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State of the art mechanisms of intracochlear drug delivery

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Abstract

Purpose of review—Treatment of auditory and vestibular dysfunction has become increasingly dependent on inner ear drug delivery. Recent advances in molecular therapy and nanotechnology have pushed development of alternate delivery methodologies involving both transtympanic and direct intracochlear infusions. This review examines recent developments in the field relevant to both clinical and animal research environments.

Recent findings—Transtympanic delivery of gentamicin and corticosteroids for the treatment of Meniere's disease and sudden sensorineural hearing loss continues to be clinically relevant, with understanding of pharmacokinetics becoming more closely studied. Stabilizing matrices placed on the round window membrane for sustained passive delivery of compounds offer more controlled dosing profiles than transtympanic injections. Nanoparticles are capable of traversing the round window membrane and cochlear membranous partitions, and may become useful gene delivery platforms. Cochlear and vestibular hair cell regeneration has been demonstrated by vector delivery to the inner ear, offering promise for future advanced therapies.

Summary—Optimal methods of inner ear drug delivery will depend on toxicity, therapeutic dose range, and characteristics of the agent to be delivered. Advanced therapy development will likely require direct intracochlear delivery with detailed understanding of associated pharmacokinetics.

Keywords

Transtympanic; intracochlear; nanoparticle; gene therapy; inner ear drug delivery

Introduction

Transtympanic delivery of gentamicin and corticosteroids has been used extensively for the clinical treatment of Meniere's disease, tinnitus, and sudden sensorineural hearing loss [1–4]. Variability in treatment efficacy and side effects has prompted significant research into pharmacokinetics and agent distribution within the inner ear using animal and computer models for various drug delivery strategies [5–7, 8*, 9**, 10*]. Recent advances in our understanding of the molecular processes and genetics involved in auditory system development and dysfunction have fueled interest in gene and cell based therapies [11–15] targeted at protection [16, 17, 18*] and regeneration [19, 20**, 21**] of inner ear tissues. This review will highlight recent advances in transtympanic and direct intracochlear drug delivery strategies.

Transtympanic Delivery

Transtympanic drug delivery is generally accomplished by one of three methods: (1) blind injection into the middle ear cavity through the tympanic membrane [22], (2) sustained or periodic delivery with a microcatheter [23] or MicroWick [24] positioned at the round window membrane (RWM), or (3) placement of a stabilizing matrix within the round window niche to provide passive sustained release of pharmacological agents. These approaches rely on transport through the RWM and result in significant basal to apical concentration gradients [8*, 10*]. No significant clinical difference in these approaches has been observed [25], although animal testing and computer modeling provide evidence that sustained release approaches result in greater control of drug concentration in the inner ear [26, 27].

Acute and sustained infusion to the round window membrane

Single transtympanic injections, continuous infusions, and periodic infusions have been used extensively, with excellent clinical reviews presented by Hoffmann [28] and Hoffer [3]. Animal studies are used to explore details of drug distribution and cellular impact with acute and sustained infusions to the RWM. Roehm examined gentamicin uptake in the chinchilla inner ear with single injections through the tympanic membrane, and sustained delivery with an osmotic pump with consistent staining patterns independent of exposure time and cochlear turn [29]. The authors indicate this could be due to saturation of cellular uptake at all sites masking an apical-basal gradient. Such a gradient was measured in guinea pigs by Plontke with continuous gentamicin application to the RWM resulting in scala tympani basal concentration of gentamicin 4000x greater than that at the apex [8*]. Plontke also measured a strong basal-apical concentration gradient of dexamethasone in guinea pig perilymph following administration directly onto the RWM [10*]. He predicts a smaller gradient in the mouse, and more significant gradients in the larger human cochlea which may contribute to variance in clinical treatment efficacy and pose problems for drugs with a narrow therapeutic range.

