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Rescuing the Cochlea: the challenges

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Introduction

The inner ear has been a target for drug based therapies for over 60 years. Firstly via systemic administration of aminoglycosides to treat severe bilateral Meniere's disease, and more recently by the application of steroids for sudden sensorineural hearing lens (SNHL). Although these therapies remain in common clinical practise, they have significant limitations including highly variable pharmacokinetics due to the blood-cochlear barrier and clinical variability (e.g. patient age; renal function; aetiology; previous inner ear pathology; genetic disposition), and potential undesirable side-effects associated with systemic drug administration.

As a result of these limitations, and in an attempt to improve the reliability of clinical outcomes, investigators began to develop drug delivery techniques specifically targeting the inner ear by delivering drugs directly to the round window (RW) niche. In the majority of cases temporary delivery of therapeutic drugs can be achieved transtympanically and the procedure performed in an outpatient setting.

Intratympanic clinical delivery techniques include transtympanic injection into the middle ear, Gelfoam™ based soak placed in the RW niche, the Silverstein Microwick™ (Micromedics; Eaton, MN, USA) and the Round Window microcatheter (Durect Corp, Cupertino, CA, USA). These techniques are used as a more targeted approach to drug delivery in the inner ear and are used mainly in Meniere's and sudden SNHL after systemic treatment has failed (McCall et al., 2010; Swan et al., 2008).

Although inner ear drug delivery via the intratympanic route is now routinely used, it only offers a short-term delivery strategy and has a number of limitations including loss of drug through the Eustachian tube, variability in pharmacokinetics due to variability and thickening of the RW membrane (Salt and Plontke, 2009; Swan et al., 2008), and the very slow diffusion of the drug through the cochlear - with some drugs failing to reach therapeutic concentrations in the apical region of the cochlear. Indeed, multiple applications of a drug are required via a RW route for that drug to reach the apical turn (Salt and Plontke, 2009).

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The most efficient route is delivery of the drug directly into the inner ear. Direct delivery of a drug into the perilymph will result in its distribution to most structures within the cochlea including the organ of Corti, the spiral ganglion neurones, the spiral ligament and spiral limbus; only the scale media and stria vascularis are not accessible via this route due to the presence of tight junctions (Swan et al., 2008). The efficiency of this drug delivery route brings with it increased risks of both short and long-term damage to inner ear structures. However, more than three decades of experience with cochlear implantation (CI) has increased our confidence in developing safe and effective drug routes involving direct application into the inner ear. A major impetus for this work is associated with the development of techniques to preserve hair cells in CI subjects with residual low frequency hearing.

The remainder of this review shall examine this rapidly growing field of targeted drug delivery to the inner ear. However, before we do so we will review the array of drugs currently being considered for clinical application.

Therapeutic drugs for direct application to the inner ear

The development of improved drug delivery techniques is progressing at a faster rate than the exploration of safe and effective drugs designed to target specific inner ear diseases. In addition to the clinical use of aminoglycosides in Meniere's disease and steroids in sudden SNHL, there are a number of drugs undergoing evaluation in experimental trials. These include the use of glucocorticoid steroids such as dexamethasone in the treatment of autoimmune inner ear disease and tinnitus, their anti-inflammatory properties to minimise the tissue response to CI, and their anti-apoptotic activity to target hair cell rescue; and neurotrophins for protection of hair cells and primary auditory neurones (Pettingill et al., 2007). Other drugs that may show therapeutic potential include antioxidants for hair cell protection, neurotransmitters for tinnitus suppression, monoclonal antibodies for autoimmune inner ear disease, and apoptosis inhibitors for hair cell rescue (Abi-Hachem et al., 2010; Salt and Plontke, 2009). The direct application of any of these drugs would require considerable biosafety investigation prior to their clinical application.

One potentially significant area of research in this field has been the development of a large scale biological screen for genes and small molecules that modulate hair cell toxicity (Ou et al., 2009). It is expected that using this approach, and selecting from a library of FDA-approved drugs, will see a significant acceleration in the number of drugs that can be targeted for hair cell protection and other inner ear diseases.

Drug Delivery Systems directly to the inner ear

Delivering drugs directly to the inner ear has only been explored relatively recently. While there are only a limited number of clinical examples, a number of exciting technologies are currently undergoing development and evaluation experimentally. Besides the clear advantage of delivering predictable amounts of a drug into the inner ear, this technique offers the potential for safe delivery of drugs that have a history of adverse side effects when administered systematically.

Although efficient, direct drug delivery into the inner ear carries with it increased risks to the patient. Regardless of the status of the ear, these delivery techniques must be designed to minimise the risks of an adverse inflammatory response, infection, or adversely affect the functional properties of the inner ear. It follows that there can be different approaches for direct drug delivery into an inner ear devoid of cochlear or vestibular hair cells compared with a functionally normal ear. In the latter case, where the transduction process must be preserved at all costs, even small fluid volume changes within the inner ear may be detrimental to hearing or vestibular function (Swan et al., 2008). Using current technologies, direct drug delivery would only have application in cases where the inner ear is already compromised.

