillation in the middle ear and, once applied, releases the medication in a controlled fashion by hydrolysis of the matrix or by basic diffusion out of the matrix (Nakagawa and Ito 2007). Hydrogels have been designed in several formulations for middle ear application including siloxane-based polymers, poly-lactic/glycolic acid (PLGA) polymers, gelatin, and chitosan glycerophosphate (Lee et al. 2007, Nakagawa and Ito 2007, Paulson et al. 2008). As an added advantage, the hydrogel matrix may be altered to change the dynamics of drug release (Paulson et al. 2008). Delivery of brain-derived neurotrophic factor (BDNF) to the inner ear by application of a hydrogel containing BDNF to the round window has been studied in the guinea pig. In this experimental model of drug induced hair cell and spiral ganglion damage, hydrogel-delivered BDNF was found in high concentration in perilymph (relative to controls) and resulted in a protective effect, manifested as both stability of ABR thresholds and preservation of spiral ganglion neuron densities (Endo et al. 2005). Hydrogels have also been used to deliver insulin like growth factor 1 (IGF-1) and dexamethasone, among other compounds, in animal models (Lee et al. 2007, Paulson et al. 2008). Some potential drawbacks to hydrogel use in human inner ear disease may include the need for accurate placement directly over the round window to permit transfer of drug to the inner ear, the potential for transient conductive hearing loss if the middle ear is overfilled with hydrogel, and the relatively quick release profile of most hydrogels under study (the majority of drug is released over several days) may not be ideal for chronic conditions. Hydrogels have yet to be used as drug carriers for clinical application in human inner ear disease and therefore these drawbacks of their therapeutic use are purely speculative at this point and will require further study as human application nears.

Nanoparticles

Nanoparticles are another methodology of medication delivery to the inner ear that has generated considerable interest in the past several years. Nanoparticles are particles with diameters less than 1000nm (Hornyak 2005) and are typically in the size range of 200nm or less when used for drug delivery to the inner ear. Nanoparticles generated from poly-lactic/glycolic acid (PLGA) form a biodegradable particle that has the potential to house therapeutic medication within and deliver the medication in a sustained release fashion (Kopke et al. 2006, Ge et al. 2007). PLGA nanoparticles have been shown to be present within the cochlea either when delivered systemically or when applied topically to the round window membrane, with an increase in intracochlear concentration when applied locally (Tamura et al. 2005). PLGA nanoparticles applied to the round window membrane distribute to the following structures: the round window membrane, perilymph, basilar membrane, stria vascularis, and within the organ of Corti (including within the inner hair cells, at the cuticular plate of outer hair cells, and within Henson, Dieter, Claudius, Boettcher, Pillar, and border cells) (Ge et al. 2007). Praetorius et al. (2007) placed Cy3 labeled silica nanoparticles against the round window membrane of mice to determine the location of these particles as a potential nonviral gene therapy delivery system. Four days later, the nanoparticles were found within cochlear and

vestibular hair cells and spiral ganglion cells on the treated side; to a lesser extent the same structures stained within the opposite ear. Nanoparticles were also found more centrally within the dorsal cochlear nucleus and superior olivary complex (Praetorius et al. 2007). Zou et al. (2008) investigated lipid nanocapsules (LNC) as a potential inner ear therapeutic delivery technique. LNCs applied to the round window membrane were shown to be taken up in the spiral ganglion, inner hair cells, pillar cells, outer hair cells, spiral ligament and stria vascularis (Zou et al. 2008). Currently, there is no published evidence that substantiates the expected ability of nanoparticles to carry drugs into the inner ear that alter inner ear physiology. As this technology remains in a very early stage of development and is likely to require substantial further investigation prior to human application to treat inner ear disease, an extensive discussion of the potential drawbacks for this application is premature. Looking forward, issues of biocompatibility, drug release profiles, and biosafety are likely to be important factors with this technology.

Potential drawbacks to intratympanic delivery of medications for inner ear absorption

Although the topical application of drugs to the middle ear for inner ear absorption has been a field of explosive growth in the past few years, several problems with their use have been encountered. Anatomic considerations with delivery of medication to the middle ear are important. The round window membrane is the primary transfer site of medication from the middle ear to the inner ear. In 33% of temporal bones, the round window membrane has been shown to be obstructed with either a pseudomembrane or a fibrous or fat plug, which could prevent the drug from reaching the inner ear (Alzamil and Linthicum 2000). Similarly, in a study of 41 patients who underwent middle ear endoscopy prior to instillation of middle ear medication, 12 patients (29%) were found to have partial or complete obstruction of the round window membrane (Silverstein et al. 1997). Loss of medication via the Eustachian tube is another anatomic consideration that can make middle ear application of medication variable.