Animal studies have demonstrated greater hair cell loss throughout the cochlea with single dose gentamicin application to the RWM as compared to continuous administration at the same dose [27]. Application of kanamycin via a microcatheter positioned at the RWM in guinea pigs demonstrated a dose dependent pattern of damage, with a significant apical-basal gradient of outer hair cell loss [30]. The otoprotective effect of a cell-permeable inhibitor of JNK mediated apoptosis, AM-111, was evaluated with noise exposure in chinchillas by Coleman [31**]. Local administration to the RWM provided superior protection over IP injection, with hyaluronic acid gel delivery providing more rapid recovery of auditory brainstem response (ABR) thresholds than continuous RWM perfusion.

Stabilizing matrices

The use of stabilizing matrices offers many potential benefits over middle ear perfusions. Medications delivered to the middle ear are ultimately dissipated by drainage down the Eustachian tube or absorption by middle ear mucosa unless a stabilizing matrix is used. For potentially toxic agents this raises significant concerns regarding isolation to target tissues.

This, coupled with superior control of dosing profiles, suggests future transtympanic delivery methodologies are likely to focus on techniques utilizing stabilizing gel matrices for passive sustained release. An excellent review of several different controlled release systems is provided by Nakagawa and Ito [32**]. Patterns of ototoxic damage in gerbils with sustained delivery of gentamicin using gelfoam, hyaluronic acid, and fibrin were compared by Sheppard with a fibrin/gelfoam combination found to be most effective [33].

Chitosan-glycerophosphate hydrogel, a liquid at room temperature and a biodegradable gel at body temperature, allows injection into the round window niche and facilitates close contact between the matrix and the round window membrane. This material has been used successfully in mouse studies to deliver dexamethasone to the inner ear through the round window membrane [34*] and has tunable delivery properties. Attenuation of noise induced hearing loss by application of recombinant human insulin-like growth factor 1 (rhIGF-1) to the RWM via hydrogel has been examined in guinea pigs and rats. Lee observed modest but statistically significant improvements in guinea pig ABR threshold shifts and outer hair cell survival, but with a strong basal-apical gradient with a 5 hour post-noise exposure delivery [18*]. Iwai tested delivery in rats 3 days *prior* to noise exposure with a more significant reduction in ABR threshold shifts and outer hair cell loss [17].

Nanoparticles

There is great potential for the use of nanoparticles for drug and gene delivery through the round window membrane. Tamura found rhodamine encapsulated PLGA nanoparticles in basal and middle portions of scala tympani following application to the guinea pig RWM via gelfoam [35]. Ge investigated augmentation of RWM transfer with magnetic fields using PLGA encapsulated iron oxide nanoparticles (10–20nm) placed on the RWM in chinchillas [36*]. Nanoparticles were found in structures lining scala tympani and vestibuli, lateral wall structures of stria vascularis, and various cells within the organ of corti including inner and outer hair cells and supporting cells. Basal and apical cochlear turns were impacted with no significant augmentation from application of the magnetic field. Transport of Cy3-labeled silica nanoparticles across the RWM in mice was investigated by Praetorius with nanoparticles found in spiral ganglion cells and inner hair cells in basal, middle and apical cochlear turns, and in vestibular sensory hair cells and spiral ganglion cells [37**]. Similar results were observed at lower intensity in the contralateral ear suggesting spread of nanoparticles to the cerebrospinal fluid (CSF) via the cochlear aqueduct. Zou developed lipid core nanocapsules (50nm) which were applied to the RWM of rats via gelfoam [38*]. These nanoparticles effectively transverse the RWM and were incorporated into spiral ligament, stria vascularis, pillar cells, and both inner and outer hair cells.

Nanoparticles have a demonstrated ability to readily cross the RWM and quickly incorporate into membranes and cells of the organ of corti. Mechanisms of transport have not been fully elucidated although size is assumed to be a key factor enabling rapid diffusion and transport across membranes. Future work should quantitatively evaluate distribution characteristics and the ability to target specific tissues and cells.

