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Interrelations Between the Middle and Inner Ear in Otitis Media

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Abstract: This article reviews the importance of the round-window membrane in exposing the labyrinth to or protecting it from the toxic effects of otitis media. Characteristics of the immune system in the human middle ear and middle-ear mechanisms against bacteria are explained. The role of bacteria and bacterial products in inner-ear damage is detailed, and related pathological events are described. The hypothetical role of inflammatory mediators in bacteria-induced inner-ear toxicity is particularly emphasized. Clinical conditions causing these events are detailed, and the most frequently involved microorganisms are mentioned. Finally, round-window membrane macroscopic and microscopic anatomy is discussed, and considerations about the exact role of membrane inflammation—protection versus damage of the inner ear—are expressed.

Key Words: bacteria; bacterial products; labyrinth; middle ear; round window; toxicity

Only in the last decades have the middle ear and the inner ear been recognized as valid and important immunocompetent structures [1]. One of the first and most important studies pertaining to the immunological aspects of the middle ear, published in 1974 [2], concerned the role of the secretory immune system in the middle ear and otitis media. The concept that the inner ear is capable of mounting an immune response dates back only to the 1980s [3].

The purpose of this article is to review the interrelations between the middle ear and the inner ear in otitis media and the role of bacteria, bacterial products, and inflammatory mediators as toxic agents acting through the round-window membrane. In this article, we emphasize the importance of continued investigations into the facilitative or protective contributions of the round-window membrane in inner-ear toxicity in the several forms of otitis media.

MIDDLE-EAR DEFENSES AGAINST BACTERIA

The middle-ear space is lined by a mucous membrane that in turn is covered by a layer of mucin (mucus) through which microorganisms must pass before they reach the mucosa itself (Table 1). Within the mucin are found substances that can either kill the bacteria or inhibit their growth: lysozyme, lactoferrin, and lactoperoxidase [4]. Sialic acid–containing oligosaccharides of the mucin form another defense mechanism and appear to act as mucin receptors for the bacteria, preventing their adherence to the epithelial wall, thus modulating bacterial colonization [5]. Ciliary function is also important because it promotes drainage of mucus and secretions or pus from the middle-ear cavity through the eustachian tube.

Once the microorganisms have reached the epithelial surface of the mucous membrane, they must overcome the rapidly dividing mucosal cells and the superficial specific mucosal immune system [4]. This specific defense system depends on the secretory antibodies, mainly secretory immunoglobulin A (IgA). This system depends on B cells derived from mucosa-associated lymphoid tissue (MALT), which consists of lymphoepithelial structures, such as those constituting Waldeyer's pharyngeal ring [6]. These MALT-induced B cells migrate through lymph and blood to target such tissues as the middle-ear mucosa, where they differentiate after extravasation to IgA-producing plasma cells. Once in the lamina propria, IgA is picked up by an epithelial transmembrane secretory component, resulting in the production of secretory IgA to the epithelial lumen

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Table 1. Middle-Ear Defense Mechanisms That Act Against Bacterial Colonization

Mucin
Physical barrier of the mucus
Substances that kill bacteria or inhibit their growth (lysozyme, lactoferrin, lactoperoxidase)
Substances that prevent adherence of the bacteria to the epithelial wall (sialic acid–containing oligosaccharides)
Ciliary function
Epithelial defense system
Rapidly dividing mucosal cells
Superficial specific mucosal immune system (secretory antibodies: secretory IgA)
Lamina propria defense systems
Nonspecific (complement, phagocytes, transferrin)
Specific (antibodies, T cells)

surface. Secretory IgA acts in immune exclusion by inhibiting uptake of soluble antigens and by blocking epithelial colonization of microorganisms [7].

If bacteria are able to overcome the mucus and epithelial layers of the mucosa, they must meet with both nonspecific and specific defense systems in the lamina propria. The first system is made up of a complement system, phagocytes (macrophages and polymorphonuclear neutrophils), and transferrin. Specific defense systems of the lamina propria involve antibodies and T cells [4].

MECHANISMS OF BACTERIAL INNER-EAR TOXICITY

Once bacteria overcome the defense mechanisms of the middle-ear mucosa, damage to the inner ear can occur. Pathological events can be caused by a direct effect of the bacteria itself: Bacterial penetration of all three layers of the round-window membrane was demonstrated experimentally and resulted in bacteria entering into cochlear turns and neuronal pathways, causing nerve degeneration and edema and hemorrhage of the stria vascularis [8]. Bacterial products also were important: Instillation of a suspension of *Escherichia coli* endotoxin into the round-window niche in rats demonstrated an inner-ear disturbance using a frequency-specific auditory brainstem response technique [9]. Other bacterial products that can promote inner-ear damage after round-window membrane penetration are exotoxins (proteins) produced by both gram-positive and gram-negative bacteria; endotoxins (lipopolysaccharides of the outer membrane of gram-negative bacteria); and such other bacterial products as peptidoglycan fragments, teichoic acids, and hydrolytic enzymes such as hyaluronidase and proteases (Table 2) [10].