Physiologic and pharmacokinetic considerations of middle ear delivery of medication for the inner ear are potentially problematic as well. Processes involved in inner ear pharmacokinetics include rate of transfer across the round window membrane, inner ear distribution of drug (primarily mediated by simple diffusion), and clearance of the drug from the inner ear (Salt and Plontke 2005). The ability to study these components of drug delivery for clinical application in humans is made difficult primarily as a result of two factors: the significantly different perilymph volume for drug distribution between animal models and humans and the significant role cerebrospinal fluid contamination plays in perilymph sampling (Salt and Plontke 2005). Secondary to a lack of understanding of inner ear pharmacokinetics, the choice of concentration and dosing for middle ear application of medications for the inner ear has largely been empiric (Salt 2005). Despite the difficulties inherent in experimentally determining inner ear pharmacokinetics, a computer cochlear fluids simulation model has been developed by investigators at Washington University (http://oto2.wustl.edu/cochlea/model.htm) for use in planning or interpreting experiments of drug delivery to the cochlea.

Delivery of medication directly to the inner ear

As investigators have begun to elucidate the mechanisms and pharmacokinetics of topical application of medication destined for the inner ear and the problems inherent therein, newer strategies of delivering medications directly to the inner ear are beginning to emerge. Such direct drug delivery is at the frontier of development for treatment of inner ear disease. Technologies designed to deliver drugs directly into the inner ear include modifications to existing cochlear implant technologies, osmotic pumps, and a reciprocating perfusion system.

Methods for direct intracochlear delivery

Application of Direct Inner Ear Drug Delivery to Cochlear Implantation

Cochlear implantation appears to be a favorable application for inner ear drug delivery as, by the nature of the procedure itself, the implant is already being placed directly into the inner ear and medication therefore could be delivered along with the implant. Investigators have taken advantage of this fact by attempting to discover ways to modify an implant to deliver therapeutic medications. Paasche et al. have investigated modifying the electrode of the Nucleus ® 24 Contour ™ device (Cochlear Ltd., Sydney, Australia) by making egress pathways connecting the stylet lumen with the scala tympani and connecting the system to an external pump system (Paasche et al. 2006). Efforts are also being made to study the potential for coating cochlear implant electrodes with a biorelease polymer permitting diffusion of medication into the inner ear (Hendricks et al. 2008). Richardson et al. have incorporated neurotrophin-3 (NT-3) into an electrically conducting polymer (polypyrrole/para-toluene sulfonate) which was applied to the surface of a cochlear implant electrode and have conducted *in vivo* experiments in guinea pigs which demonstrated release of NT-3 over time without disruption of the cochlear implant's ability to perform electrical stimulation (Richardson et al. 2009). Other biopolymers are under study for application within the inner ear, such as poly (styrene-b-isobutylene-b-styrene) which has been studied for the delivery of dexamethasone in a TNFα ototoxicity *in vitro* model using organ of Corti explants of P3 rats (Dinh et al. 2008). The potential drawbacks to modification of existing cochlear implant technologies for delivery of drug to the inner ear include the potential for a greater risk of infection and poorer implant performance – both concerns would require study prior to human application. Despite these potential risks, investigators are focusing their attention on the delivery of neurotrophins and steroids along with the cochlear implant.

The delivery of neurotrophic substances to the inner ear has been one principle focus for modification of cochlear implant technologies to achieve direct drug delivery. The objective of delivering neurotrophins to the inner ear in this setting is to attempt to preserve spiral ganglion cell counts, as it has been reasoned that the number of viable spiral ganglion cells should correlate with functional cochlear implant results (Incesulu and Nadol 1998). In contrast to this assertion, two subsequent studies of temporal bones from humans with cochlear implants either showed no correlation or a negative correlation of spiral ganglion counts with functional results (Khan et al. 2005, Fayad and Linthicum 2006). Despite these findings, at the very least it seems reasonable that a certain threshold of spiral ganglion cells must be met for cochlear implantation functionality. To maintain spiral ganglion counts, investigators have examined instillation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). BDNF has been shown to have significant effects on survival of cultured spiral ganglion cells as well as to enhance neurite outgrowth (Warnecke et al. 2007). Additionally, *in vivo* experiments in guinea pigs have demonstrated increased spiral ganglion cell survival and increased numbers of spiral ganglion cell peripheral processes with local application of both BDNF and fibroblast growth factor one (FGF-1) (Miller et al. 2007). Leukemia inhibitory factor (LIF) and neurotrophin-3 have also been shown to stimulate neurite outgrowth (Malgrange et al. 1996, Gillespie et al. 2001).

