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OTOLOGY: ADVANCES IN OTOLOGY (BD NICHOLAS, SECTION EDITOR)

The Augmented Cochlear Implant: a Convergence of Drugs and Cochlear Implantation for the Treatment of Hearing Loss

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Abstract

Purpose of Review Cochlear implantation gives us a unique opportunity to expand the pharmacological treatment of hearing loss. Delivery of pharmacological agents, cells, and gene therapy vectors to the inner ear are challenging due to anatomic and physiologic factors. Since cochlear implantation opens the inner ear, there is an opportunity to deliver therapeutics along with the electrode. This review will cover advances in drug-device development for cochlear implantation and highlight cutting-edge applications of the augmented implant.

Recent Findings Currently, clinical trials of dexamethasone-eluting cochlear implants are ongoing. Cochlear implants have also been coated with bone marrow–derived stem cells and have also been used in human trials.

Summary The development of an augmented implant that combines therapeutics with electrical stimulation can apply not only to improvement in cochlear implant outcomes but may develop into a stand-alone treatment of inner ear disease as these drug-device combinations evolve.

Keywords Drug delivery · Augmented cochlear implant · Hearing preservation · Cochlear health

Introduction

At present, treatments for hearing loss are limited to rehabilitative strategies ranging from amplification for mild to moderate losses to cochlear implantation for more severe hearing loss. Cochlear implantation has revolutionized the treatment of hearing loss and now is applied to patients with considerable residual hearing. Even with advances in signal processing and implant design, there is still variability in hearing outcomes with cochlear implants, especially in background noise [1]. While the advent of hearing preservation cochlear implantation has further improved performance, it has also added additional new risks such as insuring the long-term preservation of residual hearing. The ability to instrument the inner ear of course also suggests that the inner ear is amenable to treatment with pharmacologic agents via inserted delivery devices and that cochlear implantation in and of itself presents an opportunity for drug delivery to the inner ear (Fig. 1A, B). In parallel to this remarkable evolution of a device that can interface with the inner ear has been an explosion in understanding the molecular biology of hearing and hearing loss which significantly expands the potential range of interventions that we can contemplate to augment the capability of the cochlear implant. Key areas of development of the augmented implant include protection of residual hearing and balance, prevention of fibrosis and inflammation, improvement of implant outcomes, and the future alteration of cochlear phenotype.

Challenges in Drug Delivery to the Inner Ear

The cochlea is a unique compartment with its own blood-cochlear (labyrinth) barrier [2]. Therefore, compounds applied systemically do not always reach the cochlea requiring local application techniques. Additionally, the ratio of cochlear volume to systemic circulation argues that local delivery would be more efficient than systemic delivery.

