Cochlear implantation: an opportunity for drug development

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For many years, the fields of inner ear pharmacology and hearing devices have progressed in parallel with limited interaction. Recently, there has been a considerable advancement in our understanding of the inner ear and its pathologies. Cochlear implantation is now being adapted for patients with considerable residual hearing but minimal benefit from hearing aids. A major consequence is the recognition that devices can be implanted into the partially deaf inner ear with minimal loss of hearing. This opens the door to the concept of local drug treatment of the inner ear using implantable devices. The evolution of cochlear implantation thus presents us with an opportunity to develop a range of local pharmacologic interventions to prevent hearing degeneration.

Introduction

Hearing devices have served the hearing impaired over the past half a century with increasing sound quality. Currently, hearing loss is managed by a variety of devices, head worn or implanted, depending on the nature and severity of the condition. Mild to moderate losses are generally managed through hearing aids (HA), whereas severe to profound sensorineural losses are usually better served by a cochlear implant (CI), which bypasses the hearing mechanism and stimulates the auditory nerve directly (Fig. 1a). Until recently, it was assumed that the process of electrode insertion deep into the cochlea would destroy all remaining acoustic hearing; therefore, the criteria for implantation have been conservative, based on the level of hearing loss. HA do not always restore sound clarity [1], however, and as device performance has improved, the additional dimension of speech perception ability is now used to assist the decision to provide an implant if the patient's hearing loss is severe to profound. Current US Food and Drug Administration guidelines permit implantation in patients whose averaged hearing thresholds are 70 dB or worse and for whom open-set (novel, standardized) sentence recognition is 60% or less in the best-aided condition (using both ears).

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In general, an appropriately fitted device will have a good functional representation of speech in a quiet environment and reduced sound quality for music and difficulties (to varying degrees) in a noisy or reverberant environment [1–3]. For older adults, devices can be difficult to use. This growing group of patients represents an underserved population. With current progress in inner ear physiology and the continued development of animal models of hearing loss, it is probable that drugs, biologics and devices will soon become partners in hearing loss treatment. For example, a drug might be used in the future to reduce the severity or progression of a condition, so that a different type of intervention or reduced amplification is needed, sound is more natural and the patient receives greater benefit overall.

The opening door

A major development in the field of cochlear implantation has been the trend toward implantation of patients with considerable residual low-frequency hearing but poor speech understanding (Fig. 1b). These patients do not receive adequate benefit from standard HA. In partial deafness cochlear implantation (PDCI), an electrode is inserted into the basal turn of the cochlea with minimal loss of low-frequency hearing [4–6]. Current studies have demonstrated that in the majority of the patients implanted using a hearing preservation approach, hearing is preserved over long time periods [7]. These patients can then benefit from

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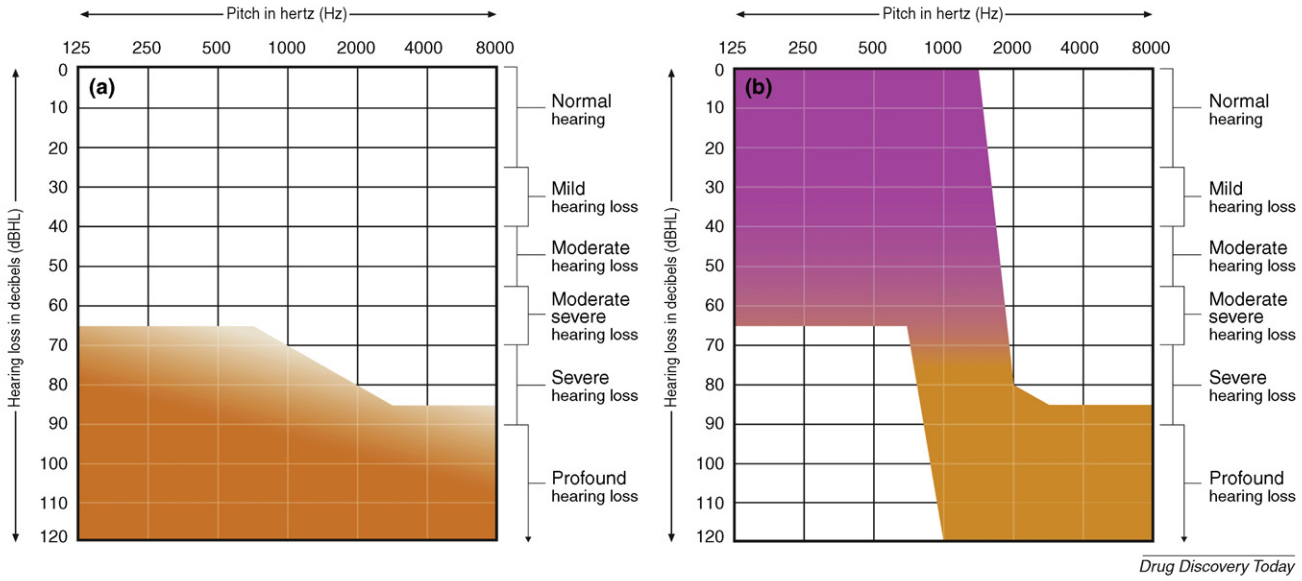