Table 2. Mechanisms of Bacterial Inner-Ear Toxicity

Penetration of the bacteria in the inner ear through round-window membrane
Penetration of bacterial products in the inner ear through round-window membrane
Endotoxins (lipopolysaccharides of the outer membrane of gram-negative bacteria)
Exotoxins (proteins produced by gram-positive and gram-negative bacteria)
Peptidoglycan fragments
Teichoic acids
Hydrolytic enzymes (hyaluronidase, protease)

CLINICAL, PATHOLOGICAL, AND MICROBIOLOGICAL SPECTRUM OF OTITIS MEDIA

The conditions caused in the middle ear by bacteria—acute otitis media, chronic suppurative otitis media, and middle-ear effusion—now are accepted as representing different phases in the spectrum of the same pathological continuum of otitis media [11]. Experimentally, the same pattern of otitis media pathological changes were observed in the round-window membrane and in the mucoperiosteum of the middle ear. These changes could account for modifications of permeability, rendering the membrane an easy pathway from the middle to the inner ear [12].

Bacteria that cause acute otitis media are predominantly aerobic, particularly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [13–15]. Even middle-ear effusion, often considered to be or described as a sterile condition, is now accepted as containing bacteria and bacterial products in a high percentage of cases [16,17], and the predominant microorganisms are the same as those in acute otitis media [18,19]. In chronic otitis media, the most common isolate is *Pseudomonas aeruginosa*, and other isolates include such aerobic organisms as *Staphylococcus aureus*, *S. epidermidis*, *Proteus mirabilis*, *P. vulgaris*, streptococci, *Klebsiella pneumoniae*, *H. influenzae*, and anaerobic isolates, including *Peptostreptococcus* and *Bacteroides* species. Bacterial products generated by some of these microorganisms and involved in deleterious inner-ear effects were mentioned by Hellstrom et al. [4] (Table 3).

ROLE OF INFLAMMATORY MEDIATORS

Also related to inner-ear damage caused by otitis media is the role of inflammatory mediators. Mediators are biochemical components produced by epithelial cells, infiltrating inflammatory cells, and endothelial cells, which mediate inflammatory reactions in a sequential manner [20]. Besides bacterial infections, endotoxins, exotoxins,

Table 3. Bacterial Products Involved in Inner-Ear Toxicity in Otitis Media

Bacteria	Gram-Stain Status	Bacterial Product
Streptococcus pneumoniae	+	Exotoxin
Haemophilus influenzae	–	Endotoxin
Moraxella catarrhalis	–	Endotoxin
Pseudomonas aeruginosa	+	Exotoxin, enzymes
Staphylococcus aureus	+	Exotoxin
Staphylococcus epidermidis	+	Exotoxin
Proteus mirabilis	–	Endotoxin
Proteus vulgaris	–	Endotoxin

+, positive; –, negative.

Table 4. Inflammatory Mediators Identified in Otitis Media

Histamine [22]
Prostaglandins [23]
Leukotrienes [24,25]
Platelet-activating factor [26]
Cytokines [27,28]
- IL-1β, IL-2, IL-6, IL-8, IL-10
- Tumor necrosis factor–α
- Interferon gamma
- Transforming growth factor β

IL = interleukin.

and other bacterial products, inflammatory mediators could be involved in the development of sensorineural hearing loss, the more frequent complication attributable to interaction between the middle ear and the inner ear [21]. Many inflammatory mediators have been identified in otitis media (Table 4) [22–28]. The round-window membrane is permeable to many substances, including inflammatory mediators, and many studies have shown that these mediators can affect inner-ear function, as seen in auditory brainstem response, cochlear microphonics, otoacoustic emissions, and cochlear blood flow studies [20].

ROUND-WINDOW MEMBRANE PATHOLOGY AND PHYSIOPATHOLOGY

Round-window membrane anatomy and structural studies disclose three basic layers: an outer epithelium, a middle core of connective tissue, and an inner epithelium (Figs. 1 and 2) [29]. Initially, round-window membrane alterations induced by otitis media were thought to be restricted to or predominantly centered in the outer epithelium, but subsequent ultrastructural studies demonstrated that the three layers participate in the resorption and secretion of substances to and from the inner ear [30]. However, a large field of knowledge remains to be elucidated about the extent to which these round-window otitis media–induced alterations influence the permeability of the membrane [31]. An equally important consideration is that at least part of the response to inflammation is protective [20]. The exact role of inflammatory consequences of otitis media in protection of versus damage to the inner ear has yet to be determined. The comprehension of these mechanisms is of fundamental importance to the development of measures to counteract inner-ear consequences of otitis media, particularly sensorineural hearing loss and tinnitus. Future studies should continue to address these objectives.