Intracochlear Delivery

A more invasive approach with the potential for much greater control is direct intracochlear delivery of therapeutic and curative agents. This method eliminates dependence on round window membrane permeability and can provide better isolation of the delivered agent to the target tissues. Intra-cochlear delivery of drugs or genes has been successfully accomplished in animal models by injection through the round window membrane [39], injection into the endolymphatic space via scala media [40,20**] and endolymphatic sac [41], and injection or infusion into the perilymphatic space via the semicircular canals [42], scala vestibuli [43, 44], and most commonly the scala tympani [45–60, 61**, 62, 63*]. Endolymph injections have provided exciting cochlear hair cell regeneration results [20**] but generally impact auditory function making them unlikely avenues for clinically relevant therapies. A perilymphatic inoculation route is technically easier and therefore more feasible for clinical applications. The most promising infusion approaches involve a cochleostomy in the basal turn of scala tympani with a microcannula connected to a syringe pump for acute infusions or an implantable osmotic pump for more chronic infusions. Recent studies [61**] have demonstrated scala tympani infusion for up to eight hours in the mouse with no detriment to ABR thresholds and distortion product otoacoustic emission (DPOAE) thresholds. Infusion of salicylate and CNQX resulted in reversible shifts in ABR and DPOAE thresholds with a significant frequency dependence suggesting a strong basal-apical concentration gradient. This ventral approach in the advantageous mouse model system allows access to the basal turn of scala tympani directly through the cochlear bone without opening the bulla, offering potential benefits for animal recovery and long term therapy development.

Cochlear Implants

Intracochlear drug delivery has the potential to greatly enhance efficacy of cochlear implants for the profoundly deaf. Eshraghi demonstrated conservation of hearing by direct scala tympani delivery of dexamethasone for 8 days following electrode insertion trauma induced hearing loss in the guinea pig [63*]. Miller chronically infused the guinea pig cochlea (basal turn, scala tympani) with brain-derived neurotrophic factor and fibroblast growth factor following deafening via a systemic aminoglycoside and diuretic treatment [64*]. Survival of spiral ganglion neurons and peripheral process regrowth were both enhanced with the treatment. The inclusion of fluidic channels within cochlear implant electrode arrays provides the opportunity to chronically infuse neurotrophic factors and pharmacological agents which may enhance efficacy of cochlear implants. Shepherd describes a drug delivery system integrated into a scala tympani electrode array designed for use in guinea pigs with demonstrated delivery of neomycin [65]. Rebscher created a similar array for guinea pigs and cats, but evidence of *in vivo* testing was not presented [66]. Paasche describes modification of a commercially available cochlear implant electrode to include a fluidic channel with multiple exit ports [67]. Dye delivery from different combination of ports and at different flow rates in a model of the human scala tympani was examined. At the clinically relevant flow rate of 1µl/hr this model required in excess of 40 hours to reach maximum concentrations. Consideration of clearance mechanisms *in vivo* suggests this approach would be ineffective at providing a uniform concentration of delivered agent

throughout the cochlea. However the inclusion of additional fluidic ports as described by Stöver [68*] has the potential to improve this innovative approach to intracochlear drug delivery specifically relevant to improved efficacy of cochlear implants.

Molecular Therapies

Molecular therapies for protection of spiral ganglion neurons and hair cells in degenerative diseases and ototoxic insult, and auditory and vestibular hair cell regeneration require delivery of target genes and/or exogenous cells to cochlear structures. Significant work in this area has been reviewed by Staecker [13] and Richardson [16]. *In vivo* animal studies demonstrated protection of hair cells from noise exposure with over-expression of glial cell derived neurotrophic factor [69] and from aminoglycoside ototoxicity with antioxidant genes [58]. Enhanced survival of neurons in the spiral ganglion following ototoxic insult has been demonstrated with over-expression of neurotrophin-3 [44], brain-derived neurotrophic factors [70], and glial cell derived neurotrophic factor [71]. Recent work with scala media inoculation demonstrated hair cell regeneration mediated by *Math1* overexpression in the intact cochlea [20**, 72], providing favorable evidence of the potential for effective gene-based deafness therapies. Staecker recently demonstrated regeneration of vestibular hair cells and restoration of balance function in mice with acute injection of Admath1.11D into scala tympani [21**].

