Vascular Pathophysiology in Hearing Disorders

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ABSTRACT

The inner ear vasculature is responsible for maintenance of the blood-labyrinth barrier, transport of systemic hormones for ion homeostasis, and supplying nutrients for metabolic functions. Unfortunately, these blood vessels also expose the ear to circulating inflammatory factors resulting from systemic diseases. Thus, although the inner ear blood vessels are critical for normal function, they also facilitate pathological mechanisms that result in hearing and vestibular dysfunction. Despite these numerous critical roles of inner ear vasculature, little is known of its normal homeostatic functions and how these are compromised in disease. The objective of this review is to discuss the current concepts of vascular biology, how blood vessels naturally respond to circulating inflammatory factors, and how such mechanisms of vascular pathophysiology may cause hearing loss.

KEYWORDS: Blood-labyrinth barrier, blood vessels, glycocalyx, immunopathology, hearing loss

Learning Outcomes: As a result of this activity, the participant will be able to (1) identify regions in the cochlea that are susceptible to damage by inflammatory factors and (2) describe how inflammatory processes in the cochlea contribute to hearing loss.

The vasculature of the inner ear plays an important role in hearing and is dynamically responsive to certain insults.[1] Control of ion and water homeostasis depends on vascular integrity to maintain the blood-labyrinth barrier. Meanwhile, the blood vessels carry immune cells, inflammatory factors, and hormones that can affect the function of the ear. When one considers the systemic delivery of steroids and other therapeutic drugs for hearing loss, the

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Proceedings of the 5th International NCRAR Conference–Expanding Our Horizons: Medical Conditions and Audiology; Guest Editors, Robert L. Folmer, Ph.D., and Gabrielle H. Saunders, Ph.D.

Semin Hear 2012;33:242–250.
DOI: http://dx.doi.org/10.1055/s-0032-1315723.
ISSN 0734-0451.

vasculature becomes an even more critical conduit and moderator of cochlear function. Despite the significant role of cochlear vasculature in health and disease, little is known of the mechanisms potentially involved in these processes. The goal of this review is to describe recent research in vascular pathophysiology and its involvement in hearing disorders.

VASCULAR PATHOPHYSIOLOGY

Current vascular biology studies have established how circulating immune cells, antibodies, cytokines, and pathogens impact blood vessels. The endothelial cells that line the capillaries have a glycocalyx covering their luminal surface (Fig. 1). This glycocalyx is made up of transmembrane proteoglycan cores with glycosaminoglycan side chains, such as heparin sulfate and chondroitin sulfate.[2–5] The glycocalyx serves as a barrier to prevent circulating immune cells and large molecules in the serum from reaching the endothelial cell surface.[6,7] However, as long as this barrier is intact, there can be no movement of inflammatory factors into the tissue surrounding the capillaries if there is an injury or infection. Thus, although the glycocalyx serves as a natural homeostatic barrier to protect the tissues, it also has to be removed to facilitate the normal inflammatory events that are required to fight disease.

Various systemic inflammatory and infectious diseases elevate the circulating levels of immune factors, which include autoantibodies in the case of autoimmune diseases, bacterial, fungal, and viral components during infections, and inflammatory cytokines and chemokines that are elevated as a result of these conditions. Some of these cytokines strip off the protective glycocalyx, which exposes the endothelial cell surface to the circulating immune factors and initiates several events (Fig. 1).[8] First, the endothelial cell itself produces its own inflammatory mediators, such as cytokines and chemokines, and releases them into the surrounding tissues.[3] Endothelial cells also produce adhesion molecules on their surface

