Local inner-ear drug delivery and pharmacokinetics

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Several drugs that are applied directly to the inner ear are in widespread clinical use for the treatment of inner-ear disorders. Many new substances and drug delivery systems specific to the inner ear are under development and in some cases are being evaluated in animal experiments and in clinical studies. However, the pharmacokinetics of drugs in the inner ear is not well defined and the field is plagued by technical problems in obtaining pure samples of the inner-ear fluids for analysis. Nevertheless, a basic understanding of the mechanisms of drug dispersal in the inner ear has emerged, which facilitates the design and interpretation of future pharmacokinetic studies.

In recent years there has been increasing interest in the treatment of inner-ear disorders by local rather than systemic application of drugs. Substances are applied intratympanically, which means they are injected into the middle-ear cavity. This procedure is based on the premise that the drug will contact the round window membrane (RWM) of the cochlea, enter the scala tympani (ST) and spread throughout the ear. The target tissues of such treatments might include the sensory hair cells, the afferent nerve fibers and supporting cells of the cochlea (hearing) or vestibular (balance) portions of the inner ear. The idea of a topical application of drugs to the inner ear is not new. Local anesthetics and aminoglycosides were applied decades ago to treat inner-ear disorders [1–3]. The present, most widely used form of intratympanic therapy is the injection of gentamicin into the middle ear in patients with Menière's disease [3–8]. Gentamicin is toxic to the sensory cells of the balance system and thereby suppresses the vertigo in these patients by partially ablating their vestibular system. There is also an increasing number of clinical reports related to the local application of glucocorticoids for acute hearing loss [9–16], glucocorticoids for Menière's disease [17–20] or for tinnitus [21–25]. Other substances that have been tested in humans include local anesthetics, neurotransmitters and neurotransmitter antagonists [26,27], and the use of growth factors, antioxidants, apoptosis inhibitors and antisense oligonucleotides is also increasing. Animal experiments have shown promising results by using locally applied drugs to provide otoprotection from noise and drug toxicity* [28–36]. An extension of such studies is local viral and nonviral gene transfer for the sustained treatment of inner-ear disorders [37–42]. It has recently been shown that *Atoh1*, a key regulator gene of hair cell development also known as *Math1*, induces regeneration of hair cells and substantially improves hearing thresholds in the mature deaf inner ear after delivery to nonsensory cells through adenoviral vectors [43]. Although the above examples show that local therapy has many advantages over systemic

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therapy, it should be noted that no drug to date has been approved anywhere in the world for local application in the treatment of inner-ear disorders.

Local application of drugs to the inner ear is based on the rationale that, despite the lower total amount of drug given, medications applied topically to the RWM can result in higher concentrations in the inner-ear fluids than with systemic application. Pharmacokinetic studies have confirmed this principle [9,34,44–47]. Potential side effects of systemic treatment and complications from a long-lasting higher-dose therapy can be avoided through topical application therapy. Substances applied locally at a low dose can be administered if there are major restrictions or even contraindications associated with systemic application.

Although in theory the local application of drugs to the inner ear has great potential, in practice there are numerous technical difficulties to overcome. Important issues that have so far received only limited consideration are:

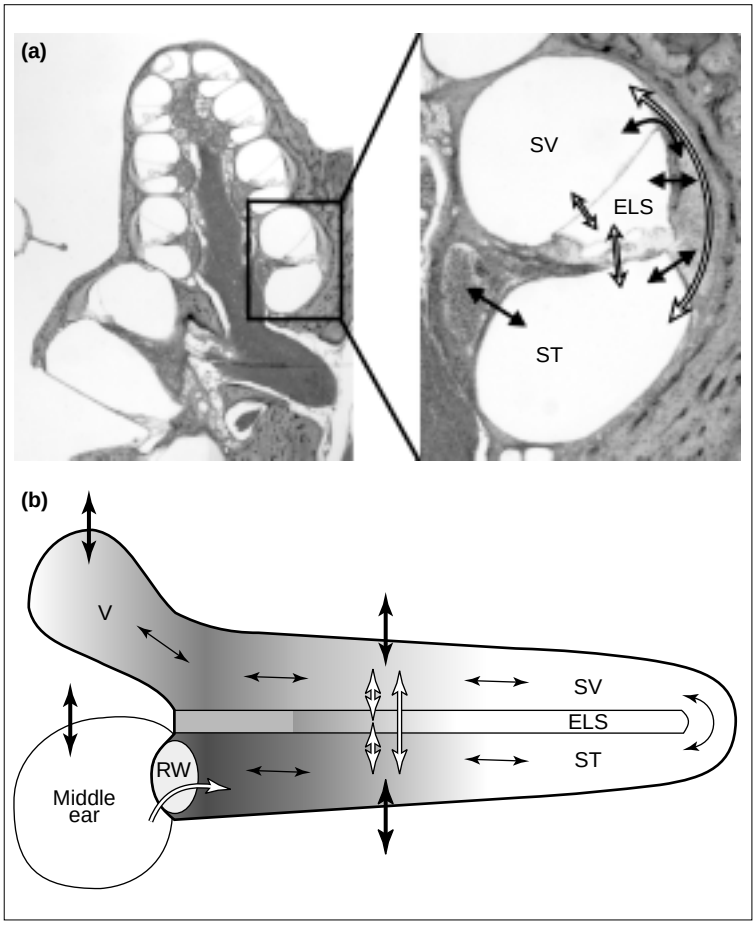

FIGURE 1

Principles of substance distribution in the inner ear. (a) Cross section through the guinea pig cochlea with an enlarged section of one turn showing the 'radial' exchange between compartments (open arrows) and the clearance from the scalae to the blood circulation or to the modiolus (solid arrows). **(b)** Schematic of an 'unrolled' cochlea showing the 'longitudinal' processes of solute movement. Longitudinal processes must take into account changes of scala dimensions, diffusion and flow along the scalae, and the contributions of the helicotrema and the vestibulum. The shading in the figure depicts the spread of drug following local delivery to RWM, which is dominated by radial exchange processes. Abbreviation: V, vestibulum.

