8 Blood Retinal Barrier

8.1 Blood-Retinal Barrier, Retinal Vascular Leakage and Macular Edema

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Core Messages
- The blood-retinal barrier forms a selective barrier, restricting ion, substrate, and water permeability, allowing for proper neuronal function.
- The blood-retinal barrier has a number of specialized characteristics that allow for barrier formation.
- Vascular endothelial cells and retinal pigmented epithelial cells physically form the blood-retinal barrier.

8.1.1 Introduction

Proper retinal function requires the presence of a well-defined blood-retinal barrier (BRB). In many of the leading causes of medical blindness this BRB is compromised. Indeed, retinopathy of prematurity and age related macular degeneration both include production of aberrant vessels with poor barrier properties. Further, diabetic retinopathy, the leading cause of blindness in working age adults, involves progressive vision loss and is closely associated with macular edema [117]. Increased fluid accumulation, as well as lipid and albumin deposits, is believed to be the result of the breakdown of the BRB that normally controls the neuronal environment. Barrier dysfunction results in increased permeability which diagnostically indicates progressive retinopathy [32]. This chapter will review the normal physiology of the BRB, the changes that occur through the course of diabetic retinopathy, and the known underlying molecular mechanisms that may lead to barrier dysfunction. Elucidating the mechanisms of barrier dysfunction in diabetic retinopathy will further our understanding of its pathogenesis and provide future therapeutic targets.

8.1.2 Characteristics of the Blood-Retinal Barrier

Essentials
- The BRB comprises vascular endothelial and retinal pigmented epithelial cells.
- Mechanisms of permeability across endothelial and epithelial barriers.
- Facilitated water and substrate transport.
- Tight junction formation.

8.1.2.1 Blood-Retinal Barrier Physiology

The BRB, similar to the blood-brain barrier (BBB), is a physiologic barrier that regulates ion, protein, and water flux into the retina. This barrier allows the neural retina to establish and maintain specific substrate and ion concentrations allowing for proper neuronal function. Additionally, it regulates infiltration of immune competent cells, blood-born toxins, and various hormones that could negatively affect neuronal function and survival. The barrier is physically established by two cell types: vascular endothelial cells that form capillary beds in the ganglion cell layer and outer plexiform layer of the retina and retinal pigmented epithelial cells (RPE) that form a barrier between the choroid capillary plexus and the retina [102, 86]. Combined, these cells regulate the flux of nutrients into the retina from the blood supply.
Cellular transport of material across the barrier can occur by two pathways: transcellular flux that is transport across the cell, or paracellular flux, transport between the cells. Transcellular flux is transport through the cell that may be passive diffusion, facilitated, or by active transport mechanisms. Fenestrations are locations in capillaries where the endothelial cell depth is reduced, and the thinning of the capillary wall facilitates transcellular transport of materials and cells out of the capillaries. Fenestrations are seen in highly permeable tissues such as the glomerular capillary wall and choroid capillary plexus [37, 102]. Endothelial cells in the BBB lack fenestrations contributing to their ability to maintain a barrier. This loss of endothelial cell fenestrations is one of the initial developmental steps of BBB formation [11, 49]. Although fenestrations have not been fully explored in the BRB, the analogous function and conservation of properties of the BRB and BBB suggest a similar paucity of fenestrations.

### 8.1.2.3 Endocytosis and Facilitated Diffusion

Cells continuously take up and sample extracellular material in a process called pinocytosis (Fig. 8.1.1). Membrane invaginations across the cell surface pinch off forming vesicles that move to the cell interior. These vesicles can move internally to be degraded or through the cell to be released at the basal-lateral membrane leading to non-specific transport of materials across the cell. Pinocytotic vesicles are selectively decreased in endothelial cells located in the BBB [16, 27, 149]. In order to maintain transport of necessary substrates for neuronal function, specific receptor-facilitated transport mechanisms are used to move materials across the BBB. Receptor mediated endocytosis may occur through clathrin or caveolin mediated endocytosis, which is ATP dependent [189]. A receptor binds to its specific substrate concentrating the substrate within the invagination to reduce transport of non-specific materials (Fig. 8.1.1). The transferrin receptor and the transport of iron across the BBB is an important example of receptor mediated transport across vascular endothelium [20]. Vascular endothelial cells of the BBB have increased mitochondria content, which generates a cell’s energy supply of ATP [126]. Elevated mitochondria levels may be necessary to supply numerous receptor-mediated transport mechanisms.

Channel-facilitated transport is a mechanism for the diffusion of specific substrates across the BBB. This is mediated by transmembrane proteins located in the cell surface that allow for the flux of specific materials across the cell membrane. The GLUT-1 glucose transporter is highly and selectively expressed in vascular endothelial cells of the BBB and supplies the neuronal tissue with necessary glucose [128]. Together these mechanisms provide the necessary substrates for neuronal function.

### 8.1.2.4 Water Transport

Facilitated transport of water out of the neuronal extracellular space is essential to maintain retinal function. RPE cells regulate water content and lactic acid removal generated by high metabolic rates in the retina. RPE cells transport water out of the retina and into the choroid capillary plexus. The force gen-

**Fig. 8.1.1.** A side view of two adjacent vascular endothelial cells is depicted. Paracellular flux of blood-borne proteins between the cells is inhibited by the tight junction complex. Non-specific transport of materials through the cell is pinocytosis. Pinocytotic vesicles are greatly reduced in barrier forming cells. To compensate for reduced permeability, receptor mediated transcytosis allows for specific substrate transport across the barrier.