Effective, specific and safe delivery vectors are critical for gene-based therapies, but therapeutic efficacy will greatly depend on intracochlear delivery providing isolation to target tissues and distribution throughout the cochlea and /or vestibular system. Praetorius examined the pharmacodynamic of adenovector distribution within the inner ear tissues of the mouse and found a significant basal to apical gradient of distribution with round window injection [73*]. Distribution to the vestibule was rapid suggesting interscalar exchange between scala tympani and scala vestibuli at the basal turn. A study of eight different adeno-associated virus (AAV) vectors with round window microinjection in the mouse model demonstrated efficient transduction of cochlear inner hair cells [74]. The authors suggest the small size of the AAV vectors (11–22nm) may allow dissemination from perilymph to endolymph where larger vector systems such as adenovirus (75nm) and retrovirus/lentivirus (>100nm) have not. This observation is consistent with results using nanoparticles of dimensions <50nm which distribute quickly and transverse cochlear membranous partitions.

Pharmacokinetics, cochlear distribution, and isolation to target tissues

Direct quantitative measures of drug distribution within the cochlea demonstrate a significant apical-basal concentration gradient which will be important for pharmaceuticals with a narrow therapeutic window, or molecular therapies involving protection or regeneration in apical cochlear structures. Applications involving modified cochlear implant arrays have the potential to enhance access to apical areas, however isolation requirements coupled with inner ear clearance mechanisms make uniform distribution difficult to achieve. Study of the pharmacokinetics of drug delivery in the inner ear will become increasingly important for optimization of clinical practice and the development of new therapeutics in animal models. An excellent overview of clinical, animal, and simulation work is provided

by Salt [75]. Computer models of the cochlea provide opportunities to test different delivery methodologies and explore potential clearance rates and modes of interscalar exchange. Plontke recently described a three-dimensional finite element computer model of the guinea pig cochlea and examined the distribution of methylprednisolone for a simulated single transtympanic injection and a continuous transtympanic infusion [9**]. The two delivery methods resulted in very different concentration time courses, peaks, and basal-apical gradients. This model also demonstrated rapid transfer to the basal part of scala vestibuli and the vestibule which is consistent with published results in guinea pig and chinchilla. In a study of human temporal bones Rask-Andersen found a trabecular meshwork within the modiolar wall of scala tympani and vestibuli in the first and second turns [76**]. This evidence of a perilymphatic communication route is consistent with clinical observations of ablation of vestibular function with retention of hearing in treatment of Meniere's disease with transtympanic administration of gentamicin.

Isolation of delivered agents to the treated cochlea will become increasingly important as more toxic substances (e.g. viral vectors for gene delivery) are used to treat auditory and vestibular dysfunction. Studies involving slow infusions or bolus injections into scala tympani often report impact to the contralateral ear. Roehm observed gentamicin transfer to the contralateral ear following middle ear perfusions, with evidence implicating the cochlear aqueduct [29]. Stöver examined this in detail with virus inoculation in the bloodstream, CSF, and scala tympani, identifying the cochlear aqueduct as the most likely route of virus spread to the contralateral cochlea [77]. Protocols involving continuous perfusion into scala tympani will result in expulsion of fluid through the cochlear aqueduct unless a fluidic exit route is provided within the cochlea. This is a clear disadvantage compared to transtympanic administration to the RWM. An intriguing approach for delivery of zero net volume directly to scala tympani involves a reciprocating perfusion system [78]. Using a guinea pig model and a pump capable of rapid infusion followed by slow withdrawal of equivalent volumes, increased compound action potential and DPOAE thresholds in response to salicylate and DNQX were demonstrated. This approach provides limited access to apical structures, but is likely to limit flow through the cochlear aqueduct to diffusion mechanisms.

Conclusions

Optimal methods of inner ear drug delivery will depend on toxicity, therapeutic dose range, and characteristics of the agent to be delivered. Advanced therapies involving long term treatments with multiple agents and incorporating gene and/or cell therapies will likely require direct intracochlear delivery. Implantable pumps with agent exchange capability and controllable flow rates and pump profiles will become increasingly important. Additional research on pharmacokinetics of gene delivery vectors and nanoparticles is required with an emphasis on isolation to target tissues and wide distribution throughout the cochlea.

Acknowledgements

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