(i) Which parts of the ear do drugs reach, in what concentration and with what time course?
(ii) How do different delivery methods or application protocols influence the drug levels at each time point at the different locations in the ear?
(iii) How variable are the drug levels achieved with different delivery protocols and what are the major sources of variation?

Currently, doses, protocols and application systems are empirically justified. This approach has led to varying results in the therapy of Menière's disease by intratympanic gentamicin treatment, which serves as an example of the uncertainties associated with different application strategies. Although some studies reported few patients with deafness as an unwanted side effect of local gentamicin treatment [7], others found complete deafness of the treated ear in more than 20% of patients [48] and in one study, in which drugs were applied for a prolonged period, 80% of the patients were deafened [49]. It is therefore necessary to acquire an understanding about the quantitative drug distribution in the inner-ear fluids when medications are applied locally with different delivery protocols.

General principles of drug distribution in the inner ear

The inner ear represents a geometrically complex structure, with characteristic large fluid-filled extracellular spaces (scalae), each with multiple interfaces with other scalae and with outside compartments, such as the systemic blood circulation and the middle ear cavity (Figure 1). ST and scala vestibuli (SV) contain perilymph, a fluid similar in ionic composition to other extracellular fluids, whereas the endolymphatic space (ELS) contains fluid with a unique, high potassium composition. In contrast to most other body fluids, the inner-ear fluids do not move or flow appreciably and are not actively 'stirred'. As a result, the spread of locally applied drugs through the ear occurs only slowly and predominantly by passive diffusion [50,51]. The diffusion coefficient, which governs the rate at which drugs spread, depends on the physical characteristics of the diffusing particles or molecules, with their molecular weight playing a major role [52].

Transfer of substances through the RWM to the ST of the inner ear also appears to be primarily a passive process. Active transport processes have been assumed particularly for larger molecules and particles, but have not been confirmed so far [53]. The rate at which medications cross the RWM to the inner ear depends on the size, geometry and tissue permeability characteristics of the RWM. Animal experiments have shown that, despite its three-layered nature, the RWM behaves as a semipermeable membrane. Many agents have been applied to the RWM and their transition into ST has been assessed either by histological methods, by direct measurement of concentrations or by indirect methods, such as through an influence on hearing thresholds [53]. The permeability of the RWM can also be influenced by simultaneous application

of other substances [54,55] or by intracochlear pressure changes that alter the distension of the membrane [56].

The processes underlying drug distribution in the ear have been subdivided into 'radial' (with respect to the modiolus, the central core of the cochlea) and 'longitudinal' processes (Figure 1) [51,57,58]. Radial distribution processes include communications between the parallel scalae of the same turn (Figure 1, open arrows) and communications with the vascular system (Figure 1, solid arrows). Communication between ST and SV via the lateral wall (the tissues at the right of Figure 1a) appears to be particularly rapid [58–60]. Communication with the blood is through the endothelial cells of the capillary beds in the lateral wall that provides a tight 'blood–labyrinth barrier', comparable with the blood–brain barrier. Longitudinal processes include diffusion and longitudinal flow along the scalae. In the normal, unopened cochlea the flow rates of endolymph and perilymph are extremely low so the effect of flow can be regarded as negligible compared with diffusion [57,61]. Other longitudinal communications include those between ST and SV through the helicotrema at the cochlear apex and the open communication between the basal part of SV and the vestibulum.

A major process that influences drug distribution in the inner ear is that of clearance, which refers to the removal of substance from the cochlear fluids via the capillary beds in the lateral wall and modiolus. Broadly speaking, clearance includes all processes that lead to the reduction of substance levels in the cochlear fluids, such as losses to the fluid spaces of the modiolus, uptake into intercellular spaces and inactivation of the applied drug by metabolism or by binding to tissues. The interplay between diffusion and clearance is key to determining the distribution in the inner ear of substances applied to the RWM. Substances cleared from the fluids at high rates will rapidly reach a steady state in which drug diffusion is balanced by clearance, so the drug can never reach the apical regions of the cochlea in appreciable concentration. Substances with slower clearance rates will diffuse further along the cochlea. The magnitude of longitudinal drug gradients following local delivery is therefore highly dependent on the rate the drug is cleared from perilymph. The greatest technical problem associated with local drug administration is the large gradients of drug concentration, with highest levels near the site of application and decreasing levels at more distant sites. These gradients can be predicted by computer simulations [59,62] and have been demonstrated experimentally by ion-electrode measurements [50] and by histological methods [41,63].

