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Microtechnologies for inner ear drug delivery

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Structured Abstract

Purpose of review—Treatment of auditory dysfunction is dependent on inner ear drug delivery, with microtechnologies playing an increasingly important role in cochlear access and pharmacokinetic profile control. This review examines recent developments in the field relevant to both clinical and animal research environments.

Recent findings—Micropump technologies are being developed that provide dynamic control of flow rates with refillable reservoirs to enable timed delivery of a series of multiple agents for protection or regeneration therapies. These micropumps can be combined with cochlear implants with integral catheters or used independently with cochleostomy or RWM delivery modalities for therapy development in animal models. Sustained release of steroids with coated cochlear implants remains an active area of research with first-time-in-human demonstration of reduced electrode impedances. Advanced coatings containing neurotrophin producing cells have enhanced spiral ganglion neuron survival in animal models, and have proven safe in a human study. Microneedles have emerged as a novel method for controlled microperforation of the round window membrane with significant enhancement in permeability, which can be combined with emerging matrix formulations that optimize biological interaction and drug release kinetics.

Summary—Microsystem technologies and associated fabrication techniques are providing enhanced and more controlled access to the inner ear for advanced drug delivery approaches, alone and in conjunction with cochlear implants.

Keywords

Inner ear drug delivery; Micropump; Cochlear Implant; Microneedle

Introduction

Effective delivery of protective and curative agents to the inner ear remains challenging due to the anatomical structure of the bony labyrinth. Key barriers include the blood-labyrinth barrier which impacts the efficacy of systemically delivered agents, and the tympanic, oval and round window membranes which are barriers to drugs delivered via the middle ear cavity. Controlling intracochlear drug concentrations, achieving therapeutic dosing, and avoiding systemic side effects have led to significant efforts in improving site-directed

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None.

delivery approaches. There are numerous review and research articles covering the broad range of approaches to inner ear drug delivery [1–4] important work in nanoparticles and hydrogels for site-directed delivery [5–8], mechanisms for propelling nanoparticles through membranes [9], and overviews of advances in molecular and cell-based therapies [10,11,12**]. Important pharmacokinetic principles have been reviewed by Salt and Plontke [13**], with novel methods emerging to quantify intracochlear transport parameters [14*]. This review focuses on state-of-the-art advances in microtechnologies for improving control, and the pharmacokinetic profile, of site-directed drug delivery to the inner ear.

Micropumps for Inner Ear Drug Delivery

Active, acute, local delivery has been done with micropipettes or syringe pumps to investigate various drug delivery features such as concentration gradients of a delivered drug from base to apex in the cochlea [15–18], or to deliver gene and stem cell therapies to the inner ear [19]. Commercially available osmotic pumps (Durect Corp, Cupertino, CA) have also been used extensively for more sustained delivery profiles [20–22]. The device enables continuous drug delivery from 1 day to 6 weeks at flow rates from 0.1 to 10 $\mu\text{L/hr}$ [23]. While straightforward to implant and power-free, these pumps have a fixed infusion rate and are not refillable once implanted. Hence several groups have pursued research into micropump technologies that can provide dynamic control of flow rates, with refillable reservoirs to enable delivery of a timed series of multiple agents.

Reciprocating Micropumps

Tandon et al. demonstrated a reciprocating micropump which was designed to be used with a head mount for guinea pigs [24*]. This microsystem consists of a drug reservoir, a fluid storage capacitor filled with artificial perilymph, and electromagnetic actuators for valves and pumping. The system operates in a push-pull mode to enable both infusion and withdrawal of fluid from the cochlear compartment, enabling net-zero volume change, with a residence time for diffusion. Each pump stroke generates pulsatile peak flows of $\sim 50 \mu\text{L/min}$ (infusion) and $\sim 15 \mu\text{L/min}$ (withdrawal). Acute *in vivo* experiments with infusion of DNQX into ST of guinea pigs demonstrated safety and efficacy of the micropump with expected auditory shifts as measured by DPOAE and CAP. The long-term impact on hearing with the push-pull delivery modality has not yet been evaluated. The size of the micropump ($40 \times 30 \times \sim 10 \text{ mm}^3$) limits application in smaller rodent models and makes implantation challenging.

