The blood-ocular barriers

When a constant level of various substances is established and maintained in the blood, the rate at which extracellular fluid concentrations approach the plasma concentration varies among different regions of the body. Physiologists have found that when the rate of penetration is very low, a barrier preventing free diffusion of solute from blood into the tissue spaces or cavities of an organ exists. This restriction has been shown to be particularly pronounced in the central nervous system and the eye.

The concept of a blood-brain barrier originated in the first decade of this century, but the existence of the ocular barriers have only recently been clarified. Information accumulated during the last 10 years has shown that the function of the blood-ocular barrier may be better understood if it is considered as two main barrier systems in the eye. The first, the blood-retinal barrier (BRB), separates the neural tissue of retina from the blood. The second, the so-called blood-aqueous barrier (BAB), regulates the exchanges between the blood and the intraocular fluids. The concept of a blood-vitreous barrier is untenable because such a barrier is entirely absent in the anterior region of the vitreous, where free diffusion is present between the vitreous and the posterior chamber.

**Blood-aqueous barrier**

A clear picture of the relationship between the blood and the intraocular fluids, particularly in the anterior segment of the eye, is available. The BAB is located mainly at the nonpigmented ciliary epithelium and endothelium of the blood vessels in iris and ciliary muscle. Both cell layers are connected by tight junctions which are probably of the "leaky" type. The leakiness or nonleakiness of cell layers is related to differences in permeability and electrical resistance of the tight junctions. Hydraulic conductivity and electrical resistance are lower in leaky epithelia because the junctions are the main diffusional pathways for water and ion flow. There is evidence that the ciliary epithelium behaves as a "leaky" epithelium, the same probably applies to the iris vessels, which have been shown to be 10 times leakier than cerebral capillaries.

A complete understanding of the BAB is very important, in that the intraocular fluids, the aqueous and vitreous, bathe the cornea, lens, and retina and equilibrate with the extracellular spaces of these tissues. The ciliary processes, which are located strategically between the anterior and posterior segments of the eye, may function like the choroid plexus of the brain by playing a fundamental role in the regulation of all intraocular fluids. The ciliary processes supply all nutritional needs of the avascular lens and central cornea and contribute to the chemical environment of the retina through exchanges between the posterior chamber and vitreous. Of particular importance is the probable sink action...
of the vitreous, which may serve as a reservoir for metabolic products that cannot leave the vitreous chamber by crossing the BRB. Finally, the rate of aqueous production is relevant in the maintenance of intraocular pressure. The importance of its alteration in glaucoma is therefore self-evident.

Blood-retinal barrier

The concept of BRB is still relatively new in ophthalmic literature. It operates at two levels, the endothelial cell of the retinal blood vessels and the retinal pigment epithelium, which form, respectively, an inner BRB and an outer BRB. Both cell types have particularly firm tight junctions (zonulae occludentes). These junctions are of the "non-leaky" type and restrict diffusion. Most substances are forced to pass through the cell walls of the vascular endothelium and pigment epithelium of the retina rather than through the intercellular spaces. Of course, gases will diffuse and water can diffuse, but most other substances do appear to move by special processes, such as facilitated diffusion or stereospecific exchange processes.

The significance of the BRB to retinal disease has become increasingly clear because of the widespread use of fluorescein angiography. This technique has demonstrated an intricate series of relationships between the breakdown of the BRB and diverse retinal diseases, particularly vascular retinopathies and pigment epitheliopathies. Examples of this relationship are seen in cystoid macular edema, systemic hypertension, and diabetes mellitus.

One disabling disease, cystoid macular edema, follows a variety of naturally occurring conditions. In this condition, retinal function fails as abnormal leakage from the perimacular capillaries destroys retinal organization. Cystoid macular edema can be iatrogenic as well. There is evidence, for example, that surgical procedures may cause a more or less pronounced transient breakdown of the BRB and induce retinal edema. When chronicity of the edema is established, irreversible damage may ensue.

In hypertension, accumulating evidence is showing that retinal and cerebral changes are due to an initial increase in pinocytosis through the vascular wall. The increased vascular transport and injury to the endothelial cells cause insudation of plasma into the vessel wall, changes in medial smooth muscle cells, and fibrin formation.

Finally, it has been demonstrated that retinal involvement in diabetes starts as an alteration of the BRB. Recently, vitreous fluorophotometry, a method of measuring fluorescein concentration in the vitreous, has provided a new and accurate index of the alteration of the BRB. This new method of clinical investigation offers the capability of detecting minimal functional changes in the BRB, changes that still appear to be reversible. It has been possible, for example, to detect with vitreous fluorophotometry an alteration of the BRB in diabetic patients before any lesion is clinically visible in the fundus, even with fluorescein angiography.

Vitreous fluorophotometry is particularly suitable for studies of early diagnosis of barrier breakdown in retinal disease. It also provides a technique for performing in vivo much-needed physiologic and pharmacologic research on the BRB.

At present, some important questions remain unanswered. How can the vascular endothelial cells and pigment epithelial cells transport everything that the retina needs to maintain its function? Which enzymes are involved in this predominantly active transport function? How can these transport systems be controlled? What role does micropinocytosis play in the molecular movements across the barrier? Is there any significant molecular movement through the tight junctions? Can the tight junctions open without damaging the adjoining cell membranes? Is the barrier phenomenon induced by the nature of the tissue in which it occurs? Are the barriers controlled by any secretion of the surrounding tissues? Is there any chemical mediator that can influence the BRB, as is known to happen with the BAB? Is the BRB influenced by light? Are there any regional differences in the BRB activity? Is the outer BRB more fragile at the macular region? Does the inner
BRB function differently in various parts of the retinal vascular tree? Does the transport activity in the arterial and venous sides of the retinal circulation have different directional characteristics? Which substances can selectively cause an alteration of the vascular endothelial cells or the pigment epithelial cells? How do immune and other inflammatory processes influence the barrier phenomena? Are the reactivity of the retinal vessels and the access to the vasoactive receptors dependent on barrier screening? Can an alteration of the BRB be induced in a controlled manner for therapeutic purposes, i.e., drug delivery? Can a diseased barrier be closed by therapeutic means? How does the BRB recover after photocoagulation and other surgical procedures?

Answers to these questions will necessarily lead to a better understanding of the mechanisms and therapeutics of ocular diseases, particularly those involving the retina.

The introduction of vitreous fluorophotometry, its use in experimental and human disease, the correlation of its findings with those of electron microscopic studies, the application of histochemical techniques, and additional use of isotopic tracer studies are some of the tools at our disposal. We greatly need further progress in this promising area of research.

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REFERENCES