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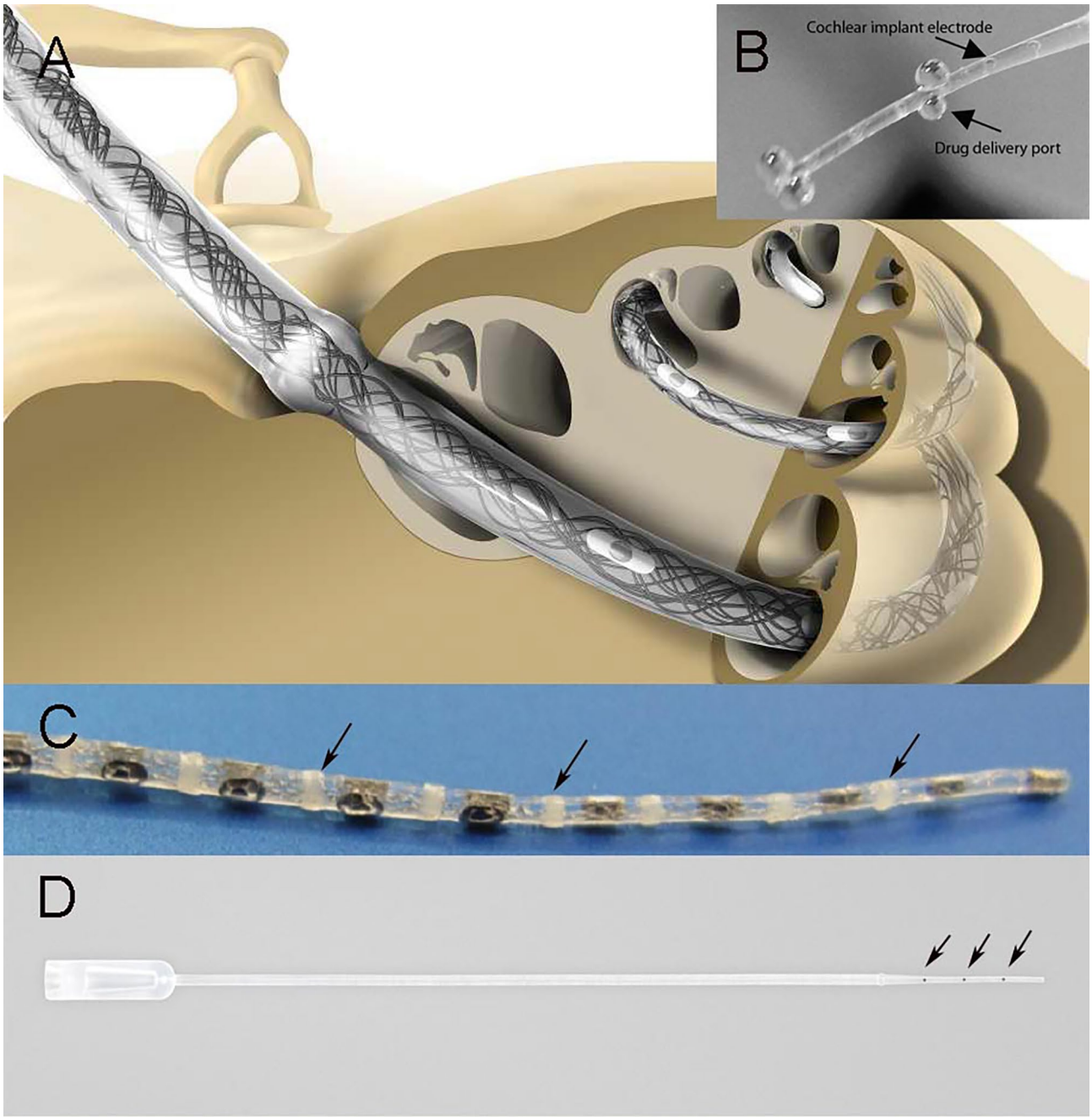

Fig. 1 Evolution of the augmented implant. Cochlear implants access the inner ear and in the case of lateral wall electrodes can penetrate to the apex of the cochlea, allowing them to directly interact with local tissues. This access to all areas of the inner ear sets up the implant as a device to enable drug delivery (**A**). Early research devices built delivery channels into the body of the electrode (**B**) allowing delivery to the regions large cochleae inaccessible to round window delivery and diffusion. The MedEl™ dexamethasone-eluting electrode carries dexamethasone-impregnated silicone bands between electrode contact allowing local release of drug in the basal, middle, and apical (*arrows*) turns (**C**). The success of hearing preservation surgery and drug delivery concepts have also led to the development of delivery devices based on electrodes (**D**). The inner ear catheter has multiple delivery ports (**D**, *arrows*) and can be inserted 20 mm into the cochlea

Transtympanic delivery of drugs is now a routine procedure in otology, e.g., for the application of high-dose steroids in patients with sudden sensorineural hearing loss, and has been extensively studied for a range of inner ear diseases. However, there are significant potential limitations to transtympanic delivery of drugs to the inner ear including lack of diffusion through the human otic capsule and the limitations of diffusion along the longer human cochlea [3, 4].

Thus, the surgical opening of the cochlea for implantation offers a route for local application directly into the inner ear and is, therefore, an invaluable clinical model for the development of novel therapeutics. To optimize the combination of drugs with a cochlear implant, the drug of interest must be infused into the inner ear either prior to implantation or alongside the implant. A final potential development is the combination of cochlear implants with gene or cell therapy in which the implant itself can be used to control the activity of the delivered transgene.

Cochlear Implant–Related Biotechnologies for Drug Delivery

Delivery from the electrode array: The electrode arrays that are implanted into the cochlea can be used as vehicles for drug loading. Silicone belongs to a class of biomaterials with a long history of clinical use in humans showing their biocompatibility, biosafety, and biostability. For drug delivery purposes, silicone elastomers have an acceptable reservoir due to their intermolecular composition allowing not only the loading with specific molecules but also due to modification techniques the release of drugs at individual rates. Pharmacologic agents could therefore be incorporated directly into the silicone or for shorter-term delivery be coated onto the implant in a dissolvable matrix. In vivo and in vitro studies demonstrate the efficacy of this approach and have led to the development of initial human clinical trials (Fig. 1C) (NCT04450290) [5–7].