Peristaltic Micropumps

Peristaltic micropumps (PMPs) offer unique capabilities for drug delivery, such as continuous flow and high-tolerance to backpressure. iPRECIO(R) SMP-310R pumps are miniature, programmable, commercially available implantable micropumps consisting of a motor-driven rotary finger capable of flow rates down to 0.1 $\mu\text{L/hr}$ [25]. These pumps were used for infusion of fluorescein isothiocyanate dextran as a marker into the guinea pig cochlea [26**]. Contrary to expectations, they observed large longitudinal gradients in dextran concentration along scala tympani after 1 and 7 days of sustained infusion. Although

these pumps provide ultra-low flow rates suitable for inner ear delivery, the overall size ($25 \times 15 \times 8 \text{ mm}^3$), weight (3.4 g), and catheter size (1.5 mm OD) can create challenges for inner ear drug delivery in small rodents such as mice.

An implantable microsystem optimized for murine inner ear drug delivery has been reported [27]. The microsystem consists of a battery-powered, wirelessly controlled phase-change-driven PMP, a 10 μL refillable microreservoir, and a microcatheter of only 0.25 mm OD. The pump demonstrated flow rates of 10–100 nL/min with 2.4 nL/min resolution [28*]. The 1-mm-thick septum of the microreservoir demonstrated thousands of refill injections without leakage [29*]. The integrated device achieved a thin profile suitable for subcutaneous implantation in mice (size: $19 \times 13 \times 3 \text{ mm}^3$, weight: 0.8 g) and was implanted in mice for delivery of salicylate to the RWM with expected shifts in DPOAE thresholds. Testing including successful long-term biocompatibility assays and chronic implantation.

Co-delivery with Cochlear Implants

Cochlear implants (CI) have provided dramatic results for the profoundly deaf, but with significant inter-user variability. Co-delivery of anti-inflammatories at the time of implantation, sustained, long-term delivery of steroids, neurotrophins, and growth factors, or delivery of gene therapy has the potential to improve cell survival and spiral ganglion neural transmission throughout the cochlea [11,30]. Integration of drug delivery modalities, either via drug elution coatings or via integrated catheters, continues to be an active area of research. Plontke provides an excellent review paper on the co-delivery of drugs with CIs [31**]. Specific recent publications in this area are presented herein.

Steroid Elution Coatings

Coatings on cochlear implants represent a delivery modality that is easily integrated with research and clinical devices. There continues to be significant work characterizing the release kinetics with the objective of achieving stable and sustained concentration profiles within ST. A simulated CI device consisting of DEX loaded silicon rods, with DEX concentrations of 0.1%, 1%, and 10%, was tested via implantation in ST of guinea pigs with perilymph sampling up to 7 weeks post-implantation [32]. Sustained concentrations of about 60 and 100 ng/mL were observed in the perilymph for the 1 and 10% loaded rods respectively, demonstrating the potential for therapeutic dosing by loading of DEX into the silicone of a CI electrode array. Commercial arrays with silicone loaded with 40% (w/w) DEX demonstrated inhibition of osteoneogenesis and reduced SGN loss four weeks post-implant in a guinea pig model of high insertion trauma [33]. Briggs and colleagues demonstrated a first-time-in-human study of a DEX-eluting investigational electrode array [34**]. The commercial array was modified with 40% (w/w) DEX in a silicone back-strap along the length of the electrode array. With experimental implants in 10 human subjects (14 controls), electrode impedances were lower for basal, middle, and apical cochlear regions for the DEX eluting CIs for up to 24 months post-implant. These results support the clinical benefit of steroid eluting CIs.

Neurotrophin Delivery via Encapsulated Cells

While the majority of coating work for CIs has focused on steroid elution to reduce inflammation, there is also interest in coatings consisting of cells that release protective factors. A cell encapsulation device was developed for releasing neurotrophic factors in deafened guinea pigs via immortalized human retinal pigment epithelial cell line transfected to encode either GDNF or BDNF [35*]. The encapsulated cell device (0.4 mm OD, 4 mm length) was positioned within ST of the guinea pig with a tether via a basal turn cochleostomy in combination with a stimulus electrode mimicking a CI. The release of neurotrophic factors (BDNF or GDNF) to the inner ear significantly protected auditory SGNs from neomycin-induced cell death and maintained their electrical responsiveness.