Preclinical studies of pharmacokinetics in the inner ear

The development and approval of medications and drug-application systems requires the study of the pharmacokinetics, toxicity and efficacy of medications applied locally to the RWM. Preclinical animal studies lay the foundation for introducing specific drug-delivery protocols into clinical practice. Only a few studies have quantitatively analyzed drug concentrations in the inner-ear fluids [9,34,45,46,63–65]. However, data from two of these studies show very different perilymph concentrations of a drug after using similar application modes [9,46]. Large deviations in pharmacokinetic profiles in animal experiments considerably limit their applicability to the human situation. For this reason, it is important to understand some of the technical problems associated with preclinical pharmacokinetic studies of the inner ear.

The withdrawal and analysis of samples from the inner ear represent a considerable technical challenge because the fluid volumes in the inner ear are extremely small. For example, the entire perilymph volume in the cochlea of the guinea pig is less than 10 µl [66,67]. In previously published studies, it was necessary to take sample volumes close to or greater than the total cochlear perilymph volume in order to have sufficient volume for pharmaceutical analysis [9,34,45,46,64,65]. When fluid is aspirated from the basal turn of the ST, such as through the RWM, it is replaced by cerebrospinal fluid (CSF), which enters the ST through the cochlear aqueduct and contaminates the perilymph [56,62,68,69]. As greater volume is taken, the sample will contain an increasing amount of CSF so that the volume taken no longer represents pure perilymph. In one study, multiple samples, each larger then the cochlear perilymph volume, were taken over time [9]. The assessment of pharmacokinetic profiles based on such fluid samples can therefore be misleading. In a recent study that used a chemical marker, the marker concentration of fluid samples taken through the RWM was compared with the perilymph concentration of the marker measured before sampling with an ion-selective microelectrode sealed into the scala. It was calculated that even a 1 µl sample taken through the RWM was contaminated with 20% CSF [56]. Larger sample volumes, such as the 10 µl samples used in some prior studies, were estimated to contain >15% perilymph and <85% CSF. A consequence is that the drug levels reported in some pharmacokinetic studies do not accurately represent the real drug concentration in the perilymph. It is therefore important to scrutinize carefully the methodology used before accepting that published values described as 'perilymph concentrations' are reliable.

Interpretation of specific delivery and sampling protocols is aided by a finite-element computer model (http://oto.wustl.edu/cochlea/model.htm) that considers the anatomy of the inner ear, general pharmacokinetic principles and solute distribution processes. This model allows the calculation of solute movements associated with a variety of drug delivery protocols. It also simulates several measurement methods, including measurement at a specific point (comparable with an ion-selective microelectrode), and several fluid-sampling techniques, including microdialysis. Volume flows associated with the aspiration of samples are incorporated into the

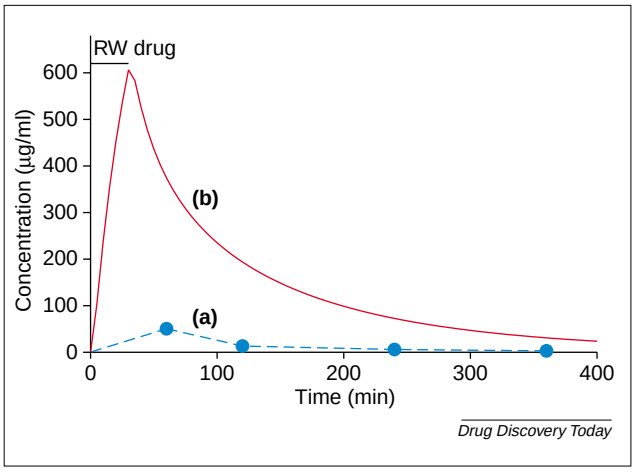

FIGURE 2

Potential misinterpretation of fluid sample measurements. Calculation of the methylprednisolone (MP) concentration in the basal turn of ST in the absence of sampling **(b)** that would account for the amount of MP detected in the four 10 µl samples taken through the RW membrane by Parnes *et al.* [9] **(a)**. Note that the perilymph MP level must be substantially higher and the MP must remain in the fluid space for longer time than the sample measurements alone suggest (data derived from [62]).

simulations. This simulator is therefore useful for the interpretation of a variety of experimental configurations. A detailed analysis of the repeated sampling study mentioned above [9] has shown that perilymph concentration of methylprednisolone (MP) in ST must have been more than 10 times higher than the presented sample concentrations, as shown in Figure 2 [62]. This analysis reconciles the disparate concentrations of steroids in the ear reported by different studies [9,46,62]. It also confirms that the major hazard of sampling perilymph from ST is that the actual perilymph drug levels might be substantially underestimated by the concentrations detected in samples.

Other studies in which perilymph was sampled from the vestibulum [52,70,71] are more readily interpretable in terms of the basic mechanisms by which drugs distribute within the inner-ear fluids. The amount and time-course concentration change of gentamicin in the vestibulum is consistent with drug entering the basal region of ST and spreading quickly to SV and vestibulum by radial diffusion pathways across the membranous structures [59]. The amount of drug reaching the apical regions of the cochlea was predicted to be substantially lower than that at the base, which is consistent with the limited hearing loss seen when moderate gentamicin doses are applied locally. Other studies have adopted sampling methods in which the animal was first sacrificed, the temporal bone removed and then the fluids aspirated from the cochlea. In this method, the perilymph withdrawn is replaced by air, so that sample contamination with CSF cannot occur [46]. The choice of sampling location is constrained by the aim of the study, specifically those studies that are interested in the vestibular effects of drugs need to sample from the vestibulum, whereas for studies focused on the auditory effects of drugs the drug concentration in ST is of greater relevance.