FIGURE 1

Criteria for cochlear implantation. A prospective implant candidate will have a variety of assessments including measurement of the audiogram. This is a plot of hearing threshold level (in dB HL) against frequency (in Hz). These two figures show (shaded) the recommended regions in which audiograms should fall for **(a)** standard cochlear implantation and **(b)** the electric-acoustic stimulation approach, in which a flexible basal turn electrode is inserted with appropriate surgical techniques.

complementary auditory input from both electrical and acoustic stimuli (i.e. electric-acoustic stimulation). The implications for drug development are that certain devices can, with appropriate expertise, be placed into the partially deaf inner ear with minimal loss of residual hearing. Applications of this hearing preservation approach to the inner ear would include not only placement of CIs but also delivery of a variety of molecules that could alter the clinical course of hearing loss.

Diagnosis and outcome assessment

One of the fundamental problems in treating inner ear disease is making a physiologically relevant diagnosis. Sensorineural hearing loss can be classified into a multitude of different diseases based on pathology [8]. Unfortunately, the standard pure-tone audiogram (which tells one how well a patient hears) does not necessarily reflect the underlying site of lesion causing the hearing loss (Fig. 2). The development of more advanced testing methods, such as evoked potentials and otoacoustic emissions, enables us to subclassify hearing losses by anatomic region even in cases of severe to profound hearing loss [9,10]. This is an important concept in terms of drug development because the efficacy of drug trials depends on recognizing the site of lesion beyond a broad classification of 'hearing loss'. Even though a CI might be indicated based on the level of hearing loss, the accompanying drug therapy for a given patient might be different if we could recognize that their impairment is due to loss of hair cells or loss of spiral ganglion cells rather than dysfunction of a potassium channel, for example. The recent developments in genetic testing hold further promise for a specific diagnosis of the hearing loss mechanism. For outcome assessment, a large range of measures of auditory function is available with varying sensitivity to different structures and aspects of the loss. Taken together, this convergence of advances in testing and pharmacotherapy, in addition to recognizing that the partially deaf inner ear can be safely accessed with an implantable device, provides an opportunity to further revolutionize the treatment of inner ear diseases.

Appropriate drug delivery technologies

One of the attractive aspects of the inner ear is the potential to deliver drugs locally. There are barriers between blood and cochlear fluids that are anatomically and functionally similar to the blood–brain barrier. Systemic treatment, therefore, is infeasible for many drugs, and local delivery offers advantages. The cochlea is a small coiled tube (approximately 35 mm in length), accessed clinically through the middle ear or surgically through the temporal bone. Within the cochlea, most of the target tissues are bathed in approximately 76 μL of perilymph [11], a fluid similar to cerebrospinal fluid. Drug delivery technologies applicable to the inner ear have been extensively reviewed recently [12–16].

Round window delivery

Because of the low risk to residual hearing, there has been a focus during the past decade on delivering drugs to the inner ear through application to the round window. This is currently achieved in some clinics on an outpatient basis using intratympanic injections, after which diffusion occurs into the inner ear. Maintaining application at the round window can increase drug penetration and duration of action [17]. Various release vehicles and devices have been developed; for example, Lehner *et al.* [18] developed a bone-anchored, totally implantable micro-drug delivery system. It included a micropump for subcutaneous,