Coatings: Coating the electrode has been proposed as a means of incorporating drugs as well as improving the insertion properties of the implant [8]. By varying the coating material, different agents ranging from small molecules to nucleic acids can be delivered. The total delivery time is related to the material properties of the coating and the thickness of the application. This would give tremendous flexibility to the type of substances that can be delivered to the inner ear.

Modeling delivery catheters on cochlear implants: Since the implant electrode has the capacity to enter the cochlea without damage, it can also form the basis of a delivery device [9]. Cochlear implants with a channel within the electrode have been experimentally tested but for long-term delivery would have to be combined with a refillable reservoir and pump to deliver over long time periods (Fig. 1B). This has led to the development of a stand-alone delivery device, the inner ear catheter, that can be used to deliver medications or biologicals alone or prior to implantation (Fig. 1D) [10].

Pharmacological Interventions to Improve Cochlear Implant Outcomes

Growth factors: One of the originally proposed applications for drug-device combinations was the unitization of neurotrophin therapy in the damaged inner ear to maintain spiral ganglion populations. The integrity of the spiral ganglion has been hypothesized to be a potential peripheral cause of implant outcome variability [11]. In animal models, damage to the organ of Corti leads to loss of neurotrophin production and degeneration of the spiral ganglion. The loss of spiral ganglion cells can clearly be arrested by the application of exogenous neurotrophins either when delivered as a protein through a pump or by genetic engineering approaches such as gene therapy or delivery of engineered cells [12]. Most studies have focused on the delivery of the neurotrophins BDNF, NT-3, and GDNF. Application in animal models of cochlear implantation has demonstrated that neurotrophin-treated animals have lower thresholds for electrical stimulation [13, 14]. Interestingly, it is only recently that we have evidence from human temporal bone pathology that a larger spiral ganglion population correlates to better speech scores, giving a rationale for finding therapeutic interventions to improve neuronal health. At this point in time, human temporal bone studies have only correlated the quantity of spiral ganglion cell bodies to speech scores [15]. This of course does not give a read-out on neuronal function, which in and of itself may be enhanced by neurotrophin delivery since these substances not only control neuronal survival but also modulate qualities such as excitability.

One of the potential problems of direct infusion of proteins into the inner ear is that delivery would need to take place for the lifetime of the patient. This would require the presence of a refillable reservoir as part of the implant delivery system that has the potential risk of contamination each time the reservoir is refilled. This led to the development of two different strategies for long-term delivery: gene therapy and cell therapy with engineered cells. Gene therapy using a variety of vector systems can clearly support spiral ganglion survival in animal models of aminoglycoside ototoxicity [16, 17]. One study has also used a large animal model to clearly demonstrate the benefit of neurotrophin therapy in conjunction with implantation [18]. Electrical stimulation by itself has the potential to induce neurotrophin signaling and there is a possibility that short-term neurotrophin therapy may just bridge the time to electrical stimulation [19, 20]. The synergistic effects that underlie the combination of electrical stimulation with neurotrophin delivery are incompletely

explored and will in part be addressed by the novel electrophysiologic measures of cochlear health that are being developed [21, 22]. Potential future development of neurotrophin therapy may involve coating the electrode in a neurotrophin-like polymer that attracts neurites towards the implant, thereby lowering stimulation thresholds and allowing more precise stimulation of different frequency bands [23]. Alternate approaches for delivering neurotrophic factors is to use genetically engineered cells that have been caged to prevent immune system inactivation of the cells. These approaches have been initially tested in the inner ear and found to be effective in rescuing spiral ganglion cells [24, 25]. Potentially less complex strategies could also be developed to deliver effective neurotrophin effects. The electrical charge delivered by the cochlear implant can be used to electroporate plasmids carrying the BDNF gene into tissue surrounding the implant [26]. This requires less complex vector construction and has been shown to generate biologically relevant BDNF expression in animal models. Since there is significant variability in outcomes, even in severely profound hearing loss patients, therefore assays that allow the determination of neurotrophin signaling status within the inner ear are needed. Perilymph sampling potentially can be used to identify cochleae with deficient BDNF signaling as has recently been described [27–29]. Selected cases could then be treated with neurotrophin therapy either at the time of implantation or in a delayed fashion if implanted with a device with delivery ports.