An alternative to fluid sampling from the cochlea is the use of microdialysis, which involves sealing a permeable probe into the scala, through which fluid is continually perfused. Analysis of repeated samples of fluid efflux from the probe allows a drug concentration time-course in the cochlea to be monitored without volume disturbance. Time courses for several substances including gentamicin and dexamethasone following application to the RWM have been presented [47,72,73]. Although this is an excellent method to quantify RWM permeability, the drug time course measured with this technique also does not accurately represent the true perilymph kinetics. This is because the leakage of drug from perilymph into the dialysis probe (which is an essential part of the method) represents a non-physiological clearance of the drug from the cochlea fluid spaces. It has been demonstrated that dialysis of small compartments *in vitro* caused rapid clearance of solute from the compartment, which could be accurately modeled [72]. In a subsequent analysis of *in vivo* dialysis experiments using dexamethasone and fluorescein it was further demonstrated that the dialysis probe significantly contributed to solute clearance from perilymph [74], making it impossible to define the physiological rate of drug clearance. The high rates of drug clearance reported in prior dialysis studies are therefore unlikely to represent the perilymph kinetics that would exist in the absence of dialysis. It is unfortunate that the errors in dialysis and sampling studies underestimate the drug concentration as well as the time the drug remains in the perilymph.

There are only few pharmacokinetic studies that use fluids samples taken from the inner ear of humans. In patients undergoing labyrinthectomy, perilymph was sampled from the vestibulum at various times following local delivery of gentamicin to the middle ear [75]. Such data will be valuable in the extrapolation of pharmacokinetic studies in animals to the situation in humans.

Drug application systems

As more candidate substances for the treatment of inner-ear disorders are being discovered, it is necessary to develop appropriate strategies for their delivery in the least invasive manner possible. In controlled-release systems, such as biopolymers or pumps that might be implanted or external, the rate of release is determined largely by the design of the device itself and is not dependent on environmental conditions. By contrast, sustained-release systems provide prolonged release but the release rate is significantly affected by environmental conditions [76]. For the local drug delivery to the inner ear, a variety of strategies exists, ranging from intratympanic injections of fluids to the use of pumps, polymers and gels.

Single or repeated intratympanic injection with or without volume stabilization and with or without visualization of the RWM

The most frequently used method for local drug application is an intratympanic injection of drug solution [1,26,77,78]. The limitation of this method is the lack of control of the drug concentration reaching the RWM and of the duration of contact of the drug with the RWM, which are important factors in determining the drug level achieved in the cochlea. During and after injection the patient usually lies with the treated ear upwards. The time the drug remains in the middle ear is uncertain, however, as drug is lost by drainage of the solution via the eustachian tube (during swallowing) or by resorption through the middle ear mucosa. Several methods have been developed to increase the time drugs remain in the middle ear. In animal experiments, fibrin glue was employed to stabilize the applied volume as a gel [45], whereas in humans hyaluronic acid [14,79,80] or resorbable gelatin-sponges [81] have been used. Despite this, the doses, dosing intervals and therapeutic durations required to achieve a specific therapeutic goal are hard to predict. Other factors that contribute to variation include anatomic obstacles, such as plugs of connective or adipose tissue, or so-called pseudomembranes of the round window (RW) niche. It has been estimated that approximately one-third of patients have obstructions of the RWM [82]. Inspection of the RWM before drug application is possible using a microotoscope (explorent®, Tuttlingen, Germany) [83]. Another approach to maintain drug in contact with the RWM is the use of the 'microwick' [84], in which a 'wick' is positioned in the RW niche via a tympanostomy tube. The external end of the wick is located in the external auditory canal, to which the patient can intermittently apply medications. Although it is possible that the device acts as a wick when it is initially placed and is dry, it remains uncertain how much volume flows along the wick when the fibers are already fluid-saturated. It is more likely that drug diffusion within the fluid spaces of the wick will dominate drug movement towards the inner ear, and this is likely to be a slow process.

Continuous or discontinuous drug application via partly or fully implantable pump systems

During brief drug applications, small permeability variations in the face of large drug gradients across the RWM, combined with variations in the brief application time, contribute significantly to variations of perilymph drug levels. In an attempt to control better the drug level at the RWM, continuous drug application has been employed, via partially or fully implantable catheter systems and pumps. In animals, the mini-osmotic Alzet pump™ (Durect, Cupertino, USA) has been widely used for drug delivery to the middle ear [85] and for intracochlear delivery of drugs [29,36,86].

A device for discontinuous drug delivery that has been evaluated in animals but that is not yet approved for use in humans is the TI-DDS® (Totally Implantable Drug-Delivery-System) [87,88]. The manually operated pump releases a defined volume of 5 or 10 µl upon push-button activation. A subcutaneously implanted reservoir can be refilled transcutaneously.

In humans, although a variety of experimental catheter systems have been employed, the round window microcatheter from Durect (RWµCath™, Durect, Cupertino, USA) represents the best characterized system to date [10,13,27,48]. In a recent nonconcurrent cohort study it was found that local continuous glucocorticoid delivery via the RWµCath™ in patients with acute, severe or profound hearing loss and failure of standard systemic therapy showed a significant improvement in hearing compared with a historical control group without local treatment [16]. However, for unknown reasons, commercial production of the Durect RWµCath™ was halted in 2004.