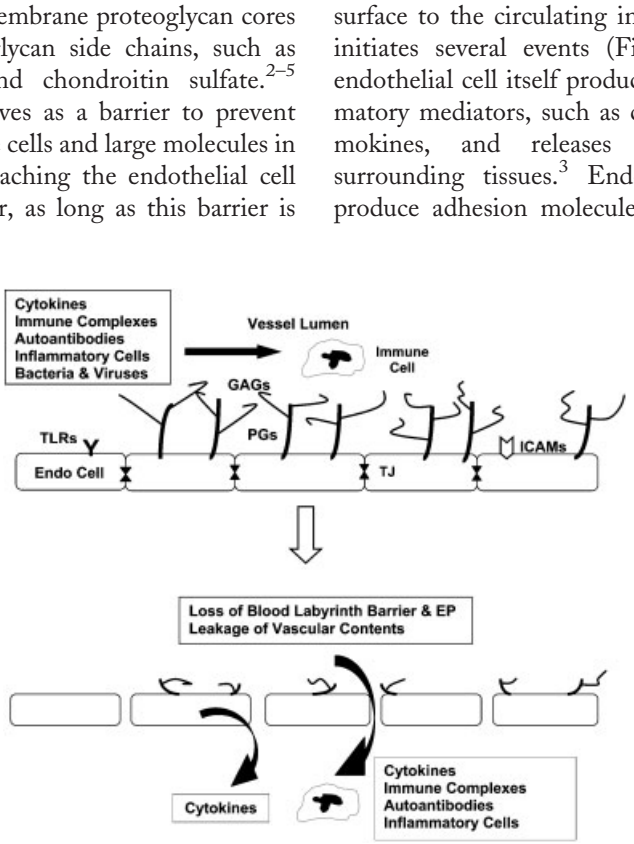

Figure 1 Vascular pathophysiology in response to circulating inflammatory factors. (Top) The glycocalyx is made up of transmembrane proteoglycan (PG) cores with glycosaminoglycan (GAG) side chains. This glycocalyx keeps red blood cells and immune cells in the central part of the capillary lumen and away from toll-like receptors (TLR) and intercellular adhesion molecules (ICAM) on the surface of endothelial cells. Endothelial cell (Endo cell) tight junctions (TJ) keep vascular components out of the pericapillary space. (Bottom) Elevated levels of circulating inflammatory factors strip off the glycocalyx and break down the tight junctions to permit movement of inflammatory factors into the surrounding tissues. Endothelial cells also produce inflammatory cytokines as part of their inflammatory response. The loss of tight junctions in the ear opens the blood-labyrinth barrier, causing compromised endolymph production and decreased endolymphatic potential (EP).

that provide attachment sites for inflammatory cells that need to move across the vascular barrier.[9,10] Some of these intercellular adhesion molecules are already on the surface and are uncovered when the glycocalyx is removed.[11] Last, endothelial cells down-regulate their production of tight junction proteins (claudins, occludins), permitting movement of serum factors and inflammatory cells (macrophages, T-cells, etc.) through the intercellular spaces into the extracapillary space.[12–14] Bacterial and viral infections also will cause this vascular reaction via various toll-like receptors that line endothelial cells, providing a mechanism for pathogens to elicit the same reaction by capillaries as part of the innate immune response. Thus, the endothelial cell is not a passive bystander, but rather an active participant in the natural immune response.

Although numerous inflammatory cytokines are increased in inflammatory disorders, the most problematic are interleukin-1, interleukin-6, and tumor necrosis factor-α (TNFα),[14,15] because they are known to quickly strip the glycocalyx and induce the endothelial changes described above. Elevated levels of these particular cytokines are responsible for significant capillary immunopathology in many inflammatory disorders. The use of anti-TNFα therapy (e.g., etanercept, infliximab) has proven to be of some value in rheumatoid arthritis and other autoimmune disorders in which TNFα is a key factor in tissue destruction.[12] The anti-endothelial antibodies common in autoimmune diseases, such as systemic lupus erythematosus, also bind to glycocalyx components and induce vasculitis and thrombosis.[16–18] These antibodies attach to β-2-glycoprotein-1 (B2GP1), a positively charged common serum protein that normally binds to the negatively charged components of the glycocalyx. This antibody binding to B2GP1 triggers the typical pathogenic endothelial cell reaction.[19,20] Unfortunately, many amino acid sequences on bacteria and viruses share epitopes with B2GP1, making it a target due to molecular mimicry.[21–23] This allows many common infections to cause endothelial cell pathology, vasculitis, and localized inflammation in locations not typically affected in specific immune disorders. Thus, inflammation can occur away from the primary location of infection due to circulating antibodies and other immune factors. Such sensitivity and pathology are seen in organs requiring a tightly regulated vascular barrier, such as the eye (blood-retina barrier), brain (blood-brain barrier), and ear (blood-labyrinth barrier).