Cochlear implantation is also under study for a relatively new application in which patients have significant high frequency hearing loss but whose hearing loss is not severe enough to warrant candidacy for conventional cochlear implantation. In an attempt to maintain residual acoustic hearing, such implantation strategies are designed to be as atraumatic as possible, and involve either the placement of a shorter electrode or the partial insertion of a conventional electrode (Turner et al. 2008). The ability to maintain residual acoustic hearing has been met with variable success using these techniques, ranging from complete anacusis to partial hearing loss to maintenance of preoperative hearing within individual subjects across various trials

(Gantz and Turner 2003, Kiefer et al. 2005, Gantz et al. 2006, James et al. 2006). Maintaining residual hearing for combined electric-acoustic hearing in selected cochlear implant recipients presents another opportunity for modifying cochlear implant electrodes to deliver therapeutic drugs, such as steroids, to the inner ear. Local application of triamcinolone to the site of cochleostomy in guinea pigs has been shown to protect hearing from the surgical trauma of cochleostomy (Ye et al. 2007). Application of dexamethasone to the round window has similarly been shown to protect hearing as demonstrated by a decrease in traumatic threshold shift over time, especially in the high frequencies or when associated with a traumatic electrode insertion (James et al. 2008). The effects of a continuous (8-day) application of dexamethasone in artificial perilymph directly into the cochleostomy site have been examined in an electrode insertion trauma model; investigators reported no significant difference in ABR thresholds in traumatized cochlea treated with dexamethasone in artificial perilymph in comparison to the untraumatized contralateral control ears across all tested frequencies 30 days after the inciting trauma (Eshraghi et al. 2007). The base form of dexamethasone (a form of dexamethasone which has limited solubility in aqueous solution but is highly soluble in organic solvents and can therefore be more easily incorporated into polymers) has similarly been shown to have a hearing protective effect in an electrode insertion trauma model (Vivero et al. 2008). However, the long-term efficacy of steroid application within the cochlea as a protective agent in the setting of cochlear implantation has been called into question and warrants further study (Huang et al. 2007, James et al. 2008).

Drug delivery via an osmotic pump

An osmotic pump has been used by investigators for direct drug delivery to the inner ear (Kingma et al. 1992, Brown et al. 1993, Prieskorn and Miller 2000). In an experiment detailing tetrodotoxin delivery to the guinea pig cochlea via an osmotic pump delivery system, Brown et al. demonstrated infusion via this system resulted in a decreased sensitivity of the cochlea across the frequency spectrum that reversed with removal of the drug delivery system (Brown et al. 1993). More recently, the micro-cannula portion of the drug delivery device has been modified to permit longer drug infusion times as well as bolus dosing (such as for viral vector delivery) (Prieskorn and Miller 2000). The potential downsides of the osmotic pump device include inability to deliver varying dosages or dosing intervals of drug, the inability for investigators to start and stop drug delivery externally (without removing the system), and the limited duration of drug delivery requiring the need for surgical access to the device if therapy is planned for a sustained period of time, such as several weeks or months (Kingma et al. 1992, Hoffer et al. 2001).

Drug delivery through a reciprocating perfusion system

Over the past decade, novel approaches to drug delivery based on microsystems and microfluidics technologies have emerged (McAllister et al. 2003, Eddington and Beebe 2004, Tao and Desai 2005, Prescott et al. 2006, Chung et al. 2008). These approaches leverage extraordinary advances in miniaturization and integration of multiple functions on a single chip; entire drug delivery systems including power, electronic control, drug reservoirs, release mechanisms, and sensors can now be packaged and implanted in small spaces within the body (Borenstein 2009). There are significant advantages to these approaches relative to existing controlled release polymeric delivery systems, including greater control and precision over delivery profiles, improved preservation of potentially unstable drug compounds for long periods prior to release, and the opportunity for timed-sequence release of multiple agents for therapeutic applications that may require complex dosing of numerous compounds (Sewell et al. 2009).