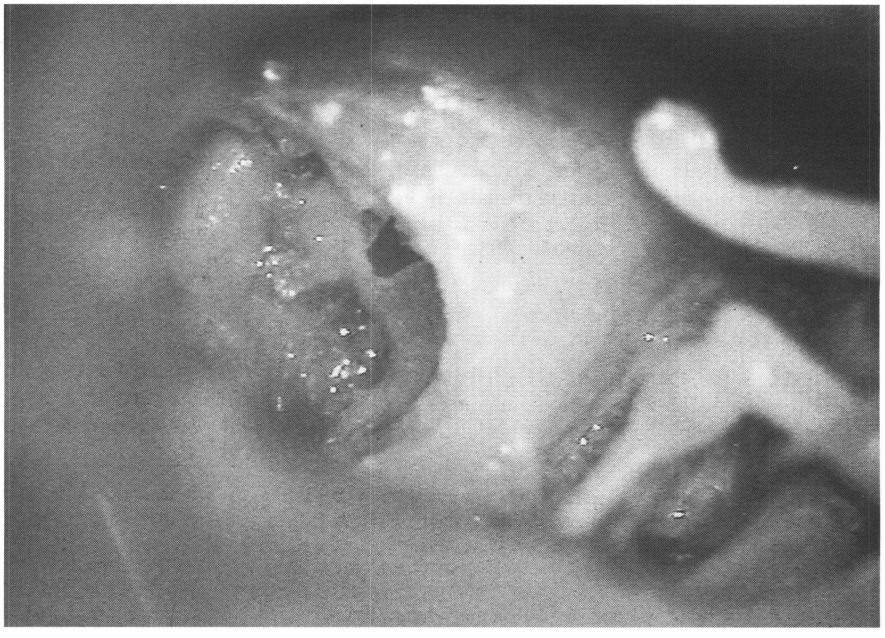

Figure 1. Only after drilling the lateral edge of the round window niche is the round window membrane clearly visible. For easy identification of the membrane for the image, the membrane was disrupted, and the lumen of scala tympani then is clearly visible.

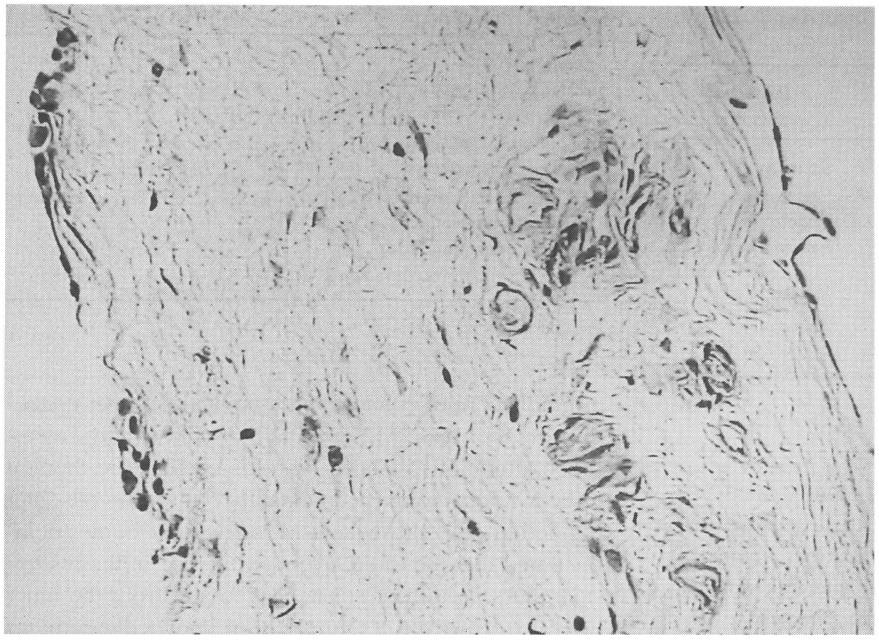

Figure 2. Photomicrograph of the normal human round-window membrane, which consists of an outer low cuboidal epithelium (left side of the image), a middle core of connective tissue, and an inner simple epithelium (right side of the image). The entire membrane might participate in the inner-ear defense mechanism, but structural changes in otitis media were confined mainly to the inner epithelium and connective tissue layers.

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