Strategies for direct drug delivery into the inner ear can be summarised into the following techniques:

a) *Delivery of drugs via hand held hypodermic syringe directly into the scala tympani*: although simple, this technique results in a high level of drug washout in association with perilymph flow on opening the cochlea, and is not regarded as a quantitative drug delivery method (Salt and Plontke, 2009).

b) *Drug delivery in association with cochlear implantation*: there are a number of options for direct drug delivery into the inner ear during CI surgery; indeed, the only techniques presently used clinically to deliver drugs into the inner ear are performed in association with CI. These techniques include:

- **i.** Application of the drug into the RW niche just prior to implantation;
- **ii.** A “single-shot” injection at the time of implantation;
- **iii.** “Bathing” the electrode array in a drug just prior to insertion
- **iv.** Drug eluting from the electrode array carrier (Jolly et al., 2010);
- **v.** Drug release from a reservoir and canula within the electrode array (Shepherd and Xu, 2002); and
- **vi.** Nanotechnology based controlled release techniques on the electrode array (see “e) Nanotechnology inspired applications”, below)

While these techniques take advantage of the surgical access to the inner ear during CI, a number of the approaches have important limitations. For example, although the application of dexamethasone into the RW niche have demonstrated hearing protection in experimental animals subject to CI (Eastwood et al., 2010), the time required for adequate diffusion to all cochlear turns make it impractical to perform during CI surgery. In addition, while delivery techniques incorporated into the electrode array are appealing because drug release will occur along the length of the array, thereby increasing the efficiency of drug delivery in the apical region of the cochlear, it is important that these techniques do not significantly change the dimensions or the mechanical characteristics of the electrode array. Therefore, catheters and hydrogels attached to an electrode array can be problematic. Any new electrode design incorporating these features would need to undergo carefully controlled electrode insertion trials to ensure they could be inserted atraumatically. The use of a large drug reservoir and

canula system directly into the inner ear is, in my opinion, not a suitable design for long-term clinical application because the risk (however small) of infection tracking along the canula into the inner ear. A cavity within an implantable biomaterial can act as a nidus for infection and is therefore not a suitable design for long-term implantation. Finally, another consideration associated with pump based drug delivery into the inner ear is the affects of fluid mechanisms on vestibular and cochlear hair cell function. Mini-osmotic pumps, for example, have drug delivery rates as low as 0.25μl/h which may be sufficient to cause adverse vestibular or acoustic side-effects.

c) *Microfluidics based drug delivery*: in contrast to the use of pump-based systems designed to continuously deliver small volumes into the inner ear, one group is developing a microfluidics system for drug delivery based on a "push-pull" technology whereby the drug is delivered in a small pulse followed by a slower rate of perilymph removal back into the pump resulting in no net change in inner ear volume (McCall et al., 2010). This approach is designed to reduce any adverse effects that a continuous delivery system may have on the fluid mechanics of the inner ear. Another advantage is that it could potentially deliver drugs for many years without the need to refill its reservoir. This technique is awaiting trials in experimental animals.

d) *Hydrogels*: are commonly used as scaffolds in a variety of tissue engineering applications that often include their incorporation with seeded cells and/or therapeutic drugs. Hydrogel based drug therapy typically involves the surgical delivery to the host site and importantly, the hydrogel is designed to completely biodegrade – there is no need to remove the scaffold following completion of the drug delivery period. Hydrogels can be designed to ensure controlled release of the therapeutic agent over a given time and in response to a biological trigger (pH, temperature etc). Hydrogels have been used successfully to deliver neurotrophins and dexamethasone to the inner ear of experimental animals (e.g. Noushi et al., 2005).

e) *Nanotechnology inspired applications*: nanotechnology based approaches offer huge potential for safe and highly targeted drug delivery to the inner ear. They include both biodegradable and non-degradable technologies; the use of nanoparticles that can cross membranous structures passively (Praetorius et al., 2007); larger nano-assembled structures capable of delivering a significant therapeutic payload (Wang et al., 2008); polymer technologies where specific drugs can be conjugated onto a polymer substrate (Thompson et al., 2006); and the application of target-specific nanoparticles designed to increase efficacy of drug delivery to a specific cell type via the use of monoclonal antibodies applied to the surface of the nanoparticle.

As with all nanoparticle applications designed for a clinical setting, their evaluation in regards to inner ear drug delivery requires ongoing safety studies, particularly with reference to the fate of non-biodegradable nanoparticles. We will briefly review two technologies that demonstrate the versatility of this approach for drug delivery into the inner ear.