Emerging microfluidics and microsystems technologies have been used toward the development of a reciprocating inner ear drug delivery system by engineers and researchers at

the Charles Stark Draper Laboratory (Cambridge, MA) and Massachusetts Eye and Ear Infirmary and applied to the cochlea in a guinea pig model (Chen et al. 2005, Sewell et al. 2009). The system is designed to deliver drugs to the inner ear with zero net fluid volume change within the perilymphatic space, with precise flow rates and delivery volumes, and by protocols that can vary in a programmable manner over time. The zero net delivery design is important, as continuous infusion strategies have been associated with expulsion of perilymph through the cochlea aqueduct with subsequent spread of infused material to the contralateral ear (Borkholder 2008) with the implication of cerebrospinal fluid contamination. This zero net delivery is accomplished by the precise addition of concentrated drug to recirculating perilymph within the device. The perilymph and drug mixture is delivered into the cochlea in a pulsed fashion such that fluid is infused at a comparatively rapid rate followed by a slower rate of withdrawal to the pump system through the same port. Once in the cochlea, the concentrated drug diffuses into the surrounding perilymph, thereby accomplishing delivery. These two processes, infusion and withdrawal, can be controlled separately, thereby optimizing drug delivery conditions. Precise drug delivery can be accomplished at extremely low volumes and flow rates through the system's micropumping elements, enabling safe delivery of drug below the threshold for hearing damage (Fiering et al. 2008). The recirculation component of the device has the added advantage of permitting delivery of constant concentrations of medication over an extended period of time through recirculation of perilymph through a concentrated drug containing reservoir. This design could potentially permit distribution of drug throughout the inner ear for years without the need to refill the reservoir. As these technologies are at the horizon of development of inner ear drug delivery, little has been written regarding their potential drawbacks. The most obvious drawback to these systems is the need for surgical implantation. However, surgical procedures of the inner ear are quite safe; in fact, over 112,000 cochlear implantation procedures have been performed worldwide with a low complication rate (NIDCD 2008). Depending upon the clinical situation, the risks associated with an implantable device for inner ear drug delivery may be justified.

Emerging breakthroughs in biology with implications for treatment of inner ear disease

Emerging developments in biology with implications for treatment of inner ear disease will likely require implementation of emerging technologies for direct inner ear drug delivery to achieve therapeutic effect as they develop into treatment strategies. Two such developments, RNA interference and stem cell therapies, are provided as examples and will now be reviewed.

RNA interference

RNA interference (RNAi) is one potentially groundbreaking method for changing the outcome of inner ear disease. RNAi involves genetic manipulation at the molecular level taking advantage of a natural process occurring within cells wherein messenger RNA (mRNA) is inactivated by particles called small interfering RNAs (siRNA). The process of RNAi involves the cleavage of double stranded RNA into twenty one base pair duplexes with a two base pair overhang at the 3 prime end – these particles are termed siRNA (Behlke 2006, Hildebrand et al. 2008). These siRNA are incorporated within a protein complex, one strand is cleaved, and the active strand is used to determine the sequence of the mRNA to inactivate (Behlke 2006, Hildebrand et al. 2008). It is this inactivation of mRNA that allows RNAi to alter gene expression. As with other forms of gene therapy, difficulties arise in delivering these molecules selectively to target tissues. Despite this concern, the direct inner ear drug delivery technologies currently under investigation may be useful in delivery of siRNA as a therapeutic agent to the inner ear. Although these RNAi techniques are in the early stages of development, their potential to dramatically alter human inner ear disease is enormous. RNAi technology seems particularly well-suited for treating dominant-negative forms of hearing loss by reducing the

amount of aberrant mRNA available for translation. In fact, RNAi technology has been successfully applied in a mouse model for GJB2 related hearing loss caused by an autosomal dominant non-syndromic form of hearing loss caused by a dominant-negative mutation (Maeda et al. 2005). RNAi has also been used to reduce cisplatin related hearing loss in a rat model (Mukherjea et al. 2008).

Stem cell therapy

Stem cell therapy for the inner ear has primarily been directed toward developing strategies for hearing rehabilitation. Early work in the field showed that stem cells harvested from the hippocampus of the rat injected into the inner ears of neonatal rats were sometimes found to have the morphologic features of hair cells (Ito et al. 2001). This finding generated considerable interest with the obvious implication for hearing rehabilitation in patients who had lost hearing as a result of loss of the hair cell population. The finding that exogenously derived stem cells applied to the inner ear may form hair cells, while exciting, has numerous challenges to clinical application. Such challenges include the need to deliver the cells to the organ of Corti within the human, the need to strictly control the differentiation of the implanted stem cells into the desired end cell line, and the need to develop surrounding support structure and innervation within a given ear.

