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Advances in nano-based inner ear delivery systems for the treatment of sensorineural hearing loss☆

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ABSTRACT

Sensorineural hearing loss (SNHL) is one of the most common diseases, accounting for about 90% of all hearing loss. Leading causes of SNHL include advanced age, ototoxic medications, noise exposure, inherited and autoimmune disorders. Most of SNHL is irreversible and managed with hearing aids or cochlear implants. Although there is increased understanding of the molecular pathophysiology of SNHL, biologic treatment options are limited due to lack of noninvasive targeted delivery systems. Obstacles of targeted inner ear delivery include anatomic inaccessibility, biotherapeutic instability, and nonspecific delivery. Advances in nanotechnology may provide a solution to these barriers. Nanoparticles can stabilize and carry biomaterials across the round window membrane into the inner ear, and ligand bioconjugation onto nanoparticle surfaces allows for specific targeting. A newer technology, nanohydrogel, may offer noninvasive and sustained biotherapeutic delivery into specific inner ear cells. Nanohydrogel may be used for inner ear dialysis, a potential treatment for ototoxicity-induced SNHL.

Contents

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1. Introduction

The inner ear consists of the cochlea and vestibule, and it is a crucial drug delivery target for the treatment of hearing and balance disorders, respectively. Routes for drug entry into the inner ear include the systemic circulation, which feeds the labyrinthine artery that supplies the cochlea and vestibule, and the round window membrane (RWM), which connects the middle ear with the inner ear. Anatomic challenges for drug delivery into the inner ear include the blood-inner ear barrier, limited labyrinthine artery supply, and difficult access to the RWM. Mechanistic challenges for drug delivery into the inner ear include variations in RWM permeability, biotherapeutic instability, uncontrolled drug elimination, and nonspecific drug delivery. While inner ear diseases have historically been treated with systemic therapies, local intratympanic (IT) injection can offer more efficient and less systemically toxic drug delivery. Hydrogel, another localized drug delivery system, has the additional advantages of sustained and controlled drug release, which can reduce inter-patient variability in drug elimination while maximizing drug diffusion. Although these forms of drug delivery have been used successfully in the treatment of various inner diseases, such as sudden sensorineural hearing loss (SHL), autoimmune inner ear disease (AIED), and Meniere's disease, they can neither stabilize newer therapeutics, including biomaterials, nor target therapies to specific cell types within the inner ear. Nanotechnology may be able to address these current limitations and offer a noninvasive, sustained and targeted drug delivery system.

1.1. Systemic drug delivery

Systemic drug delivery can be accomplished via the intravenous, intramuscular or oral route, and it has been successfully used to treat inner ear diseases such as sudden hearing loss (SHL), autoimmune inner ear disease (AIED), and Meniere's disease. Oral corticosteroids are commonly prescribed for the treatment of SHL, defined as a 30 decibels or greater hearing loss in 3 consecutive frequencies over less than 72 h [1]. A pioneering study by Wilson et al. demonstrated that oral corticosteroids could effectively reverse SHL with a recovery rate of 61%, as compared with a placebo recovery rate of 32% [2]. Additional studies have since demonstrated SHL recovery rates of 57–66% with oral corticosteroid use [3,4]. More long-term courses of oral corticosteroids are used in the treatment of AIED, which presents as progressive bilateral asymmetric sensorineural hearing loss (SNHL) occurring over weeks to months, with possible vestibular deficit [5–7]. The current treatment protocol for AIED is 4 weeks of high-dose oral prednisone and subsequent tapering to the lowest possible dose while maintaining therapeutic effect; the rate of hearing preservation using this regimen is reportedly between 53 and 70% [6]. Like SHL and AIED, Meniere's disease has also been successfully treated with systemic drug therapy. Aminoglycosides, which were historically delivered intra-muscularly, are indicated for the treatment of vertigo in patients with who have failed more conservative medical therapies [1]. Although inherently ototoxic, well-titrated doses of aminoglycosides can preferentially ablate vestibular structures that are responsible for balance, thereby reducing vertigo symptoms in Meniere's disease patients [8,9]. However, even with current titration methods, hearing loss associated with treatment is not uncommon.