Antioxidative and anti-inflammatory treatments: With the rapid expansion of hearing preservation cochlear implantation maintaining cochlear health is a priority in the development of the augmented implant. The exact causes of hearing loss after cochlear implantation are not clearly defined. Certainly, there are mechanical factors such as translocation of the implant into the scala media that can cause hearing loss and cannot be addressed by drug therapy but for the most part hearing loss is delayed and insidious. Hypothesis for the underlying pathophysiologic process includes inflammation, electrotoxicity, and changes in the venous outflow from the cochlea [30]. Inflammation induced by implantation has the potential to induce loss of residual hearing through several mechanisms. Mathematical modeling demonstrates that fibrosis alone could potentially affect hearing through micromechanical dampening of the traveling wave [31]. Guinea pig models of cochlear implantation show upregulation of pro-inflammatory genes (Cxcl1, IL-1b, TNFα _,and Tnfrsf1a/b) and upregulation of remodeling genes such as TGF beta and matrix metalloproteinases [32, 33]. Human temporal bone studies have demonstrated a granulomatous reaction associated with electrodes in most available cases [34, 35] suggesting that an inflammatory response after implantation is common in humans. Animal studies of hearing preservation cochlear implantation also correlate the extent of intracochlear tissue growth with the degree of hearing loss [36, 37]. A major modulator of this process is intracochlear bleeding during implantation which accelerates the process of fibrosis and ossification [38]. The key initiators after trauma are M2 macrophages [39]. Animal models also demonstrate that increasing systemic immunity increases the response to implantation and that this effect can be at least partially countered by pretreatment with dexamethasone [40]. Since dexamethasone is rapidly cleared from the inner ear, research has focused on developing pretreatment strategies or drug-eluting electrodes [41, 42]. Takumi et al. demonstrated that the use of steroid-eluting electrodes could mitigate the pro-inflammatory gene expression seen with implantation [33]. The use of dexamethasone in increasing doses decreases post-implantation fibrosis, preserves hair cells, and decreases hearing loss and impedances [5]. Besides the use of steroids, growth factors such as IGF-1 may also protect the inner ear during the implantation process [43, 44].

At present, different concentrations of dexamethasone can be incorporated into silicone and can be made into standardized electrodes (Fig. 1C). Alternately, a range of different coatings can be applied to implants. For example, coating electrodes with 2-methacryloyloxyethyl phosphorylcholine polymer protected the hearing and morphology of normal guinea pigs after implantation [45]. Polymer coatings may further be modified to prevent fibroblast adhesion to the implant [46]. Different coatings potentially also alter the mechanical properties of the implant electrode during insertion, thereby decreasing insertion forces and protecting the inner ear from mechanical trauma [47].

Biologically Augmented Implants

Cell therapy and implantation: A novel approach for immunomodulation and control of inflammation in cochlear implantation is the use of autologous cell transplantation. Cells and cytokines of the adaptive immune system play a prominent role in the initiation and progression of fibrosis. Fibrosis is mainly a consequence of a Th2 cytokine–dominated inflammatory response [48]. The cytokines interleukin-4 and interleukin-13 are potent initiators of fibrosis. By contrast, Th1 cytokines such as interferon gamma and interleukin-12 suppress fibrotic tissue formation. Thus, modulation of responses to inflammation or foreign body reaction could suppress or ameliorate fibrotic tissue formation during cochlear implantation, improve implant performance, and protect residual hearing. Cell therapy may have additional benefits beyond immunomodulation. Increased neurogenesis is associated with enhanced activation of microglia [49]. However, immune cells have multiple effects on neurogenesis either supportive or detrimental and these are