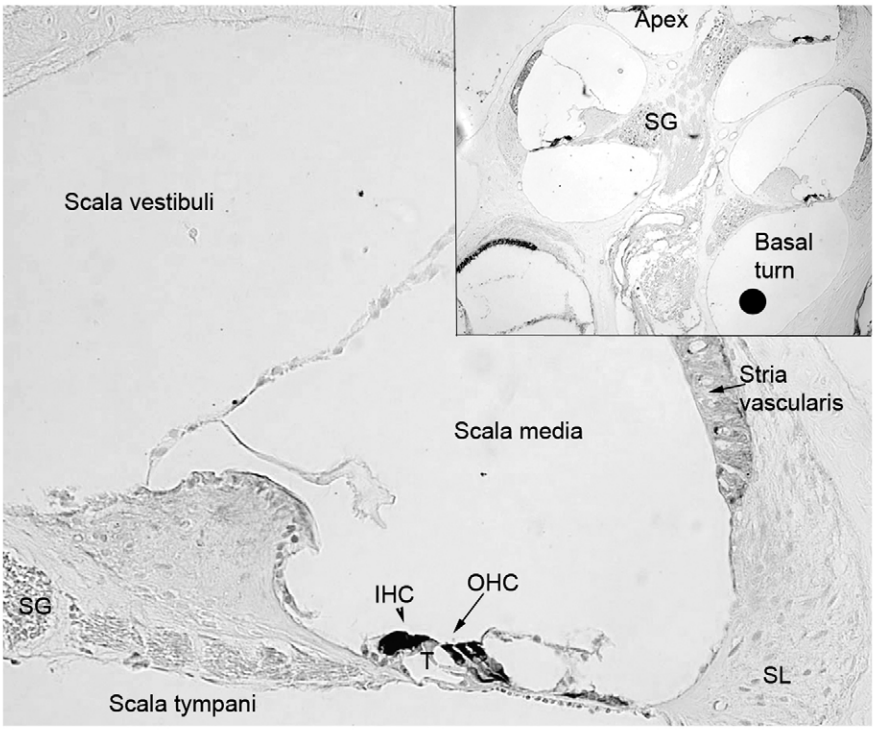

FIGURE 2

The inner ear is a complex organ with a variety of different cell types, all of which are important for hearing function and which, potentially, will require individualized drug delivery approaches. In this section through a mouse cochlea immunostained for sensory hair cells, several different features are evident. The main sensory cell in the inner ear is the inner hair cell (IHC), which transduces a sound vibration into an electrochemical potential. This results in depolarization of auditory neurons that lie at the base of the inner hair cell. The cell bodies of these afferent neurons lie in the adjacent spiral ganglion (SG) and are dependent on hair cell and supporting cell production of a variety of neurotrophic factors. This process is powered by a chemical potential produced by the stria vascularis. This series of cells maintains a high potassium concentration in the scala media, which is separated from the perilymph-containing scala vestibuli and scala tympani by tight junctions. The base of the hair cells rests in perilymph, resulting in the generation of an electrochemical potential between the apical end and inside of the hair cell. When a sound wave enters the inner ear via the stapes, it is propagated via the scala vestibuli to the apical end of the cochlea (inset) and down the scala tympani to the round window. This sets up a wave, which displaces the hair cell at a position along the length of the inner ear proportional to the input frequency. This wave is modified by contraction of outer hair cells (OHC) resulting in amplification of the signal. The resulting movement triggers the opening of potassium channels in the hair cell stereocilia, resulting in depolarization. The supporting cells under the hair cells and components of the spiral ligament (SL) function to recirculate potassium. For partial deafness implantation, the cochlear implant electrode array rests in the basal to mid turn region of the scala tympani (black circle). Delivery of drugs via a cochlear implant would result in drug infusion into the perilymph of the scala tympani.

patient-controlled activation, a drug reservoir and a septum port to enable long-term delivery of different substances. Two devices have been available for active round window delivery over the past decade [19,20]. Both devices have been used successfully in early clinical trials to deliver steroids against sudden hearing loss [21,22]; however, neither has achieved widespread use. Limitations of current devices have included complexity in placement and lack of approved drugs for inner ear diseases. In economic terms, placement of drug delivery devices requires longer operating room time than an injection and is currently not reimbursable as a procedure.