Though drug delivery to the inner ear can be achieved via systemic administration, limited local blood supply and poor penetration of the blood-inner ear barrier often results in subtherapeutic local concentrations. Administration of large doses of medication is required to produce the desired therapeutic effect, often leading to severe toxicities. Systemic corticosteroids can lead to hypertension, hyperglycemia, osteoporosis and immunosuppression, along with more long-term adrenal suppression at high doses [1]. In a prospective study by Alexander et al. of AIED patients receiving oral prednisone, 17.6% of patients developed of hyperglycemia in a dose-dependent manner and 39% of patients experienced weight gain of 10 lb or more. Although the hyperglycemia appeared to be reversible, the weight gain persisted even after drug discontinuation [7]. Aminoglycoside toxicity, too, can produce hearing loss and persistent disequilibrium [9–11]. Although certain aminoglycosides, such as streptomycin and gentamicin, are more vestibulotoxic than cochleotoxic, high doses can lead to cochlear damage and sensorineural hearing loss [8–10].

1.2. Intratympanic drug delivery

To improve the efficacy and reduce the adverse effects of systemic drug delivery, more localized drug delivery systems were developed to target inner ear disease. Schuknecht et al. was the first to introduce intratympanic (IT) injection as a means of delivering streptomycin into the inner ear for the successful treatment of Meniere's disease patients [12]. IT injection of a drug into the middle ear space allows for drug diffusion across the round window membrane (RWM) into the inner ear. In bypassing the labyrinthine artery and blood-inner ear barrier, IT injection provides a more direct and efficient approach as compared to systemic drug administration. In fact, drug concentrations measured in the inner ear fluids, perilymph and endolymph, are significantly higher with IT injection than with oral or parenteral administration [6,13]. Not only can IT injection more efficiently deliver drugs into the inner ear, it can also avoid many of the side effects associated with systemic therapy.

Due to these advantages and the relative ease of performing the procedure in the office, IT injection of corticosteroids and aminoglycosides is now commonly used for treatment of SHL and Meniere's disease. [1,13]. For example, IT corticosteroid injections can be used as primary or salvage therapy for SHL and for patients with contraindications for systemic corticosteroid therapy [14]. A large randomized prospective trial by Rauch et al. found that primary IT corticosteroid therapy and primary oral corticosteroid therapy were equally effective at restoring hearing in patients with SHL, although the latter was associated with systemic side effects such as hyperglycemia and appetite changes [15]. A more recent study by Filipo et al. found that while IT and oral corticosteroid therapy produced similar improvement in the pure tone averages of patients with SHL, IT injection led to significantly better hearing threshold improvement, suggesting the therapeutic superiority of primary IT injection [4]. IT corticosteroid injection for the treatment of AIED is less well-studied, and the few reports published involve AIED patients who have failed or could not tolerate systemic steroid and/or methotrexate therapy. While high dose oral corticosteroids continue to be the standard of care for AIED, IT corticosteroids have shown promise as at least a salvage treatment option for these patients [6].

Although IT delivery is efficient and has reduced the toxicities associated with systemic drug delivery, it continues to demonstrate inconsistency in delivering standard doses of drugs into the inner ear. Because IT injection relies on diffusion for the drug to reach the inner ear from the middle ear, its success is directly related to the amount of drug that comes into contact with the RWM. Any drug that is not in contact with the RWM is eliminated via the Eustachian tube. Differences in RWM permeability can thus lead to variable rates of drug retention and elimination. This inconsistency is evident in the application of IT aminoglycosides for Meniere's disease treatment. As mentioned, aminoglycosides are inherently ototoxic and can cause hearing loss and permanent disequilibrium at inappropriately high doses. Early studies of IT streptomycin delivery for Meniere's disease showed that although vertigo was relieved in the majority of patients, hearing loss developed in greater than 25% of patients [12,16]. In an effort to reduce toxicity, the clinical endpoint of therapy changed over time from complete ablation to alteration of the number of vertiginous attacks, and various timing and dosage regimens of IT gentamicin injection were tested [1,17]. A meta-analysis by Chia et al. evaluated the efficacy of vertigo control and hearing loss rate of scheduled drug delivery, including various