There remains an intense interest in the development of safe, effective and minimally invasive drug-delivery systems for the inner ear, with several groups working on intracochlear catheter-based application systems. One approach has been to combine drug delivery with an existing device, such as by incorporating a drug delivery cannula into a cochlear implant electrode [89]. Other groups are working on specific implantable drug delivery devices usable in normal ears, as for example Fiering *et al.* [90]. This group is hoping to combine developments in biomedical engineering that will allow the incorporation of more elements from micro- and nanotechnology (sensors, processors, effectors and actuators) into a delivery device specifically for the inner ear.

Biodegradable biopolymers

In addition to the use of gels to stabilize the volume of drug-containing solutions in the middle ear, there is also enormous interest in the use of biodegradable biopolymers for the controlled delivery of substances to the inner ear. The two main roles of these polymers are diffusion control of active agents and disintegration control of the polymer, which results in release of the active agent.

Advantages of polymeric controlled-release devices include a specific release kinetic for prolonged delivery and the possibility of drug targeting. Of special interest are so-called 'smart polymers' that are able to respond to chemical or physical changes of the environment, such as pH, temperature and electric field, that might allow them to be incorporated into auto-regulated implantable drug-delivery systems. Disadvantages are the limited amounts of drug that can be incorporated in a given application form [76,91,92].

Two recent publications have reported on the use of biopolymers for local drug delivery to the inner ear [65,93]. Another application in this area is the coating of cochlea implant electrodes with biodegradable carrier substances to release drugs. In this application, glucocorticoids, antioxidants, apoptosis inhibitors or neurotrophins could be employed to counteract side effects of electrode

insertion, to aid survival of the spiral ganglia or to stimulate neurite growth towards the implant electrodes [94].

Influence of the application system on pharmacokinetics with RW application

Based on analyses and simulations of experimental inner-ear pharmacokinetic studies in animals [59,62], it has been established that the application protocol is a major factor in determining the absolute drug level reached in the inner ear. The time that the drug remains in the middle ear plays a primary role, with highest intracochlear drug levels found with continuous delivery and lower levels found with brief applications. In addition, the relative distribution of drugs in the ear varies with application protocol because of the interactions between the duration of application with clearance processes.

Conclusions for clinical applications

The applied concentration of drug and the delivery protocol required to achieve a specific goal in humans is likely to differ substantially from that demonstrated in experimental animals. As drug concentrations in the inner-ear fluids depend on dispersal by diffusion, they are influenced by the differing scala lengths and volumes of the inner ear in different species. For example, to achieve the same active dose in the vestibulum of humans, higher middle-ear and basal-turn drug levels will be required compared with experimental animals with smaller cochlear fluid volumes. This is particularly important in the therapy of Menière's disease by intratympanic drug application, where one also has to consider the relative vestibulotoxicity and cochleotoxicity of specific protocols. A major factor affecting the drug level in the ear is the time the drug remains in the middle ear. It is therefore of major importance that application methods are developed in a way that the amount of drug in the middle ear and the application duration are closely controlled.

Basal to apical concentration gradients generated by local drug application are also of clinical relevance. Concentration gradients will be greater in the human cochlea than in experimental animals because of the longer cochlear spiral of the human. Whereas drug applied to the RWM of mice will readily reach the cochlear apex, the same is not true for humans, as the cochlea is substantially longer. Gradients in drug concentration between the basal (high-frequency) regions compared with apical (low-frequency) regions of the cochlea partially account for the limited hearing loss in humans with Menière's disease treated with vestibulotoxic levels of gentamicin. Drug gradients can be exploited for the treatment of other inner-ear disorders, such as high-frequency tinnitus and high-frequency hearing loss. By contrast, it will be difficult to treat hearing disorders in the middle and lower frequency range by present-day intratympanic drug application methods.

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References

1 Ersner, M.S. *et al.* (1951) Transtympanic injection of anesthetics for the treatment of Menière's Syndrome. *AMA Arch. Otolaryngol.* 54, 43–52

2 Völger, G. (1952) Beseitigung von Labyrinthliquordruckstörungen bei dem Menièrschen Symptomkomplex durch das Hyaluronidasepräparat Kinetin. *HNO* 3, 142–147

3 Schuknecht, H.F. (1956) Ablation therapy for the relief of Meniere's disease. *Laryngoscope* 66, 859–870

4 Nedzelski, J.M. *et al.* (1992) Chemical labyrinthectomy: local application of gentamicin for the treatment of unilateral Meniere's disease. *Am. J. Otol.* 13, 18–22

5 Toth, A.A. and Parnes, L.S. (1995) Intratympanic gentamicin therapy for Meniere's disease: preliminary comparison of two regimens. *J. Otolaryngol.* 24, 340–344

6 Minor, L.B. (1999) Intratympanic gentamicin for control of vertigo in Meniere's disease: vestibular signs that specify completion of therapy. *Am. J. Otol.* 20, 209–219

7 Lange, G. *et al.* (2004) Long-term results after interval therapy with intratympanic gentamicin for Meniere's disease. *Laryngoscope* 114, 102–105