Drug eluting electrically conducting polymers, such as polypyrrole (Ppy), can be coated onto CI electrodes without adversely affecting the electrical characteristics of the electrode array. Importantly, therapeutic drugs can be incorporated and released from Ppy surface. A major advantage of Ppy over other polymers is that the drug release can be induced and controlled with electrical stimulation. Using *in vitro* techniques, we demonstrated that neurotrophin-3 (NT3) could be incorporated into a Ppy matrix on the surface of CI electrodes, observed slow diffusion of the drug from the electrodes in the absence of electrical stimulation and large increase in its release when the electrodes were pulsed with an electrical stimulus (Thompson et al., 2006). Significantly, the incorporation of the NT3 into the Ppy matrix did not adversely affect the biological activity of the drug. More recently we chronically implanted NT3-coated electrodes into deafened guinea pig cochleae. These animals showed significantly lower electrically-evoked thresholds and greater neural survival compared to controls. Furthermore, the Ppy polymer did not exacerbate fibrous tissue formation or adversely affect CI function (Richardson et al., 2009).

Controlled release nano-encapsulation technologies, such as nanoporous poly-glutamic acid (PGA) spheres, have important application where drug release must be sustained over extended periods of time (Wang et al., 2008). A feature of this technology is that materials such as PGA are well established biocompatible and biodegradable system that release the drug over time as the polymer slowly biodegrades. We have encapsulated the neurotrophin brain-derived neurotrophic factor (BDNF) into the PGA nanoporous spheres (Glynn et al., 2008). BDNF is a basic protein and forms an electrostatic attraction with the PGA scaffold; its release is triggered at 37°C in a physiological pH solution. We measured up to 6 mg of BDNF release over a 60 day monitoring period *in vitro*; these are relatively large amounts of drug release using this technology. Moreover, the technology is adjustable, allowing the development of nanoporous spheres with different release profiles. Finally, we have demonstrated that encapsulating BDNF in PGA based nanoparticles did not adversely affect the biological activity of the neurotrophin *in vitro*. The versatility of the technology, together with the well known biocompatibility of PGA offers great promise for the development of a safe and effective drug delivery system for use in the inner ear. *In vivo* safety studies are currently being planned.

f) *Cell-based therapies*: cells that naturally release high concentrations of therapeutic proteins (e.g. Islet cells releasing insulin; choroid plexus neuroepithelium releasing neurotrophins) (Skinner et al., 2009), or cells genetically modified to over-express these proteins, offer an elegant solution for the delivery of proteins expressed under genetic cues. Although there is good evidence that cells transplanted into the scala tympani of the mammalian cochlea can survive long periods of time, there is extensive dispersal of the transplanted cells, including sites outside the implanted cochlea (Coleman et al., 2007), potentially reducing any therapeutic effect of the cell therapy. An effective method of overcoming cell dispersal and isolating allo- or xenogeneic cells from the host immune system is to encapsulate them in a biocompatible polymer such as alginate. This provides a protective semi-permeable membrane that admits oxygen and nutrients and releases bioactive cell secretions while restricting passage of larger cytotoxic agents from the host immune system.

These techniques have been used to rescue neurones in the spinal cord, eye and ear in experimental animals and have demonstrated survival times for the encapsulated cells of 6 months or more (Skinner et al., 2009). Another advantage of this technique is that relatively constant physiological levels of therapeutic drug are being delivered.

Conclusion

In this brief review I have highlighted a number of emerging technologies designed to improve the efficacy of drug delivery to the inner ear. These technologies are currently undergoing pre-clinical evaluation and while there is great optimism that some of these approaches will lead to their clinical application, promising preclinical studies do not necessarily lead to successful clinical outcomes. In addition to establishing basic safety and efficacy of the drug delivery technology, important manufacturing issues must also be satisfactorily addressed prior to widespread clinical use. These include: 1) the maintenance of the bioactivity of the drug when incorporated into a device, during storage on the shelf, and *in vivo* at 37°C; 2) sterilization of the device; and 3) altered mechanical/design characteristics of a device incorporating a drug delivery system that may result in increased risk of surgical trauma and/or infection. Although the drive to clinical application is very challenging, I am confident that we will see new delivery technologies available to Otologist's in the near future.

What areas of ear disease will be treated with direct drug delivery techniques? Replacing lost cells will be far more challenging that protecting existing cells. Therefore, in the foreseeable future we will see most activity in the areas of: 1) minimising the adverse effects of tissue reaction and residual hair cell loss following CI; 2) protecting residual hair cells from noise and ototoxic drug damage (particularly when known ototoxic's are being administered for life threatening diseases); and rescuing primary auditory neurones from ongoing degeneration after loss of sensory hair cells. Longer-term goals would include more effectively targeting tinnitus and Meniere's disease, other forms of SNHL not directly targeting the hair cell, and genetic based hearing loss.

Finally, this work needs to be performed as a close collaboration between engineers, scientists and clinicians in order to ensure the development of clinically relevant drug delivery techniques and the specific pharmacokinetics are understood so that the most appropriate regions of the inner ear are targeted.

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