STEROID TREATMENTS FOR INFLAMMATORY DISEASES

The therapeutic glucocorticoids (dexamethasone, prednisolone, and prednisone) have numerous functions that help to reduce inflammation. For example, these medications suppress the production of inflammatory cells and cause apoptosis of existing cells that proliferated during inflammation. Another key function of steroids is to suppress the production of inflammatory cytokines by the various immune cells and endothelial cells within the inflammatory site. Glucocorticoids also suppress the production of antibodies against foreign antigens (infections) or the body's own proteins that are sometimes perceived as antigens (in autoimmune disease). Activation of the glucocorticoid receptor also can stimulate the production of inhibitory factors that interrupt various inflammatory cascades within cells.[24] Finally, steroids trigger up-regulation of endothelial cell genes involved in the production of junctional proteins to reseal the capillary lining and reduce movement of these factors into the tissues.[25–27]

INNER EAR VASCULAR PATHOPHYSIOLOGY

The high metabolic demands of the inner ear require a fully functional vasculature.[1] In particular, the stria vascularis and underlying spiral ligament have unique homeostatic functions that require an uncompromised local blood flow. Endothelial cells of the stria vessels are connected by tight junctions to establish the blood-labyrinth barrier and control the movement of circulating inflammatory cells and other large proteins. This barrier also allows the endolymph to maintain the high potassium (K^+) levels required for the endocochlear potential (EP) and normal cochlear function. Any compromise of this barrier function by vascular

leakage would lead to an immediate hearing loss. Furthermore, these cochlear lateral wall capillaries are physically connected with other cells via gap junctions for effectively moving K^+ through the stria and into the endolymph.[28] This critical transport function of lateral wall structures requires a tightly regulated vascular supply and blood-labyrinth barrier. Table 1 summarizes the vascular issues that are potential links between systemic inflammation and inner ear disease.

Because the cochlear vasculature is very sensitive to circulating inflammatory factors, hearing and vestibular functions can become at risk in even the most minor of vascular changes (Table 1). The normal vascular reaction to inflammatory factors would be harmless in most organs, but in the ear this can lead to breakdown of strial integrity and loss of the blood-labyrinth barrier (Fig. 1), changes that would ultimately be detrimental to endolymph production and maintenance of the EP.[29,30] The anionic sites on lateral wall vascular endothelial cells that are stripped off by immune reactions presumably include negatively charged glycocalyx components.[31,32] However, because the lateral wall can repair itself, hearing loss that is not due to permanent changes in the sensory organ can be restored. Glucocorticoids, which are known to cause tight junctions to reform,[26,27] are often used to treat reversible hearing loss. Studies in autoimmune mice show that circulating inflammatory factors cause suppression of numerous inner ear ion homeostasis genes, including the tight junction and gap junction genes.[33,34] However, their gene expression is restored by glucocorticoid therapy.

VASCULAR PATHOPHYSIOLOGY IN HEARING DISORDERS

Systemic inflammatory factors may cause hearing loss by disrupting vascular endothelial cell integrity in the stria, causing breakdown of the blood-labyrinth barrier and endolymph ion homeostasis. This theory was proposed as far back as 1953 by Hilger as a potential explanation for sudden hearing loss.[35] Elevated inflammatory cytokines have been measured in various types of hearing loss (Table 2), suggesting the sensitivity of the inner ear to these circulating immune factors. The potential involvement of cytokines in hearing loss may represent a final common pathway for numerous systemic immune-mediated conditions, and some of the changes might be facilitated by genetic components. Ménière's disease and sudden hearing loss have been correlated with altered genes for the cytokine interleukin-1α.[36] Also, defects in expression of interleukin-1β and its receptor are correlated with steroid-responsive autoimmune hearing loss.[37,38] Targeting the cytokine TNFα with blockers for immune-mediated hearing loss has met with inconsistent results. Positive[39,40] and negative[41,42] results with such drugs suggest that TNFα may vary in its pathogenic role in different patients.

Table 1 Vascular Factors in Ear Disorders

Systemic
Vasculature carries hormones responsible for normal organ function.
Vasculature carries immune factors from systemic infectious and inflammatory diseases.
Endothelial cells are active participants in tissue response to circulating inflammatory factors.
Endothelial cell tight junctions are opened for extracapillary movement of serum factors.
Inner ear
Vasculature is the connection between the body and the ear.
Vascular endothelial cells are the gatekeepers to the ear.
Nothing enters the ear without passing either through or between endothelial cells.
Serum inflammatory factors are commonly seen in numerous hearing disorders.
Breakdown of the blood-labyrinth barrier is the first vascular reaction to inflammation.
Steroids cause blood-labyrinth barrier restoration by up-regulating tight junction genes.