With this approach, dosage control is challenged by the variable permeability of the round window membrane between patients and according to disease state [23]. The pharmacokinetics of local drug delivery to the cochlea has been studied in animal models and computer simulations, for example by Salt and coworkers [24–28]. They have demonstrated that many drugs typically take hours to days to diffuse throughout the cochlea and, depending on their molecular weight and rate of radial clearance from the perilymph, might only reach the higher turns of the larger human cochlea in very low concentrations. This might challenge the treatment of the low-frequency region at the apex. Verification of the applicability of the model to the human cochlea might be assisted by recent studies in which a contrast agent was applied to the round window in patients [29], yielding structural and diagnostic information in MRI scans.

Intracochlear delivery

An alternative approach is delivery directly into the cochlear fluids through an opening into the inner ear (e.g. through a cochleostomy, through the round window or into one of the semicircular canals). Injection using a microsyringe is a feasible and potentially accurate method of intracochlear drug delivery for acute drug application to the base of the cochlea. It has been performed in humans before cochlear implantation for the delivery of a depot steroid to reduce the inflammation associated with implantation

trauma [30] and the subsequent increase in electrode impedance. The main challenges to overcome with such a technique are the creation of pharmaceutical formulations appropriate for intracochlear delivery and the limited depth of insertion achievable with a rigid needle.

For deeper penetration of a drug or biologic with reduced risk of trauma, the feasibility of a flexible disposable catheter has been evaluated [31]. A prototype made of medical-grade silicone elastomer is shown in Fig. 3a and b. The dimensions and overall flexibility have been selected after experience with CI electrode arrays designed to minimize insertion trauma during hearing preservation implantation. The device is intended for acute use only, rather than for long-term implantation. Insertion depths of up to 20 mm (according to the indication) are achievable without noticeable resistance. At slow delivery speeds, the drug is distributed from the catheter tip back to the insertion point. Experiments delivering a dye solution into a Perspex model of the cochlear lumen have demonstrated minimal basal movement of the emitted substance after removal of the catheter, believed to be because of the low volume of the catheter. A general diffusion of the substance was then seen toward the apex of the cochlea. The formulation could alternatively be diluted in the local perilymph using a series of holes along the array (Fig. 3c). The device is likely to be applied initially for drug application before CI electrode insertion.

For longer term delivery of drugs in fluid form, a pump and/or reservoir is required. An effective solution is the osmotic pump, first used in the animal cochlea by Brown *et al*. [32]. Chen *et al*. [33] and Fiering *et al*. [34] have reported the early development of an implantable microfluidic pump designed for intracochlear delivery. This is an advanced concept, enabling fine control and (potentially) delivery of multiple compounds over many years.

Drug delivery from the electrode array of a cochlear implant

The cochlear implantation procedure includes the insertion of a silicone elastomer electrode carrier up to 31 mm inside the cochlea. It then resides in the perilymph in proximity to all targetable cells. Jolly *et al*. [31] demonstrated that pharmaceutical-grade micronized dexamethasone can be homogeneously mixed with the medical-grade silicone elastomer used in the CI electrode array (Fig. 3d). The resulting combination will elute at a steady rate determined by the drug percentage loading and the geometry of the silicone device. Elution of a low dose is thus possible for weeks to years. Clearly, there are many advantages associated with such a regime: uniform delivery and chemical simplicity, for example. Jolly *et al*. [31] demonstrated the efficacy of such a system in reducing hearing loss in an animal model of cochlear implantation. Bio-release coatings could also be applied to the electrode, using materials tailored to the required duration

