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Nanoparticle drug delivery systems for inner ear therapy: An overview

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ABSTRACT

Local drug delivery based on nanoparticles (NP) represents a novel strategy to improve inner ear treatments. The intratympanic delivery of NP may be suitable to treat or prevent hearing loss originating from damage to hair cells and spiral ganglion neurons in the cochlea. Numerous experimental studies support *in vitro* and *in vivo* the biocompatibility of NP, their physical stability, target specificity, cell/tissue uptake and ability to internalize therapeutic agents. The topical use of NP helps to reduce the amount of drug required and avoid systemic side effects. This review focuses on recent findings and applications of different NP systems locally delivered to the inner ear. The perspectives for clinical application of NP in inner ear drug delivery are also discussed.

Contents

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1. Introduction

The treatment of inner ear diseases through drug delivery (DD) faces numerous challenges [1], among which the limited blood flow to the inner ear [2], the presence of physical barriers acting as a selective filter for drug transportation to the inner ear from the circulatory system [3], the small size of the cochlea and its isolated location in the petrous bone. As a result, research in local drug applications and medications has recently attracted interest because it is a more effective and preferable treatment than the systemic one. Case studies involving steroids [4] and gentamicin treatment for Meniere's disease [5] have been documented, but these approaches could be improved for clinical protocols by the development of controlled and targeted delivery systems.

Nanoparticles (NP) are a possible option to improve existing therapeutic strategies [6]. The NP with size between 10 and 200 nm are useful for application in biology and medicine for innovative DD systems. NP-based strategy could be more efficient and reduce drug-associated side effects because of the ability to deliver the therapeutic agent to the target site. Moreover, the controlled release of compounds conjugated to NP results in a lower dose of drug required to achieve the therapeutic effects [1,7].

The cochlea is a good model for studying the NP-based DD due to its isolated structure and the perilymph rheology. The intratympanic delivery of NP could be suitable to treat the hearing loss and prevent its progression when hair cells and spiral ganglion neurons are damaged [8].

Several works and reviews have been published in the past decade, focusing on NP type, pathology involved, delivery approach or a combination of these topics [1–4,6–8]. The goal of the present review is to provide an updated general overview of NP-based strategies and their advantages and disadvantages for local DD into the inner ear.

2. Ear barriers

The human inner ear consists of two main parts, the auditory system (the cochlea) and the vestibular system. The cochlea is a bony spiral canal, about 30 mm long and divided in three fluid-filled compartments: the scala tympani, the scala media and the scala vestibuli. The round window membrane (RWM), the blood inner ear barrier (BB) and the oval window are physical barriers that isolate the cochlea from the middle ear and from the circulatory system (Fig. 1). The RWM is a three-layer semi-permeable membrane, composed of an outer epithelial cell layer, a middle connection layer and an inner connection layer facing the perilymph of the scala tympani [9]. In humans, the variable thickness of RWM affects the response of patients to DD treatments. In animal models, its thickness is different among species but its composition is similar [10].

Both the RWM and the oval window membranes have been investigated for DD, as connections between the middle ear cavity and the cochlear perilymph. The DD strategies for the inner ear currently rely mostly on RWM [11]. The passage of molecules across this membrane is not only influenced by thickness, but also by its morphological integrity, inflammation and weight, concentration, liposolubility and external charge of the therapeutic compound [12]. The drugs deposited topically in the middle ear cavity are internalized by pinocytosis and transported to the perilymph through blood vessels or by diffusion. Thus the direct application of drugs in the proximity of RWM is a suitable approach for treatment of inner ear pathologies [13].

The BB is a major barrier in the stria vascularis separating the cochlear tissues from the circulatory system [14]. Its role is to maintain the homeostasis of cochlear fluids and protect the inner ear integrity. Its main components are principally the endothelial capillaries whose cells are connected by tight junctions, which lay over a basement membrane. However numerous accessory cells have recently been observed in the complex structure of the barrier, such as perycites and perivascular resident macrophage-like [11]. The BB has been described to act as a physical and biochemical barrier through an efflux pump, the P-glycoprotein 1 (P-gp) [15]. The BB is therefore considered a rate-limiting barrier in the passage of therapeutic agents from the circulatory system to the inner ear. However, the current knowledge about drug transportation processes through BB is still limited [16].

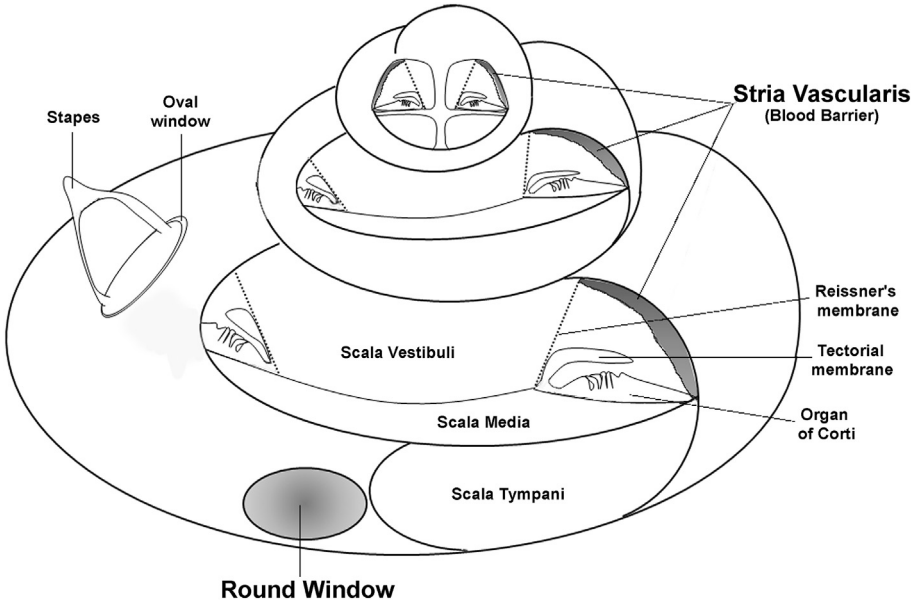

Fig. 1. Scheme of the cochlea structure, highlighting the cochlear barriers, the round window and the stria vascularis.