



**Karolinska  
Institutet**

**Institutionen för klinisk vetenskap, intervention och teknik**

## Local Pharmacological Treatment of Inner Ear Disorders

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras på svenska språket i ÖNH-klinikens föreläsningssal (A602), plan 2 i huvudbyggnaden, Karolinska Universitetssjukhuset, Solna

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av

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## ABSTRACT

Hearing disorders are among the top 10 in terms of burden of disease in middle- and high-income countries, affecting 250 million people worldwide. During the last few decades researchers have made significant advances in understanding the basic mechanisms and molecular biology of inner ear diseases. The principal challenge in treatment of the inner ear is that the targets for pharmacological therapy are inaccessible due to the various barrier systems of the inner ear, and that the inner ear is embedded in the base of the skull. New technologies to provide safe and efficacious delivery of drugs to the inner ear are of great clinical interest. Local administration of medication to the inner ear would solve some of the problems associated with systemic delivery, such as drug interaction and systemic side effects. The aim of the research presented in this thesis was to elucidate different aspects of drug delivery to the inner ear using a local application technique.

The round window membrane (RWM) is believed to be the main route for drug delivery to the inner ear when a drug is administered to the middle ear i.e. by an intratympanic injection. A morphological study of the round window performed on cynomolgus monkey described in Paper I showed the existence of a local defense system housed within the rim of the RWM. Previously undescribed gland-like structures were identified in the loose connective tissue of the mucosal layer near the bony insertion of the RWM. These findings could explain why labyrinthitis is rare despite the close proximity of the infection-prone middle ear. A local immunodefense system would also most likely affect the transport of drugs from the middle ear cavity to the inner ear and needs to be taken into consideration when developing new strategies for local drug administration in the middle ear.

In the studies on which Paper II is based, the rheological and safety aspects of three candidate vehicles for intratympanic drug administration were investigated. The results speak in favor of sodium hyaluronate (HYA gel) which, in contrast to carboxymethyl cellulose and poloxamer 407, did not cause lasting or significant increases in hearing threshold after intratympanic injection in the guinea pig. Studies of vehicle elimination and morphological investigations support HYA gel as the most promising candidate for intratympanic administration.

An important factor for local administration of drugs to the middle ear aimed for inner ear treatment is the adherence of the vehicle to the RWM. The distribution and elimination of HYA gel after intratympanic injection to the auditory bulla in guinea pig were investigated by magnetic resonance imaging in Paper III. HYA gel was distributed in a predictable way and filled the middle ear cavity well. The HYA gel remained close to the RWM for more than 24 hours. A myringotomy was needed before middle ear administration to allow air to escape and prevent trauma to the RWM.

The hypothesis that higher concentrations of a drug in the inner ear could be achieved by local administration than through systemic administration was investigated in Paper IV and V using the antioxidant thiosulfate, which has previously been identified as a promising otoprotector against cisplatin-induced ototoxicity. The concentration of thiosulfate in scala tympani perilymph was much higher after intratympanic delivery to the guinea pig using an injection of a thiosulfate-containing HYA gel than after i.v. administration of a thiosulfate solution. The levels of thiosulfate in blood remained low after intratympanic administration, confirming that this delivery system will not risk decreased antitumoral effect due to cisplatin inactivation in tumor tissue.

The final study, Paper V, demonstrated that ototoxicity in guinea pigs treated with the antineoplastic drug cisplatin was reduced by injection of thiosulfate-containing HYA gel three hours prior to the systemic cisplatin injection. This confirms the hypothesis of thiosulfate being a promising otoprotector for cisplatin induced hearing loss and also shows that drugs can be delivered locally to the inner ear by intratympanic injection using HYA gel as a vehicle.