8 Carey, J. (2004) Intratympanic gentamicin for the treatment of Meniere's disease and other forms of peripheral vertigo. *Otolaryngol. Clin. North Am.* 37, 1075–1090

9 Parnes, L.S. *et al.* (1999) Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope* 109, 1–17

10 Kopke, R.D. *et al.* (2001) Targeted topical steroid therapy in sudden sensorineural hearing loss. *Otol. Neurotol.* 22, 475–479

11 Chandrasekhar, S.S. (2001) Intratympanic dexamethasone for sudden sensorineural hearing loss: clinical and laboratory evaluation. *Otol. Neurotol.* 22, 18–23

12 Gianoli, G.J. and Li, J.C. (2001) Transtympanic steroids for treatment of sudden hearing loss. *Otolaryngol. Head Neck Surg.* 125, 142–146

13 Lefebvre, P.P. and Staecker, H. (2002) Steroid perfusion of the inner ear for sudden sensorineural hearing loss after failure of conventional therapy: a pilot study. *Acta Otolaryngol.* 122, 698–702

14 Gouveris, H. *et al.* (2005) Intratympanic dexamethasone with hyaluronic acid in the treatment of idiopathic sudden sensorineural hearing loss after failure of intravenous steroid and vasoactive therapy. *Eur. Arch. Otorhinolaryngol.* 262, 131–134

15 Ho, H.G. *et al.* (2004) Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment. *Laryngoscope* 114, 1184–1189

16 Plontke, S. *et al.* Outcomes research analysis of continuous intratympanic glucocorticoid delivery in patients with acute severe to profound hearing loss: basis for planning of randomized controlled trials. *Acta Otolaryngol.* (in press)

17 Itoh, A. and Sakata, E. (1991) Treatment of vestibular disorders. *Acta Otolaryngol. Suppl.* 481, 617–623

18 Shea, J.J., Jr and Ge, X. (1996) Dexamethasone perfusion of the labyrinth plus intravenous dexamethasone for Meniere's disease. *Otolaryngol. Clin. North Am.* 29, 353–358

19 Silverstein, H. *et al.* (1998) Dexamethasone inner ear perfusion for the treatment of Meniere's disease: a prospective, randomized, double-blind, crossover trial. *Am. J. Otol.* 19, 196–201

20 Sennaroglu, L. *et al.* (1999) Transtympanic dexamethasone application in Meniere's disease: an alternative treatment for intractable vertigo. *J. Laryngol. Otol.* 113, 217–221

21 Coles, R.R. *et al.* (1992) Intra-tympanic injections in the treatment of tinnitus. *Clin. Otolaryngol.* 17, 240–242

22 Silverstein H., *et al.* (1996) Intratympanic steroid treatment of inner ear disease and tinnitus (preliminary report). *Ear Nose Throat J.* 75, 468–471, 474, 476 passim

23 Sakata, E. *et al.* (1997) Clinical experiences of steroid targeting therapy to inner ear for control of tinnitus. *Int. Tinnitus J.* 3, 117–121

24 Shulman, A. and Goldstein, B. (2000) Intratympanic drug therapy with steroids for tinnitus control: a preliminary report. *Int. Tinnitus J.* 6, 10–20

25 Cesarani, A. *et al.* (2002) Intratympanic dexamethasone treatment for control of subjective idiopathic tinnitus: our clinical experience. *Int. Tinnitus J.* 8, 111–114