depending on the quality and degree of immune cell activation [50]. The exact underlying mechanisms that are regulating these effects are unclear. The levels of cytokines and growth factors produced by immune cells may be one factor that determines supportive or detrimental neurogenesis. Growth factors, like insulin-like growth factor (IGF)-I and neurotrophins, e.g., brain-derived neurotrophic factor (BDNF) that are known to be neuroprotective, are released by these cells. Other trophic factors released include glial cell line–derived neurotrophic factor (GDNF), a member of the transforming growth factor-β (TGF-β) superfamily [51]. Neural progenitor cells (NPC) have been transplanted intrathecally after trauma to the spinal cord and significantly decreased scar formation and increased neuronal survival [52]. These effects are most likely due to the paracrine effects of NPC and seem accompanied by the increased bioavailability of neuronal growth factors. Excellent results have been achieved by NPC transplantation in experimental models of spinal muscular atrophy and amyotrophic lateral sclerosis [53]. Furthermore, anti-inflammatory effects of NPC were demonstrated in vivo in neuroinflammatory diseases [54]. This may be associated with a regulation of the production of proinflammatory cytokines and immunomodulatory effects of transplanted NPC have been demonstrated in several studies [55]. Mesenchymal stem cells (MSC) isolated from the bone marrow or other sources such as the umbilical cord also exert immunomodulatory and anti-inflammatory effects [56]. The therapeutic activity of stem or progenitor cells can be boosted by the interplay of transplanted and resident cells resulting in a site-specific coordination of neuroprotective, immunemodulative, and antioxidative properties. Thus, the environment in which stem or progenitor cells are transplanted can be stably changed to a more permissive and reparative state allowing regeneration rather than inflammation and fibrotic transformation.

In recent years, autologous transplantation of cells obtained from a patient's bone marrow has been used in conjunction with cochlear implantation [57]. In addition, cells can be applied to the inner ear by coating the surface of the electrode array [58]. Along with cell therapy, several other interventions can further influence the interaction of the cochlear implant with native tissue. Many of the immunomodulatory actions of mesenchymal stem cells are mediated by extracellular vesicles (EVs) produced by the MSCs [59]. Initial limited studies have evaluated the application of MSC-derived EVs in conjunction with cochlear implantation [60•].

Genetic disorders and alteration of phenotype: Beyond the delivery of growth factors, several other gene therapy–based applications for cochlear implantation are coming into focus. Several genetic disorders cause spiral ganglion dysfunction. A recent comparison of genotype to implant outcomes has demonstrated that several genetic disorders can affect cochlear implantation [61]. Amongst the most common of these are mutations in TMPRSS3, a serine protease that affects both hair cell and spiral ganglion function and is the gene that underlies DFNB8/10. Cochlear implantation in patients with this recessive mutation can result in poor speech outcomes that have been related to deficient spiral ganglion function [62•]. Combining gene therapy for TMPRSS3-induced hearing loss could optimize patients' hearing and improve implant outcomes. Similarly, the development of optogenetic implants will require gene transfer of optimized channel rhodopsin into the spiral ganglion followed by light-based stimulation [63].

Trial/Regulatory Considerations

The field of cardiology provides us with some guidance on how drug-device combinations may be developed. Dexamethasone-eluting pacemaker leads have been marketed since the early 1980s and at present have a significant safety track record [64]. Since these devices are regulated as drugs, a more complex yet navigable regulatory process is envisioned. For the inner ear, initial efforts should probably focus on combining known devices (i.e., a cochlear implant alone without a pump) along with a well-characterized pharmaceutical agent such as dexamethasone. Factors that need to be addressed are the methodology of combining the drug with the electrode (coating versus incorporation into the body of the implant). As with any drug study, pharmacokinetic profiling, stability testing, and safety studies are needed. Given the variability of cochlear implant outcomes, one of the major challenges will be defining the primary outcomes of a clinical trial. Potential outcome targets include preservation of residual hearing and maintenance of neuronal integrity. Ideally, animal models for testing combination devices would include near-human-sized inner ears with human-like physiology such as minipigs.

Conclusions

The development of an augmented implant can take several forms depending on therapeutic goals and the time course needed to treat patients. With an increased understanding of the molecular basis of hearing loss, we can envision a range of devices that allow acute delivery of drugs, viral vectors, or therapeutic cells at the time of implantation. Electrodes impregnated with pharmaceutical agents can be designed to deliver for the first month after implantation at high levels throughout the inner ear. Finally, implants that deliver a medication intermittently or chronically using reservoirs can deliver over long time periods. Initial targets will focus on the preservation of hearing and the prevention of postoperative intracochlear fibrosis. These initial steps will allow

the delivery of substances that improve and maintain neuronal health. This platform of combined electrical stimulation and drug delivery can be expanded to include a variety of more complex pharmaceutical or biological therapeutic interventions.

Declarations

Conflict of Interest Drs. Staecker and Warnecke are shareholders in Rescue Hearing, a gene therapy company. Dr. Staecker is a member of the surgical advisory board of MedEl.
The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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