Brain-derived neurotrophic factor-producing MSCs encapsulated in alginate have been used to deliver BDNF in combination with CI insertion in a guinea pig model [36,37*]. In deafened animals, the alginate-MSC coating on the CI significantly reduced insertion forces and SGN degeneration, demonstrating the potential for cell-mediated drug delivery in combination with a CI. Interestingly, direct injection of the alginate-MSCs into ST did not provide neuroprotective effects. Roemer and colleagues conducted a human safety study with a biohybrid CI [38**]. Autologous mononuclear cells were isolated from the patient's bone marrow (BM-MNC) and were coated on a silicone-based CI array using fibrin adhesive. *In vitro* analysis demonstrates human BM-MNCs release cytokines, chemokines, and growth factors that provide anti-inflammatory and neuroprotective effects with neonatal rat SGNs. There were no adverse effects in a trial with three human subjects, although the CI performance was highly variable, making it difficult to assess the benefits of the BM-MNC coated array.

MEMS-based Scaffolds

A microelectromechanical system (MEMS)-based microscaffold cochlear electrode array (MiSCEA) was recently developed for steroid elution into the inner ear following CI insertion [39*]. The MiSCEA consists of a flexible electrode array and a 3D microscaffold porous scaffold created with two photon polymerization and subsequently coated with titanium for biocompatibility. The scaffold is 4.28 mm long, 0.27 mm tall, and 0.61 mm wide, and was coated with a DEX-poly lactic-co-glycolic acid (PLGA) mixture for sustained release of DEX. *In vitro* results demonstrated six weeks of continuous release of DEX. *In vivo* experiments with implantation in guinea pigs demonstrated non-statistically significant improvements in hearing thresholds relative to control.

Integral Catheters

An alternate approach to drug elution matrices (polymer or cellular) is direct delivery of therapeutics via a catheter integrated with the CI, where the catheter is connected via a coupler to a pump. This approach has the potential to provide dynamic control of intracochlear drug concentrations, and can enable time sequenced delivery of multiple agents if connected to a pump with a refillable reservoir. There are two basic approaches to catheter integration, either direct molding within the CI array during production, or by

external coupling to a prefabricated CI. Shepherd and Xu developed a custom CI with a 0.163 mm polyimide catheter embedded within the core of a silicone molded array, with fluid efflux at the tip driven by an osmotic pump [40]. More recently, Salt and colleagues affixed a 0.102 mm ID polyimide catheter to the exterior surface of a commercially available CI array, with the tip positioned after the second electrode [26**]. A commercial PMP was used for delivery of FITC-labeled dextran markers as described above.

Microneedles

Transtympanic delivery of therapeutic agents to the middle ear represents a clinically accessible route which has been recently reviewed [4]. One key challenge is variable absorption through the RW and OW resulting in inconsistency in intracochlear concentrations. Several recent investigations attempt to improve the RWM permeability via chemical (reviewed at [41]) and physical methods. Ultrasound-aided microbubble cavitation has been used to enhance RWM permeability, with 11.2× enhancement of DEX delivery to the guinea pig RWM [42,43,44*]. However, there has been increasing interest in physical disruption of the RWM using microneedles which have demonstrated a 35× increase in the permeability coefficient of the guinea pig RWM membrane [45*], with permeability enhancement dependent on perforation size and the drug delivered [46]. Yu et al. showed that for a guinea pig model, a 100 μm microneedle can leave a $93 \times 35 \mu\text{m}^2$ hole that heals within a week after perforation [47]. Microneedles were also tested on frozen human temporal bones with $154 \times 16 \mu\text{m}^2$ and $103 \times 8 \mu\text{m}^2$ perforations using 150 μm and 100 μm microneedles respectively [48*].

One of the challenges of using microneedles is controlling insertion depth to ensure perforation while not damaging the sensitive tissues within ST. Silver-plated microneedles as silver/silver chloride electrodes were tested *in vitro* and demonstrated the ability to detect the moment of penetration across the RWM [49]. This will be an important capability in clinical translation of this technology to ensure consistency and efficacy of the procedure. Effective microneedle design requires an understanding of the microanatomical and mechanical properties of the RWM along with the mechanical properties of the microneedle to minimize tissue damage and needle failure [48*,50]. Different shapes for the microneedles have been fabricated, including tapered [48*,50], serrated [51], and dual-wedge [52]. Polymers, silicon, and metals have all been used as substrates or coating materials to fabricate microneedles using various fabrication processes including micromachining, micro-milling, electrical discharge machining, and two-photon polymerization lithography which are reviewed in [50].