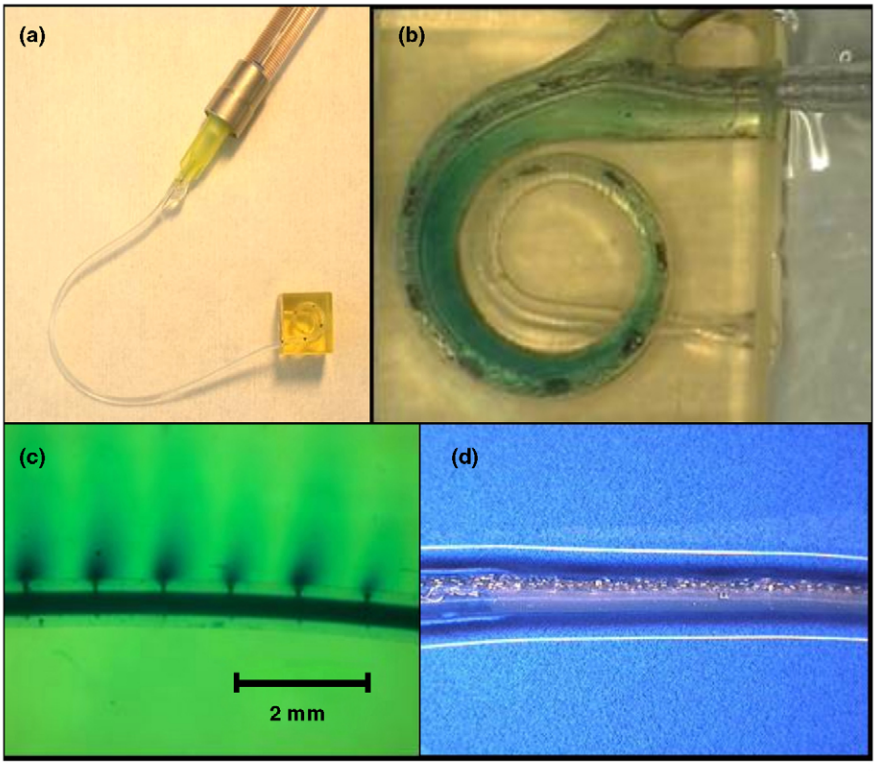

FIGURE 3

Two simple methods for delivery of drugs to the cochlea in conjunction with cochlear implantation. **(a)** Prototype of a soft, thin, flexible catheter with rounded trip for atraumatic drug delivery deep into the cochlea before implantation, inserted into a Perspex model of the cochlea. A Hamilton syringe is attached. **(b)** The electrode array of a cochlear implant inserted into a Perspex model of the scala tympani fluid space, inserted after the delivery of green dye through the prototype cannula. **(c)** Drug release from laser-ablated holes (each 50 μm diameter, 1 mm separation) for distributed delivery of a drug and subsequent dilution by the local perilymph. **(d)** One realization of a dexamethasone-eluting electrode, in which the lower (opaque) section contains the drug.

of release. Such a development, however, carries with it the difficulties of alteration of electrode flexibility, the difficulties of masking the electrode contacts during manufacture and achieving adequate drug loading, and the potential toxicity of the additional materials. Conducting polymers [16] and hydrogel coatings [12] are also feasible. An alternative solution circumventing some of the problems associated with coatings is to incorporate the drug in gel or fluid form inside a reservoir situated along the length of the electrode array. This approach is particularly appropriate for the short-term distributed release of larger molecules, particles and possibly biologics. Longer term delivery might be achieved using a port and septum approach [35], in which an implanted structure contains a rigid membrane designed for repeated drug injections into a lumen with minimal risk of bacterial penetration.

The convergence of pharmacotherapy with cochlear implantation

In the immediate future, three areas of opportunity emerge for the concurrent use of drugs with implantable devices: (i) medications to use in conjunction with the implantation process to reduce trauma to the inner ear, (ii) medications to prevent further degeneration of the hearing after implantation and (iii) treatment of patients with CIs with neurotrophins to support the auditory nerve. Successful implementation of these interventions will enable development of more sophisticated approaches for a variety of inner ear diseases. The selection of a therapy for a patient might then depend on their audiogram, speech discrimination ability (Fig. 4), psychophysical testing, genetic tests and region-specific tests, such as evoked potentials and otoacoustic emissions.

Reduction of trauma during implantation

Successful structural and functional preservation of the inner ear during the implantation process can achieve multiple goals. As already mentioned above, a growing area of cochlear implantation is to provide electric-acoustic stimulation to patients with residual low-frequency hearing and poor speech discrimination. This is a particularly common pattern of hearing loss and includes patients suffering from the primary form of presbycusis (age-related hearing loss) [36]. It is a common misconception that older adults are not candidates for cochlear implantation; however, two recent