26 Ristow, W. (1968) Zur Behandlung der Menière-Krankheit mittels temporärer

Labyrinthanästhesie. *Z. Laryngol. Rhinol. Otol.* 47, 442–448
27 Schwab, B. *et al.* (2004) *Laryngorhinootologie* 83, 164–172
28 Keithley, E.M. *et al.* (1998) GDNF protects the cochlea against noise damage. *Neuroreport* 9, 2183–2187
29 Shoji, F. *et al.* (2000) Differential protective effects of neurotrophins in the attenuation of noise-induced hearing loss. *Hear. Res.* 146, 134–142
30 Li, G. *et al.* (2001) Round window membrane delivery of L-methionine provides protection from cisplatin ototoxicity without compromising chemotherapeutic efficacy. *Neurotoxicology* 22, 163–176
31 Korver, K.D. *et al.* (2002) Round window application of D-methionine provides complete cisplatin otoprotection. *Otolaryngol. Head Neck Surg.* 126, 683–689
32 Wang, J. *et al.* (2002) Riluzole rescues cochlear sensory cells from acoustic trauma in the guinea-pig. *Neuroscience* 111, 635–648
33 Wang, J. *et al.* (2003) A peptide inhibitor of c-Jun N-terminal kinase protects against both aminoglycoside and acoustic trauma-induced auditory hair cell death and hearing loss. *J. Neurosci.* 23, 8596–8607
34 Chen, Z. *et al.* (2003) Pharmacokinetics of caroverine in the inner ear and its effects on cochlear function after systemic and local administrations in Guinea pigs. *Audiol. Neurootol.* 8, 49–56
35 Hight, N.G. *et al.* (2003) Noise-induced hearing loss in chinchillas pre-treated with glutathione monoethylester and R-PIA. *Hear. Res.* 179, 21–32
36 Takemura, K. *et al.* (2004) Direct inner ear infusion of dexamethasone attenuates noise-induced trauma in guinea pig. *Hear. Res.* 196, 58–68
37 Raphael, Y. *et al.* (1996) Adenoviral-mediated gene transfer into guinea pig cochlear cells *in vivo*. *Neurosci. Lett.* 207, 137–141
38 Lalwani, A.K. *et al.* (1996) Development of *in vivo* gene therapy for hearing disorders: introduction of adeno-associated virus into the cochlea of the guinea pig. *Gene Ther.* 3, 588–592
39 Dazert, S. *et al.* (1997) Transfection of neonatal rat cochlear cells *in vitro* with an adenovirus vector. *Int. J. Dev. Neurosci.* 15, 595–600
40 Staecker, H. *et al.* (1998) Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol. Head Neck Surg.* 119, 7–13
41 Stover, T. *et al.* (1999) Cochlear gene transfer: round window versus cochleostomy inoculation. *Hear. Res.* 136, 124–130
42 Kawamoto, K. *et al.* (2004) Antioxidant gene therapy can protect hearing and hair cells from ototoxicity. *Mol. Ther.* 9, 173–181
43 Izumikawa, M. *et al.* (2005) Auditory hair cell replacement and hearing improvement by *Atoh1* gene therapy in deaf mammals. *Nat. Med.* 11, 271–276
44 Tran Ba Huy, P. *et al.* (1986) Kinetics of gentamicin uptake and release in the rat. Comparison of inner ear tissues and fluids with other organs. *J. Clin. Invest.* 77, 1492–1500
45 Hoffer, M.E. *et al.* (1997) Use of sustained release vehicles in the treatment of Meniere's disease. *Otolaryngol. Clin. North Am.* 30, 1159–1166
46 Bachmann, G. *et al.* (2001) Permeabilität der runden Fenstermembran für Prednisolon-21-Hydrogensuccinat. *HNO* 49, 538–542
47 Hibi, T. *et al.* (2001) Perilymphatic concentration of gentamicin administered intratympanically in guinea pigs. *Acta Otolaryngol.* 121, 336–341
48 Thomsen, J. *et al.* (2000) Preliminary results of a new delivery system for gentamicin to the inner ear in patients with Meniere's disease. *Eur. Arch. Otorhinolaryngol.* 257, 362–365
49 Schoendorf, J. *et al.* (2001) Continuous intratympanic infusion of gentamicin via a microcatheter in Meniere's disease. *Otolaryngol. Head Neck Surg.* 124, 203–207
50 Salt, A.N. and Ma, Y. (2001) Quantification of solute entry into cochlear perilymph through the round window membrane. *Hear. Res.* 154, 88–97
51 Salt, A.N. (2002) Simulation of methods for drug delivery to the cochlear fluids. *Adv. Otorhinolaryngol.* 59, 140–148
52 Hobbie, R.K. (1997) Transport in an infinite medium. In *Intermediate Physics for Medicine and Biology*, pp 85–90, Springer
53 Goycoolea, M.V. (2001) Clinical aspects of round window membrane permeability under normal and pathological conditions. *Acta Otolaryngol.* 121, 437–447
54 Chandrasekhar, S.S. *et al.* (2000) Dexamethasone pharmacokinetics in the inner ear: comparison of route of administration and use of facilitating agents. *Otolaryngol. Head Neck Surg.* 122, 521–528
55 Selivanova, O. *et al.* (2003) The effects of Streptolysin-O and sodium hyaluronate on the permeability of the round window membrane in guinea pigs – an electrophysiologic study. *Laryngorhinootologie* 82, 235–239
56 Salt, A.N. *et al.* (2003) Contamination of perilymph sampled from the basal cochlear turn with cerebrospinal fluid. *Hear. Res.* 182, 24–33
57 Ohyama, K. *et al.* (1988) Volume flow rate of perilymph in the guinea-pig cochlea. *Hear. Res.* 35, 119–129
58 Salt, A.N. *et al.* (1991) Radial communication between the perilymphatic scalae of the cochlea. II: Estimation by bolus injection of tracer into the sealed cochlea. *Hear. Res.* 56, 37–43
59 Plontke, S. *et al.* (2002) Analysis of gentamicin kinetics in fluids of the inner ear with round window administration. *Otol. Neurotol.* 23, 967–974
60 Saijo, S. and Kimura, R.S. (1984) Distribution of HRP in the inner ear after injection into the middle ear cavity. *Acta Otolaryngol.* 97, 593–610
61 Salt, A.N. *et al.* (1986) Direct measurement of longitudinal endolymph flow rate in the guinea pig cochlea. *Hear. Res.* 23, 141–151
62 Plontke, S.K. and Salt, A.N. (2003) Quantitative interpretation of corticosteroid pharmacokinetics in inner ear fluids using computer simulations. *Hear. Res.* 182, 34–42
63 Laurell, G. *et al.* (2002) Local administration of antioxidants to the inner ear. Kinetics and distribution(1). *Hear. Res.* 173, 198–209
64 Hoffer, M.E. *et al.* (2001) Transtympanic versus sustained-release administration of gentamicin: kinetics, morphology, and function. *Laryngoscope* 111, 1343–1357
65 Arnold, W. *et al.* (2005) Novel slow- and fast-type drug release round-window microimplants for local drug application to the cochlea: an experimental study in guinea pigs. *Audiol. Neurootol.* 10, 53–63
66 Thorne, M. *et al.* (1999) Cochlear fluid space dimensions for six species derived from reconstructions of three-dimensional magnetic resonance images. *Laryngoscope* 109, 1661–1668
67 Shinomori, Y. *et al.* (2001) Volumetric and dimensional analysis of the guinea pig inner ear. *Ann. Otol. Rhinol. Laryngol.* 110, 91–98
68 Scheibe, F. *et al.* (1984) On sources of error in the biochemical study of perilymph (guinea pig). *Arch. Otorhinolaryngol.* 240, 43–48
69 Hara, A. *et al.* (1989) Perilymph composition in scala tympani of the cochlea: influence of cerebrospinal fluid. *Hear. Res.* 42, 265–271
70 Balough, B.J. *et al.* (1998) Kinetics of gentamicin uptake in the inner ear of Chinchilla langier after middle-ear administration in a sustained-release vehicle. *Otolaryngol. Head Neck Surg.* 119, 427–431
71 Hoffer, M.E. *et al.* (1999) Morphologic changes in the inner ear of chinchilla laniger after middle ear administration of gentamicin in a sustained–release vehicle. *Otolaryngol. Head Neck Surg.* 120, 643–648
72 Hahn, H. *et al.* (2004) Microdialysis for studying pharmacokinetics in the inner ear and interpretation of results using a finite element model *27th Annual Meeting of the Association for Research in Otolaryngology*. 22-27 February 2004, Daytona Beach, FL, USA (Abstract No.1552)
73 Hunter, B.A. *et al.* (2003) Estimation of perilymph concentration of agents applied to the round window membrane by microdialysis. *Acta Otolaryngol.* 123, 453–458
74 Hahn, H. *et al.* (2005) Use of microdialysis for quantification of dexamethasone and fluorescine entry into scala tympani during round window application. *28th Annual Meeting of the Association for Research in Otolaryngology*. 19-24 February 2005, New Orleans, LA, USA (Abstract No. 874)
75 Becvarovski, Z. *et al.* (2002) Round window gentamicin absorption: An *in vivo* human model. *Laryngoscope* 112, 1610–1613
76 Wise, D.L., ed. (2000) *Handbook of pharmaceutical controlled release technology*, Marcel Dekker
77 Lange, G. (1995) 27 years experiences with transtympanic aminoglycoside treatment of Meniere's disease. *Laryngorhinootologie* 74, 720–723
78 Schuknecht, H.F. (1957) Ablation therapy in the management of Meniere's disease. *Acta Otolaryngol.* 47, 1–42
79 Arriaga, M.A. and Goldman, S. (1998) Hearing results of intratympanic steroid treatment of endolymphatic hydrops. *Laryngoscope* 108, 1682–1685
80 Kroath, F. (1960) Transtympanale Injektion zur Behandlung des Menièreschen Syndroms. *Z. Laryngol. Rhinol. Otol.* 39, 190–195
81 Silverstein, H. *et al.* (1999) Direct round window membrane application of gentamicin in the treatment of Meniere's disease. *Otolaryngol. Head Neck Surg.* 120, 649–655
82 Alzamil, K.S. and Linthicum, F.H., Jr (2000) Extraneous round window membranes and plugs: possible effect on intratympanic therapy. *Ann Otol Rhinol Laryngol* 109, 30–32
83 Plontke, S.K. *et al.* (2002) Transtympanic endoscopy for drug delivery to the inner ear using a new microendoscope. *Adv. Otorhinolaryngol.* 59, 149–155
84 Silverstein, H. (1999) Use of a new device, the Microwick, to deliver medication to the inner ear. *Ear Nose Throat J.* 78, 595–598
85 Brown, J.N. *et al.* (1993) Osmotic pump implant for chronic infusion of drugs into the inner ear. *Hear. Res.* 70, 167–172