Some of the obstacles to the utilization of exogenously derived sources of embryonic stem cells for delivery to the inner ear could potentially be overcome with the recent discovery that endogenous sources of stem cells exist within the inner ear in the adult mammal. Li et al. demonstrated the presence of stem cells within the adult mouse utricle and, more recently, stem cells have been isolated from the cochlea of the neonatal mouse (Li et al. 2003, Oshima et al. 2007). With the discovery and isolation of endogenous stem cells located within the inner ear (Li et al. 2003, Wang et al. 2006, Oshima et al. 2007, Zhang et al. 2007), investigators have been examining the potential of utilizing these stem cells for inner ear therapy. The potential utility of endogenous stem cells within the cochlea is uncertain in adults because of the apparent decrease of stem cells numbers with age in the developing mammalian cochlea. It remains to be determined if the decrease in stem cell numbers denotes a loss of stem cells or represents a repression of stem cell activity by the maturing cochlear endorgan (Oshima et al. 2007). However, the existence of stem cells within the mammalian cochlea does allow for the possibility of cochlear regeneration from the differentiation of stem cells to replace damaged or lost inner ear cells (Martinez-Monedero et al. 2007).

Additional challenges exist in using stem cells for hearing restoration. For example, in many instances, hearing loss is the result of loss of both the native hair cell population and degeneration of spiral ganglion neurons. This represents an additional degree of complexity, as one would conceivably need to regenerate both hair cells and spiral ganglion neurons, and achieve a functional neural synapse between the two. Despite the challenges, considerable progress is being made. Injection of embryonic stem cell derived progenitor cells (of both the mouse and human) into the cochlear nerve (of the gerbil) have been shown *in vivo* to direct neurite outgrowth to the Organ of Corti in a primary neural degeneration model (Corrales et al. 2006, Shi et al. 2007). Functional synapses between stem cell derived neurons and hair cells has also been demonstrated (Wei et al. 2008).

An alternative approach for cochlear hair cell regeneration that does not rely upon the existence of stem cells located within the developed inner ear involves the process of transdifferentiation. Transdifferentiation involves one type of differentiated cell changing into another type of differentiated cell with or without an intervening mitosis; these cell types are usually closely related developmentally (Batts and Raphael 2007). Functional hair cells have been generated by the transdifferentiation of non-sensory cells within the mammalian inner ear by the transfection of the transcription factor Atoh1 (Izumikawa et al. 2005). Although promising,

this technique does face some significant obstacles including the need to selectively target supporting cells within the Organ of Corti to avoid generating ectopic hair cells, the problem of generation of hybrid cells with characteristics of dual differentiation, and in some instances, the lack of closely related cells to transdifferentiate, such as the complete replacement of the Organ of Corti with simple epithelial cells in longstanding severe hearing loss (Batts and Raphael 2007).

As the fields of stem cell research and transdifferentiation in the inner ear mature and the potential for human application rises, novel strategies will need to be applied to provide the correct environment to promote appropriate differentiation *in vivo*. As numerous growth factors are utilized in the developmental processes of stem cells, it is conceivable that delivery of these growth factors *in vivo* with a form of inner ear drug delivery will be necessary.

Conclusions

Delivery of medication to the inner ear is a field undergoing rapid development. Initially, treatments aimed at the inner ear were given systemically. In an attempt to alleviate some of the problems associated with systemic delivery, primarily the systemic side effects, researchers and clinicians have been investigating application of medications topically to the middle ear to permit diffusion through the round window membrane and into the inner ear. Two of the most widely used applications of this form of therapy in current use are intratympanic gentamicin for Meniere's disease and intratympanic steroids for idiopathic SSNHL. Some evolving technologies designed to improve delivery to the inner ear via topical middle ear application include hydrogels and nanoparticles. Middle ear application of medications has limitations as well, such as anatomic obstruction of the round window membrane, loss of medication via the Eustachian tube, and unclear pharmacokinetic profiles. In an attempt to address these obstacles, forms of direct delivery of medication to the inner ear have been under development. These include modification of existing cochlear implant technology, direct delivery via an osmotic pump, and direct delivery via a reciprocating perfusion system. These systems also have the potential for use alongside some novel applications being considered for therapy in inner ear disease such as RNA interference and stem cell applications. Although direct drug delivery techniques are currently at an early stage of development; with refinement and continued study, treatment of human inner ear disease will very likely be altered by their use. Of the direct drug delivery technologies, modifications of the cochlear implant appear to be the closest to clinical application whereas the reciprocating perfusion system may ultimately show the broadest clinical applicability in human inner ear disease.

Acknowledgments

This work was supported in part by grant number 5R01DC006848-03 from the National Institutes of Health, National Institute on Deafness and other Communication Disorders.

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