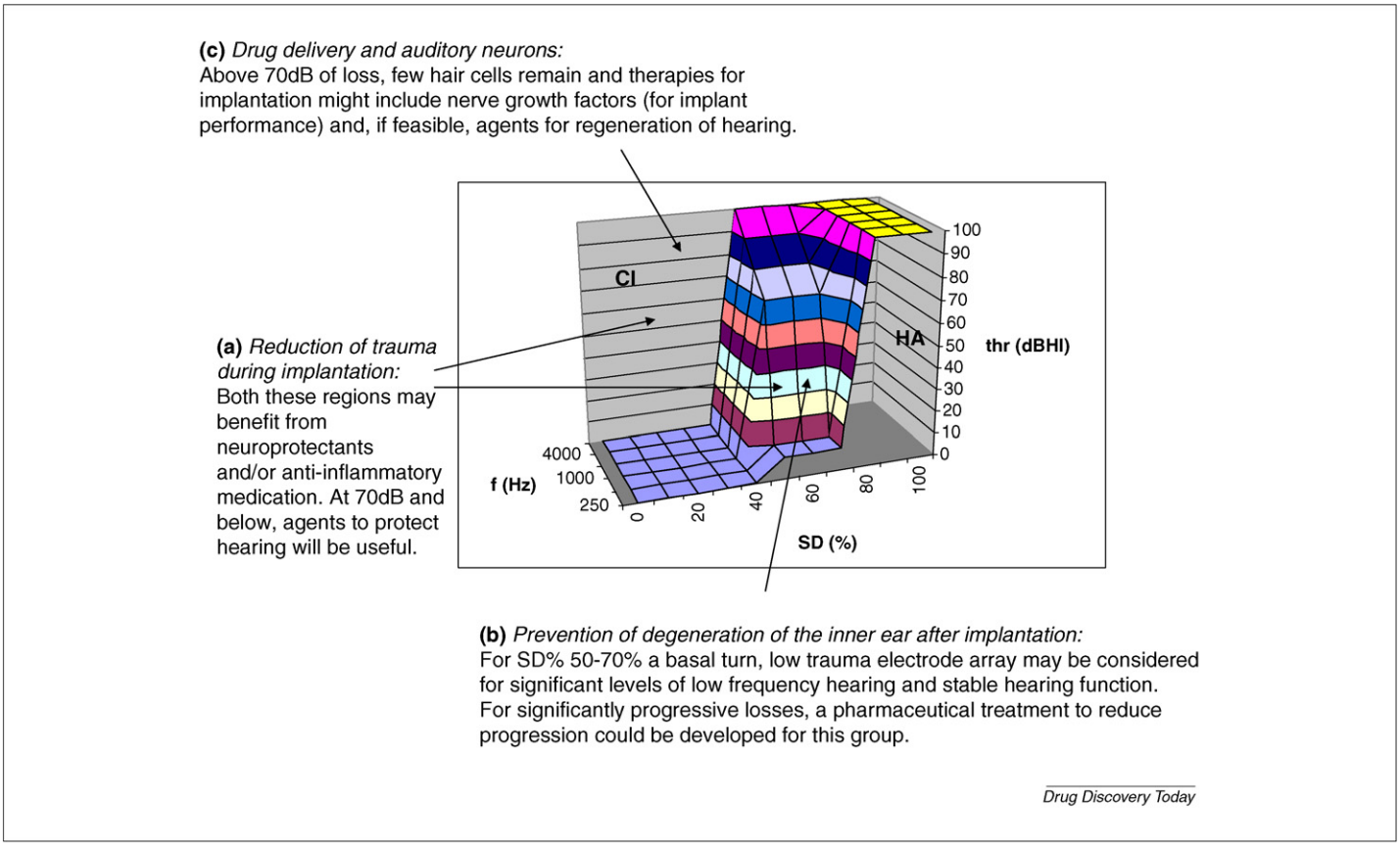

FIGURE 4

A boundary surface plotted in three-dimensional space suggesting hypothetical future indications for device-based treatment of sensorineural hearing loss. Hearing loss can be thought of in terms of both absolute loudness and clarity of a percept. At the outset of cochlear implantation, implants were reserved for patients with the absence of sound perception. Currently, implant criteria are moving toward implanting patients with considerable residual sound perception but poor clarity of perception. This boundary surface is plotted on a three-dimensional grid in which the three respective dimensions are loudness perception in decibels (dB HL), the audible range of sound frequencies (Hz) and speech discrimination scores for words (SD%). Patients whose hearing and discrimination falls under the three-dimensional surface can be treated with hearing aids (HA). Patients whose hearing and discrimination falls above the surface might be more effectively treated with cochlear implants (CI). Approved investigations are examining the effects of cochlear implantation in patients with SD scores of up to 70%, for a variety of audiogram types, including less severe high-frequency losses. The figure also illustrates the regions likely to be appropriate for applying the three types of drug therapy described in this section.

reviews of a total of 48 implantees older than 75 concluded that audiologic performance and quality of life were improved statistically significant [37,38]. A considerable number of older patients fit within the current criteria for the electric-acoustic stimulation approach.

