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# Does the Blood-brain Barrier Play a Role in Glaucoma?

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**Abstract.** The optic nerve head, although part of the central nervous system, lacks classical blood–brain barrier properties. The tissue of Elschnig does not totally separate the optic nerve head from fenestrated peripapillary choriocapillaries. The microvessels in the prelaminar region of the optic nerve head have less effective barriers than those in the laminar or retrolaminar regions. In glaucoma, the blood–brain barrier in the optic nerve head may even be weaker. Incomplete blood–brain barrier renders circulating molecules, such as endothelin-1 (ET-1), direct access to smooth vascular muscle cells and pericytes both in the prelaminar part of the optic nerve head and to adjacent retinal tissue. This potentially leads to some vasoconstriction as observed in the peri-papillary retinal vessel in glaucoma patients. In extreme situations, this may provoke retinal vein occlusion. The direct access of these molecules also influences the barrier function. If, simultaneously, ET-1 reduces endothelial tight-junctions and matrix-metalloproteinase (MMP)-9 degrades the basement membrane, not only macromolecules but even red blood cells may cross the blood–brain barrier and lead to what is clinically observed as optic disk hemorrhages. (**Surv Ophthalmol 52**:S115–S121, 2007. 

**Key words.** basement membrane • blood–brain barrier • endothelin-1 • glaucoma • matrix metalloproteinase • optic nerve head • optic disk hemorrhage • tight-junction • vascular dysregulation

## Blood–brain Barrier

The central nervous system (CNS) is a very sensitive system in the human body. Specialized structures are required to maintain a stable ionic environment, to ensure appropriate neuronal activities, and most importantly to isolate their neurons from blood or cerebrospinal fluid.

The blood–brain barrier (BBB) is a highly selective barrier with tight junctions between endothelial cells.[46] Endothelial cells of these vessels lack fenestrations,[22] have low numbers of pinocytotic vesicles,[72] and specific transporters. The tight junction complex between the endothelial cells is formed mainly by two classes of transmembrane molecules, namely, occludin and claudin; both interact with transmembrane proteins on adjoining endothelial cells, thereby forming a physical barrier to paracellular diffusion of even small molecules.[27,38,40] Endothelial cells and pericytes are surrounded by a basement membrane composed of collagen type IV, laminin, fibronectin, and heparin sulfate proteoglycan,[21] which is ensheathed by end-foot processes of astrocytes. The selectivity of the BBB depends largely on the size and the hydrophilicity of the molecules. Almost 100% of large molecules (>400 Da) do not cross the BBB. Moreover, more than 98% of all small, hydrophilic molecules cannot pass this barrier.[61]

The fact that the eye develops from the forebrain, the optic nerve is the junction between the eye and the brain, and the optic nerve head (ONH) is the primary site of glaucomatous damage suggests that the blood–brain barrier could play a role in glaucoma.

## Blood–ocular Barriers

In the eye, there are different types of blood–tissue barriers with variation in the degree of leakiness of vessels. In the anterior segment, non-fenestrated endothelial cells with tight junctions are found in the iris capillaries, a semi-permeable barrier in the





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ciliary body.[73,75,84] The retina, being part of the brain, has a similar arrangement with tight junctions, both between the endothelial cells of the retinal vessels and between the retinal pigment epithelial cells forming inner and outer blood–retinal barrier. Thus, the permeability of the retinal capillaries is similar to that of the cerebral vessels with no, or only minimal, leakage of fluorescein, or even sodium ions.[16,41]

## Blood–brain Barrier in the Optic Nerve Head

Previous studies have proposed that the entire optic nerve, including the ONH, has BBB characteristics.[57,62,66] However, exogenous tracers such as sodium fluorescein[30] and horseradish peroxidase in light and electron microscopic studies[24] were found in the prelaminar region (PLR) and the lamina cribrosa of the ONH. It was assumed that these extravasated tracers were the result of diffusion from the highly permeable peri-papillary choroid and not from the leakage of capillaries in the ONH.[9,15,23,35,81]

Principally, the ONH has two blood–tissue barriers similar to the retina. The microvessels of the prelaminar part form the inner BBB, and the tissue of Elschnig form the outer BBB.

