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Review

# Advances in research on labyrinth membranous barriers

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**Abstract**

Integrity of the membranous labyrinth barrier system is of critical importance, which promotes inner ear homeostasis and maintains its features. The membranous labyrinth barrier system is divided into several subsets of barriers which, although independent from each other, are interrelated. The same substance may demonstrate different permeability characteristics through different barriers and under different conditions, while different substances can have different permeability features even in the same barrier under the same condition. All parts of the membranous labyrinth barrier structure, including their morphology, enzymes and channel proteins, and theirs permeability characteristics under various physiological and pathological conditions are reviewed in this paper. Infections, noise exposure, ototoxicity may all increase permeability of the barriers and lead to disturbances in inner ear homeostasis.


*Keywords:* Membranous labyrinth; Barrier; Permeability; Inner ear homeostasis

**Contents**



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## 1. Introduction

Structures of biological barriers often control their permeability and restrict penetrance of substances across the barrier by various mechanisms to maintain stability in the barrier environment. Such barriers especially serve to protect the dynamic balance of inner ear fluids. Inner ear homeostasis depends on the dynamic equilibrium of inner ear fluid secretion and absorption involving inner ear blood supply, peri- and endolymph, ion transport system and integrity of the membranous labyrinth barrier system. The membranous labyrinth is divide into different chambers by a barrier system, which separates the endolymph, perilymph, cerebrospinal fluid (CSF) and serum. Previous studies have proposed that membranous labyrinth barriers are blood-labyrinth barriers (BLB), but failed to clearly explain permeability characteristics of each barrier (Hawkins, 1973; Juhn and Rybak, 1981; Ge, 1989; Yamasoba et al., 1996a; Liu et al., 2013; Hirose et al., 2014; Li et al., 2014; Wu et al., 2014; Zhang et al., 2015). In this review, we propose that the so called BLB (or intra-ear fluid barrier) consists of the blood–endolymph barrier, blood–perilymph barrier, cerebrospinal fluid–perilymph barrier, middle ear–labyrinth barrier and endolymph–perilymph barrier. All these barriers can be called membranous labyrinth barriers. Each barrier permits penetrance by different substances, which can be employed to administrate drugs into the inner ear.

## 2. Morphological basis of membranous labyrinth barriers

### 2.1. Blood–endolymph barrier

The blood–endolymph barrier is seen in the stria vascularis. Hawkins first proposed the concept of blood-labyrinth barrier (BLB) in 1960 and re-emphasized the importance of this barrier when he researched mechanisms of aminoglycoside antibiotics induced ototoxicity in 1973 (Hawkins, 1973). He pointed out that functions of this barrier relied on the integrity of the stria vascularis and spiral ligament (as the stria vascularis, Reissner's membrane and spiral limbus secrete endolymph), and also on the integrity of endolymph spiral prominence, external sulcus, endolymphatic sac, which absorb endolymph. Hawkins believed that aminoglycosides induced pathological changes of the above mentioned structures, leading to disturbed endolymph secretion/absorption balance, followed by dysfunction of the membranous labyrinth and protein synthesis and compromised inner ear homeostasis, as the mechanisms of aminoglycoside ototoxicity. Juhn and Rybak (1981) proposed that substances being transported into the labyrinth may involve simple diffusion, ultrafiltration, osmosis, lipid solubility, special tissue affinity and metabolic activities of inner ear tissues. Sakagami et al. (1984) found that, in the stria vascularis, endolymph barrier structures constituted of tight junctions of marginal cells, and perilymph barriers of tight junctions of basal cells. The space between the two barriers is called the vascular space, which is further sealed off by tight junctions of spindle cells at the junction of the stria vascularis and vestibular membrane, as well as at the spiral prominence. Zhang et al. (2012), Neng et al. (2013a), Neng et al. (2013b) found large number of perivascular-resident macrophage-like melanocytes (PVM/Ms), perivascular cells and F4/80 + GST + melanocyte-like macrophages inside the barrier space. Epithelium derived factor (PEDF), a 50-kDa glycoprotein, is expressed in primary cultured PVM/Ms, and affects the expression of tight junction associated proteins, whereas PEDF receptor (PEDFR) is expressed in primary cultured endothelial cells (ECs). Studies implicate PEDF signaling between PVM/Ms and ECs as an important mediator of the effect PVM/Ms have on expression of tight- and adherens-junction proteins such as occludin, ZO-1 and ve-cadherin. Wu et al. (2014) indicated that a large number of tight junction proteins (TJs), including mainly Claudin-5 and Occludin, contributed to the integrity and permeability of BLB by connecting adherens proteins in pericytes and other TJs. Using rt-PCR and western blot, Neng et al. (2013a) found that signals secreted from either pericytes or PVM/Ms had an effect on the expression of TJs, directly linking pericytes and PVM/Ms with a mechanism that accounts for the changes in endothelial barrier permeability and increase of fluorescent antigen exudation from EC monolayer. Weber et al. (2001) found that Sodium-potassium-chloride cotransporter (NKCC) was present in the basolateral membrane of strial marginal cells as well as in type II, type V and limbal fibrocytes, which maintain $K^+$ and $Na^+$ homeostasis in the human cochlea. Deficiency of NKCC leads to compromised endolymph translation from marginal cells, reducing endolymph potential (EP) while increasing permeability of BLB which allows more water molecules and other substances into endolymph, resulting in endolymph hydrops. Yang et al. (2011) delineated that 625 proteins from isolated stria vascularis capillaries were identified in adult CBA/CaJ mouse cochlea. $Na^+/K^+$-ATPase a1 (ATP1A1) is the most abundant protein in the stria vascularis capillaries directly interacting with PKCg, an essential mediator of ATP1A1-initiated occludin phosphorylation, and is involved in the integrity of the BLB. The physiological and morphological basis of stria vascularis, called “sandwich-dissociation”, is comprised of a dense capillary network, indicating that endothelial cells, surrounding pericytes, PVM/Ms, TJs, PEDF/PEDFR, NKCC, ATP1A1 and PKCg kinase all participate in forming blood–endolymph barrier, which prevents some materials in blood from entering endolymph while allows others to pass. The permeability of this barrier, however, is very weak under physiological conditions.

### 2.2. Blood-perilymph barrier

By testing penetration of [3H] taurine (molecular weight 125) into the scala vestibule perilymph (PLV) at 1 and 2 h after intravenous infusion in nephrectomized animals, Angelini et al. (1998) found that blood–perilymph barrier was similar to blood–brain barrier. They concluded that there was a passive entry of taurine (as a tracer) into the perilymph