Patients with residual functional low-frequency hearing clearly perform better in background noise when combining residual acoustic hearing with their electric hearing [6]. Atraumatic implantation may also have benefits in terms of preserving residual neurotrophin-producing elements of the inner ear, thereby ensuring health of the auditory nerve [39], and by limiting damage to the vestibular portion of the inner ear [40]. Key elements in successful atraumatic implantation are modification of the surgical technique to ensure implantation into the scala tympani [4,5,41,42], avoidance of contamination of the perilymph with bone dust and blood and the use of a thin flexible electrode [43]. Addition of anti-inflammatory medications and/or antiapoptotic medications in the preoperative and perioperative period will decrease the risk of implantation-induced hearing loss [44,45], which is vital as implantation moves closer to a patient population that is currently treated with standard HA alone. At present, we have human clinical experience with the use of glucocorticoids in conjunction with implantation, delivered preoperatively via manual application at the entry to the cochlea and continued via systemic application in the perioperative period. Studies of implant trauma [46–48] suggest that several different mechanisms are at work. These include mechanical trauma, oxidative stress and inflammation, which induce a mix of apoptotic and necrotic cell death. On the basis of these findings, it is probable that a variety of different stress pathways would need to be treated to ensure that hearing loss is minimized. A tremendous variety of potential molecules could be applied to this problem. Studies of cochlear protectants abound. This list can be further developed by looking at the general neuroprotection literature, which offers an additional advantage in that many agents have been tested in human populations (stroke, closed head injury and spinal cord injury). What remains to be done is to test more of these agents in animal models of implantation.

The use of drug therapy to reduce the risk of hearing loss after implantation thus seems to be a feasible goal. This, in itself, is an exciting development because it might ultimately enable earlier implantation of progressive losses, with supplementary electrical stimulation, and the opportunity to treat the progressive loss with local application of drugs through the body of the electrode array.

Prevention of degeneration of the inner ear after implantation

Residual hearing can degenerate suddenly or progressively months or years after implantation [49]. Probably causes include changes owing to either the presence of the electrode array or the ongoing progression of the underlying disease. Cochlear implantation itself has the potential to produce long-term changes in the homeostasis of the inner ear, especially when considering the human life span. Several temporal bone and animal studies have documented the inflammation and fibrosis that can occur after cochlear implantation [50]. In addition, most disease processes that result in a patient losing hearing and becoming a CI candidate are generally progressive. Currently, in PDCI, implantation for losses that are known to be progressive is avoided, leaving a large area of unmet need. Prevention of hearing loss progression caused by disease has been demonstrated in a variety of animal models. Caloric restriction prevents hearing loss in mouse models of progressive hearing loss [51], suggesting that oxidative stress is important in the mechanism of age-related hearing loss. Animal models of presbycusis have also been studied, and in some cases, progression of hearing loss has been slowed through pharmacologic intervention [52]. One human study in a progressive hearing loss family with a mitochondrial mutation has demonstrated that mitochondrial protectants (in this case, the antioxidant Coenzyme Q-10) can slow the progression of hearing loss [53]. Application of these types of agents locally to the inner ear could potentially enhance their efficacy.

CIs are currently indicated only when hearing loss is severe to profound [54]. Treatment of more moderate degrees of loss typically found in presbycusis might, at some point, become a natural extension of the PDCI technique. Such an approach might enable continual elution of protective substances to reduce the progression of the loss. Finally, the anticipated move toward totally implantable devices could eliminate many of the problems associated with HA use.

Drug delivery and auditory neurons

Probably the most documented and studied area of potential interaction between CIs and drug therapy has been delivery of neurotrophic factors to support the auditory nerve (quantified by the spiral ganglion population). The cochlear hair cells release the neurotrophins BDNF and NT3, which support the nerve's survival and attachment. In animal models, the loss of neurotrophic support after destruction of the organ of Corti results in progressive degeneration of the spiral ganglion population [55]. The CI can provide remarkable functional benefit [56]. Several limitations remain, however, impeding complete restoration of sound quality. In particular, pitch information might not be optimally represented because of two factors: (i) current spread in the perilymph and limitation of the number of electrodes (according to rational design), resulting in inability of the device to target nerve fibers in the small groups that can be targeted in normal hearing [57] and (ii) hypothetically, poor temporal representation of the signal within the degenerated nerve owing to reduced myelination and firing abilities [58]. It is possible that the implanted human cochlea receives adequate neurotrophic support through residual hair cells and through endogenous factors released during electrical stimulation [59]. In several animal models, however, the additional delivery of various growth factors to the cochlea has resulted in increased preservation of neurons after deafness, regrowth of peripheral processes and reduction of the threshold of electrical stimulation (for a review, see Ref. [16]), suggesting potential benefits for CI function. Hearing loss in which the spiral ganglion is disproportionately affected, such as neural presbycusis [60], might also benefit.

