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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* See review by Leonard P. Rybak and Craig A. Whitworth in this issue, pp. 1313-1321.

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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:

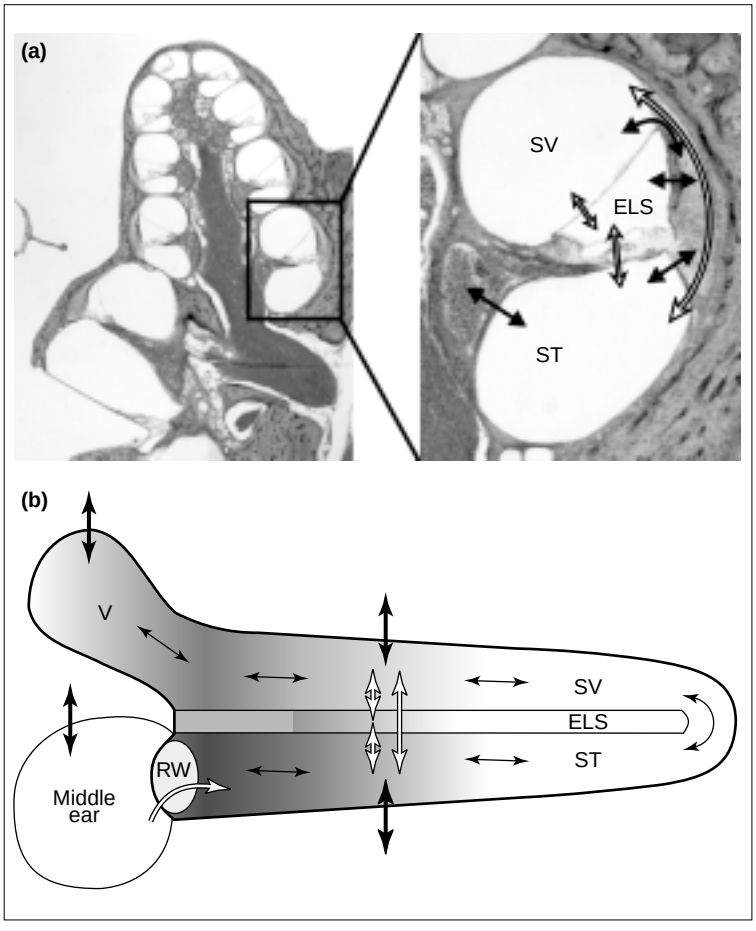

FIGURE 1

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