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Review Article

# Communication pathways to and from the inner ear and their contributions to drug delivery

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The environment of the inner ear is highly regulated in a manner that some solutes are permitted to enter while others are excluded or transported out. Drug therapies targeting the sensory and supporting cells of the auditory and vestibular systems require the agent to gain entry to the fluid spaces of the inner ear, perilymph or endolymph, which surround the sensory organs. Access to the inner ear fluids from the vasculature is limited by the blood-labyrinth barriers, which include the blood-perilymph and blood-strial barriers. Intratympanic applications provide an alternative approach in which drugs are applied locally. Drug from the applied solution enters perilymph through the round window membrane, through the stapes, and under some circumstances, through thin bone in the otic capsule. The amount of drug applied to the middle ear is always substantially more than the amount entering perilymph. As a result, significant amounts of the applied drug can pass to the digestive system, to the vasculature, and to the brain. Drugs in perilymph pass to the vasculature and to cerebrospinal fluid via the cochlear aqueduct. Conversely, drugs applied to cerebrospinal fluid, including those given intrathecally, can enter perilymph through the cochlear aqueduct. Other possible routes in or out of the ear include passage by neuronal pathways, passage via endolymph and the endolymphatic sac, and possibly via lymphatic pathways. A better understanding of the pathways for drug movements in and out of the ear will enable better intervention strategies.



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## 1. Introduction

The bony otic capsule represents a major anatomic and physiological barrier to the inner ear, isolating labyrinthine fluids and tissues from adjacent structures, such as the middle ear and the brain. The bony encasement of the inner ear, present in the early evolution of vertebrates (Carey and Amin, 2006), is an adaptation to optimize effective transduction of sound and head movements into electrical signals. The inner ear can be regarded as a membrane-bound tube containing endolymph suspended within a rigid-walled compartment containing perilymph, with compliant openings at the round window membrane and stapes. This arrangement enables responses to mechanical stimuli, including sound waves delivered by the stapes and head motions, while attenuating body-generated pulsations, such as those associated with respiration, heartbeat, coughing and sneezing.

A second type of barrier separating the inner ear from other organs, is created by specialized cell layers. The lipid membranes of either epithelial or endothelial cell layers, combined with tight junctions between adjacent cells of the layer restrict solute movement (Giepmans and van Ijzendoorn, 2009). The blood vessels of the inner ear allow exchange of gases, $O_2$ and $CO_2$, while restricting the passage of even small molecules and cells (Hirose et al., 2014). The vessels have properties that are dynamic and are influenced by temperature, pH, muscle tone, $O_2$ and $CO_2$ content as well as cytokines/chemokines and inflammatory molecules. They form the blood-labyrinth barrier which consists of barriers of at least two distinct types. The blood-perilymph barrier separates blood from perilymph. The blood-strial barrier separates the blood from the cochlear intrastrial space. Epithelial cells which line the endolymph compartment provide a tight barrier between endolymph and perilymph, limiting solute movements between the two fluids. A respiratory pseudostratified columnar epithelium and non-keratinizing epithelium line the middle ear. These epithelia cover the middle ear spaces and contribute to the barriers between the middle ear and perilymph at the round window membrane and stapes. Passage of molecules across cellular barriers depends on many factors, including the lipophilicity, polarity and size of the molecule, and whether they pass the barrier membranes by active or passive transport processes.

The major communication pathways in and out of the ear are summarized in Table 1. Pathways between the ear and adjacent spaces include the cochlear aqueduct the endolymphatic duct and sac, the internal auditory canal through which the cochlear, vestibular and facial nerves pass. Under some conditions, passage through the dense petrous bone of the otic capsule can play a role. Knowledge of entry and exit pathways and whether they have substance-specific characteristics is important to understanding pharmacokinetics of the ear with local and/or systemic drug delivery. Communication pathways of the ear have been reviewed elsewhere from a clinical perspective (Ciuman, 2009).

## 2. Perilymph, endolymph, and tissues of the inner ear

The sensory hair cells of the cochlea are located in the organ of Corti and lie on the boundary between the perilymph and endolymph. In early anatomic studies, the basilar membrane, on which the organ of Corti rests, was first recognized as a prominent anatomic boundary and became defined as the boundary between scala tympani and scala media. The basilar membrane comprises layers of collagen fibers (Liu et al., 2015), with a cellular, tympanic covering layer lacking tight junctions, thereby allowing it to be permeable to small molecules. The basilar membrane does not provide a barrier to the movement of fluid or small molecules. It provides an example of an anatomic boundary that is structurally identifiable with light microscopy but does not create a barrier for perilymph. In the organ of Corti, the main physiological barrier is instead formed by the reticular lamina, comprising those cells contacting endolymph, including hair cells, Deiter cells, Claudius and Hensen cells and the cells lining the inner sulcus, which are coupled together at their apical membranes by tight junctions (Jahnke, 1975), forming a tight boundary there. The same is true for other structures bounding endolymph, which in the cochlea includes Reissner's membrane, marginal cells of stria vascularis and outer sulcus cells. Reissner's membrane forms the boundary between scala vestibuli and scala media and comprises of two cuboidal cell layers separated by a basal lamina. The cell layer facing endolymph has tight junctions between the apical membranes of the cells, while the layer facing perilymph contains larger cells only loosely joined together. While physiologists initially ascribed Reissner's membrane a permeable role involved in radial fluid flow, subsequent studies have shown its permeability properties are comparable with the organ of Corti, with circulating current flows of similar magnitude through both structures (Zidanic and Brownell, 1990). It is therefore important to recognize that for many structures, permeability does not correlate with the number of cell layers or thickness of the structure. Rather, it depends more on the properties of the cellular boundaries and adhesion molecules between cells. For all cells bordering endolymph, the primary boundary is the apical membrane in contact with endolymph, in conjunction with the tight junctions between cells at their apical surfaces.

Perilymph is ionically comparable to other extracellular fluids, having high $Na^+$, and low $K^+$ content, but differs slightly in composition between scala tympani and scala vestibuli, with scala vestibuli having slightly higher $K^+$ content (Wangemann and Marcus, 2017). Solutes in perilymph readily equilibrate with the extracellular spaces of most of the tissues of the inner ear, including the spiral ligament, spiral ganglion, organ of Corti and the canaliculi in the bony walls of the ear.

### 2.1. Perilymph

Perilymph homeostasis is affected by a vast number of processes. Perilymph is not secreted through an exocrine gland, such as

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