Feasible methods for short-term delivery of these agents include single-shot injection of particles, delivery from a pump or from a reservoir within the body of the electrode array, polymer-based delivery [61] or delivery from cells coating the electrode array [62]. Longer term delivery might be obtained using, for example, encapsulated cells [16] or local cell manipulation through gene-therapy-based approaches. Several workers have proposed the

regrowth of peripheral nerve processes onto the electrode array to improve spatial selectivity [63], although control of the direction of growth might be crucial to such a development. Recently, regrowth of nerve processes into the deafened epithelium (and thereby closer to the electrode array) after treatment with brain-derived neurotrophic-factor-promoting adenovirus has been demonstrated [64]. This is a promising approach, although the potential performance characteristics for transfer of information remain to be estimated. Finally, stem cell transplantation might, in the future, offer direct augmentation of the severely degenerated auditory nerve [65]. Progenitor cells, recently discovered within the adult auditory nerve and in the vestibular system, are also targets for drug therapy [66].

Correlation between the findings from animal models and the human patient has been difficult. A recent human temporal bone study has suggested that degeneration of the human nerve is less closely related to hair cell loss than in animal models [67]. Analysis of temporal bones from humans who underwent cochlear implantation does not show a correlation between spiral ganglion population and implant function in terms of word discrimination scores [68]. This is not surprising; early studies relating spiral ganglion survival to hearing threshold showed that auditory threshold was affected only when most spiral ganglion cells were gone [69]. This study did not take into account the effect of dendritic outgrowth or duration of deafness and, of course, could not determine the excitability of the surviving spiral ganglion cells. For a valid human neurotrophin therapy trial to be carried out, either a methodology for prior estimation of spiral ganglion neuron population size and function or an outcome parameter more sensitive than audiometric threshold or speech understanding is needed. Modern implant systems carry a telemetry system that enables regional recording of the compound action potential from the auditory nerve, which enables regional functional measurements such as nerve refractory period (shown for single-fiber recordings to be dependent on the duration of deafness [70]), measures related to chronaxie [58] and rate-dependent threshold. Some of these have been correlated with nerve survival in animal models [58] and now need to be evaluated through auditory nerve measures and psychophysical studies in humans.

Cochlear implants and regenerative approaches

A logical progression of partial deafness implantation is partial electrode insertion in the severely deaf ear followed by restoration of low-frequency hearing through hair cell and neuron repair or regeneration. This approach still faces many challenges [71] and would require the supply of genetic material or stem cells and an associated drug regime. For example, viruses, particles or biologics might be delivered into the deafened cochlea before electrode insertion in a single injection. An associated drug might then be supplied via the electrode array. More complex regimes might be supported by multistage microfluidic pumps.

Concluding remarks

Delivery of pharmacological substances through the round window to the inner ear shows promise for some indications. Improvements in delivery technology are likely to widen the scope of this approach. Cochlear implantation affords us the opportunity to merge two disparate treatment approaches: device-based rehabilitation and rational pharmacotherapy. Success in combining these would open the door for developing purely intracochlear drug development interventions for the inner ear once the safety and reliability of drug delivery devices had been established in CIs. Diseases such as Meniere's disease and acute sensorineural hearing loss could also potentially be treated with agents that have systemic side effects. Key to the development of this type of therapy is the combination of model information with screenings for available compounds.

In summary, the next decade is likely to see the advent of additional round window therapies and clinical trials of combination-type products for the improvement of CI outcomes and the treatment of hearing loss. Local delivery, simple design and careful selection of the indication will minimize the risk:benefit ratio. Future research needs to focus further on the applicability of PDCI to selected cases of presbycusis and on pharmacological approaches using animal models of progressive hearing loss.

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