Table 2 Inflammatory Cytokines in Hearing Disorders

Interleukin-1α[36,85,86]
Interleukin-1β[37,85]
Interleukin-1 receptor 2[38]
Interleukin-4[87,88]
Interleukin-5[63,88]
Interleukin-6[89]
Interleukin 8 (human/MIP-2 mouse)[85]
Interleukin-10[75,88]
Interleukin-13[88]
Transforming growth factor-β[85,88]
Tumor necrosis factor-α[24,58,75,85,86,90–92]
Interferon-γ[62,63,75,88,93]
Vascular endothelial growth factor[57,58,94]
Matrix metalloproteinase-3[89]

Immune-mediated vascular disruption in the stria vascularis could explain a final common pathway for a variety of steroid-responsive hearing disorders. A vascular etiology has been proposed for immune-mediated hearing loss,[43–46] Ménière's disease,[47–50] and sudden hearing loss.[51–54] Even the numerous putative antibody-mediated causes[55,56] of hearing loss would seem to employ disruption of endothelial barriers to access the inner ear. Noise, ototoxic drugs, and trauma also cause inflammatory processes within the cochlear vasculature, which places at risk ion transport functions required for endolymph production.[1,24,57–59] Viral infections have been shown to induce movement of immune cells through vascular endothelial cells.[60] Thus, proposed cell-mediated mechanisms for hearing loss also would involve disruption of the barrier to permit inflammatory cells access to cochlear tissues.[61–63] Hearing loss following viral and bacterial infections also can include the anti-endothelial (antiphospholipid) antibody attack of glycocalyx components.[22,23,64]

Such a vascular theory also fits with what we know about hearing and vestibular dysfunction in systemic autoimmune diseases. All known systemic autoimmune diseases have a very high incidence of inner ear disease, generally running 30 to 50%, and vascular compromise in the ear is the proposed etiology because it is common in such diseases.[65–69] These cases often have high levels of antiendothelial and antiphospholipid antibodies,[43,70–75] which are known to target the glycocalyx. Many cases of autoimmune hearing loss occur as sudden hearing loss.[46,70,71,76–79] In fact, often the inner ear is the first organ affected in systemic autoimmune diseases, probably due to the fact that a mild vascular pathology affects the ear faster than any other organ system. In studies of autoimmune mice, the primary defects in the inner ear include breakdown of the stria vascularis blood vessels,[80] loss of blood-labyrinth barrier integrity,[81,82] loss of EP,[83] and hearing loss,[84] all of which are restored by glucocorticoid treatments, such as dexamethasone, prednisone, and prednisolone. These medications may serve two functions: suppressing systemic inflammation that caused the inner ear dysfunction in the first place, and also reestablishing ionic homeostasis within the ear. The therapeutic glucocorticoids have a significant effect on recovery of ion transporters and channels, as well as up-regulating genes for tight junction proteins.[33,34] Better characterization of the vascular pathophysiology in the ear, along with increased knowledge regarding which steroids best induce recovery of those cellular and molecular processes at risk, will help guide efforts to develop more targeted treatments in the future.

SUMMARY

Sensitivity of the cochlear vasculature to circulating inflammatory factors places the ear at considerable risk. Endothelial cell activation by circulating inflammatory factors is a natural cellular process by which the body regulates and controls infection. This process is part of the innate immune response and is necessary for survival. However, elements of this process that are virtually inconsequential to other organs can be highly detrimental to the cochlea. These natural inflammatory processes compromise the critical vascular endothelial cell blood-labyrinth barriers of the cochlea and cause hearing loss. This final common pathway from systemic inflammation is likely responsible for a variety of hearing disorders. Because the lateral wall of the cochlea can repair itself and restore normal functions, some spontaneous recovery of

hearing is seen in patients with mild hearing loss. As we increase our understanding of the principles of vascular sensitivity and control, we may be able to improve treatments for patients who experience hearing loss due to vascular disruption.

ACKNOWLEDGMENTS

This work was supported by Grant NIH-NIDCD R01 DC05593 (D.R.T.).

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