86 Prieskorn, D.M. and Miller, J.M. (2000) Technical report: chronic and intracochlear infusion in rodents. *Hear. Res.* 140, 212–215
87 Lehner, R. *et al.* (1997) A totally implantable drug delivery system for local therapy of the middle and inner ear. *Ear Nose Throat J.* 76, 567–570
88 Praetorius, M. *et al.* (2001) A novel microperfusion system for the long-term local supply of drugs to the inner ear: implantation and function in the rat model. *Audiol. Neurootol.* 6, 250–258
89 Paasche, G. *et al.* (2003) Technical report: modification of a cochlear implant electrode for drug delivery to the inner ear. *Otol. Neurotol.* 24, 222–227
90 Fiering, J.O. *et al.* (2005) Microfluidic System for Long Term Intracochlear Drug Delivery, *28th Annual Meeting of the Association for Research in Otolaryngology*. 19–24 February 2005, New Orleans, LA, USA (Abstract No. 158)
91 Park, K. *et al.* (1993) *Biodegradable hydrogels for drug delivery*, Technomic Publishing Company
92 Okano, T. (1998) *Biorelated polymers and gels: controlled release and applications in biomedical engineering*, Academic Press
93 Endo, T. *et al.* (2004) A novel drug delivery system into the inner ear. Abs. *27th Annual Meeting of the Association for Research in Otolaryngology*, 22–27 February 2004, Daytona Beach, FL, USA (Abstract No. 1054)
94 Scarpidis, U. *et al.* (2003) Arrest of apoptosis in auditory neurons: implications for sensorineural preservation in cochlear implantation. *Otol. Neurotol.* 24, 409–417