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Cover Story

Pharmacokinetic studies for cochlear drug delivery

Hearing loss is one of the most common disabilities in developed countries across the world. Hearing loss is a life-long impairment that places a continuing burden on the community through the cost of hearing aids and prostheses, reduced economic independence, and social supports. It is a high priority to develop a therapeutic intervention to treat hearing loss. Neurotrophin-3 is a protein growth factor that helps the survival and differentiation of existing neurons, as well as the growth and differentiation of new neurons and synapses. Localized neurotrophin-3 delivery to the cochlea has been extensively studied as a means to protect and repair auditory neurons and their synapses that are damaged in hearing loss. However, the cochlea presents some unique challenges for localized drug delivery. The safe and effective drug delivery to the cochlea requires understanding of pharmacokinetic profiles of the locally administered neurotrophin-3, but such pharmacokinetic studies have not been easy.

In this issue, Professor Rachael Richardson and her colleagues report on a powerful method to examine cochlear pharmacokinetics [1]. A radiolabel tracer (^{125}I) was attached to neurotrophin-3 to quantify the retention and tissue uptake of the protein following localized administration to the cochlea. The method presents a few advantages over other techniques that use fluid-sampling to measure drug retention and distribution in the cochlea. First, the percent retention of drug in the cochlea can be determined by sensitive gamma counting methods without disturbing the cochlear fluids which can otherwise result in fluid flow and contamination with cerebrospinal fluid. Second, the disposition of neurotrophin-3 in the cochlear tissue can be measured via autoradiography techniques providing high resolution data on drug distribution. Third, the uptake in the neuronal target tissue can be visualized and measured.

The study by the Richardson team showed that smaller dosing volumes actually resulted in a higher percentage retention when neurotrophin-3 was directly injected into the cochlea. This is because the cochlea is encased in a bony capsule that cannot expand. As the fluid volume inside the cochlea is artificially increased by injection of a drug, the increased pressure leads to loss of the drug, most likely through the cochlear aqueduct. The team also found that high concentrations of the dosing solution resulted in a greater percentage retention due to higher tissue disposition. The autoradiography methods provide a detailed histological view of the distribution and uptake of neurotrophin-3 in the cochlea. The data showed that the distribution was non-uniform between different cell and tissue types, and that the relative disposition was reduced in the higher turns of the cochlear spiral. The data highlights the challenges in drug delivery to the cochlea in terms of protection and repair of low and high frequency hearing, targeting the relevant tissue and reducing distal spread and potential off-site effects.

The Richardson team's study provides a simple and effective method to study cochlear pharmacokinetics that will enable researchers to compare the relative effectiveness of different drug delivery strategies for a cochlear therapy. Direct intracochlear injection carries the risk of damaging the sensitive sensory cells of the cochlea but may be considered in scenarios when the cochlea is already being accessed, e.g., during cochlear implantation. In this situation, the impact of the cochlear implant on pharmacokinetics and neurotrophin-3 distribution will need to be examined. Other strategies include extracochlear drug delivery relying on the drug crossing a semi-permeable membrane which significantly reduces the drug concentration in the cochlea relative to the implanted dose. The technique will enable researchers to provide supportive data towards a clinical trial of neurotrophin-3 therapy for hearing loss. The Richardson team has demonstrated that the pharmacokinetic study of neurotrophin-3 in the limited space of the cochlea can be done with high accuracy and resolution which are necessary for understanding the drug efficacy and duration. This is a kind of painstaking study the drug delivery field needs, instead of simply measuring small differences in the outcome that may occur between the control and treated groups.

Reference

[1] R.T. Richardson, Q.-Y. Hu, F. Shi, T. Nguyen, J.B. Fallon, B.O. Flynn, A.K. Wise, Pharmacokinetics and tissue distribution of neurotrophin 3 after intracochlear delivery, J. Control. Release 299 (2019) 53–63.

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