Miscellaneous Microtechnologies

Recently new methods are being developed to create drug delivery matrices of controlled composition and shape. Porous scaffolds have been created using electrospinning fabrication, utilizing current to print charged fibers from a metformin and polylactic acid (PLA) solution onto a surface [53]. The reservoirs were 2 mm in diameter, 0.15–0.25 mm thick, with fiber diameters ranging from ~0.35 to 1.1 μm . *In vitro* experiments showed at least 6 weeks of continuous elution of metformin through a model of RWM, however, the

protective efficacy of metformin was not observed using Sh-Sy5y cells. Nonetheless, this novel and tunable drug delivery mechanism has potential for inner ear drug delivery.

Hot-melt extrusion was recently used to fabricate PLGA-based thin rod-shaped biodegradable implants (0.3 mm OD, 3 mm long) for controlled intracochlear release [54*]. The extrudates had 10% of DEX, while PEG was used in different compositions to improve flexibility and release rate. *Ex-vivo* experiments demonstrated the right balance of stiffness and flexibility for implant in the guinea pig ST. *In vitro* experiments showed weeks of DEX release with the rate depending on the composition of PEG/PLGA. Simulations show controlled release over a period of 35 days suggesting this type of implant could provide sustained DEX concentrations within ST. However, morphological analysis of the implant demonstrates significant swelling (43% length, 77% diameter) over a 21-day period. The impact of this swelling on the confined ST space is unknown. At four weeks the implants disintegrated into several fragments, suggesting the potential for full disintegration over time.

Diamond-shaped DEX microcrystals were synthesized and coated with poly L-lysine (PLL) and silk fibroin (SF) to improve mucous adhesive properties [55*]. The DEX-PLL/SF microcrystals enhanced adherence to the RWM, with guinea pig *in vivo* results demonstrating sustained release kinetics based on perilymph sampling and HPLC analysis. The research highlights the importance of engineering drug delivery vehicles at the micro-scale to achieve the right balance of biological interaction and drug release kinetics.

Conclusions

Microsystem technologies have enabled new classes of micropumps with precise dosing control and multi-agent delivery that create opportunities to advance emerging protective and restorative therapies for the inner ear. These pumps can be combined with CIs in the future for co-delivery of steroids, neurotrophins, and other agents to reduce insertion-related inflammatory response, and to preserve SGNs. Advances in coating technologies with demonstrated DEX sustained release, and neurotrophin delivery via encapsulated, engineered cells offer a near-term opportunity to improve CI success and reduce inter-user variability. For drug delivery through the RWM, mechanical microperforation with microneedles has yielded promising results for transient enhancements in RWM permeability. These techniques can be combined with emerging microfabricated matrix formulations and engineered microcrystals to improve the consistency and dosing of RWM drug delivery approaches. Future research will leverage the potential of these microsystem technologies in emerging otoprotective and regeneration therapies.

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Abbreviations

BDNF

Brain-Derived Neurotrophic Factor

BM-MNC	Bone Marrow derived Mononuclear Cells
CAP	Compound Action Potential
CI	Cochlear Implants
DNQX	6,7-dinitroquinoxaline-2,3-dione
DPOAE	Distortion Product Otoacoustic Emissions
DEX	Dexamethasone
FITC	Fluorescein IsoThioCyanate
GDNF	Glial Cell-Derived Neurotrophic Factor
ID	Inner Diameter
MEMS	MicroElectroMechanical Systems
MiSCEA	MicroScaffold Cochlear Electrode Array
MSC	Mesenchymal Stem Cells
PEG	Polyethylene Glycol
PLGA	Poly(Lactic-co-Glycolic Acid)
PMP	Peristaltic MicroPump
OD	Outer Diameter
RWM	Round Window Membrane
SGN	Spiral Ganglion Neurons
ST	Scala Tympani

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Key Points

- Effective inner ear therapies require accurate control of intracochlear drug concentrations over time.
- Microtechnologies are improving cochlear access and pharmacokinetic profile control.
- Micropump technologies with refillable reservoirs are sufficiently miniaturized for chronic implantation in mice for programmed delivery of multiple curative agents, with or without cochlear implants.
- Drug-eluting cochlear implants with steroids or live-cell-produced neurotrophic factors have seen first-time-in-human use.
- Microneedles can transiently increase round window membrane permeability to enhance the efficacy of middle ear drug delivery approaches.