In the brain, the non-BBB marker PAL-E is present only in the permeable capillaries as observed in the choroid plexus and the dura mater, but is absent in capillaries with BBB.[69] Likewise, PAL-E was found in the eye in permeable microvessels of the choroid and ciliary processes, but not in the retina.[68] Interestingly, in the capillaries in the PLR of the ONH, PAL-E has been clearly localized, indicating a lack of classical BBB properties.[39] This may indicate non-specific permeability of the microvessels in the PLR, possibly mediated by vesicular transport. In addition, the outer BBB, formed by tissue of Elschnig, is also incomplete (Fig. 1). The peripapillary choriocapillaris is largely fenestrated, which allows free leakage of materials from the blood. The glial barrier of Kuhnt between ONH and retina prevents, to some extent, further extravasation from the choriocapillaris into the subretinal space.[81] It is unclear why the ONH does not have all the advantages attributed to the barriers in the CNS or the retina. The lack of classical BBB may ensure adequate supply of the adjacent structures with a possible drawback of being exposed and vulnerable to noxious, circulating substances.

## Blood–brain Barrier and Vascular Dysregulation

People with primary vascular dysregulation (PVD) have the predisposition to react differently to various stimuli such as cold, emotional stress, but also mechanical stress such as vibrations.[26] This can be an inappropriate vasoconstriction (vasospasm) or an inadequate vasodilatation. The clinical characteristics of vascular dysregulation have been described in detail earlier[26] and are subject of another article in

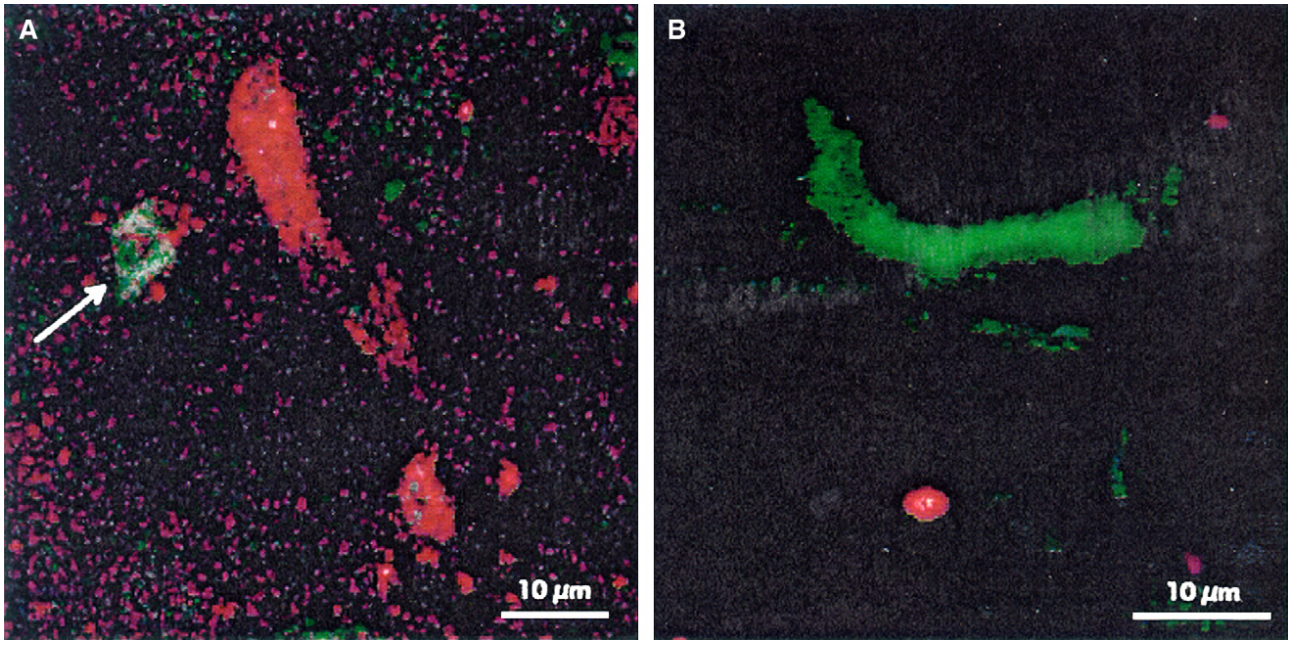


*Fig. 1.* Immunofluorescence double staining of human prelaminar region of the ONH (*A*) and lamina cribrosa (*B*) with non-BBB marker PAL-E (red fluorescence) and transferrin receptor (green fluorescence). The arrow indicates a microvessel that coexpresses both markers. (Reprinted from Hofman et al[39] with permission of *Investigative Ophthalmology and Visual Science.*)

this supplement.[31] In brief, subjects with vascular dysregulation, on average, more often have cold hands, low blood pressure,[58] orthostatic problems, tinnitus, disturbed sleep-onset,[59] reduced feeling of thirst,[80] migraine,[28,37] and altered drug sensitivity.[87] Vascular dysregulation occurs more frequently in women than in men,[63] in Japanese than in Caucasian patients,[7,51] and in intellectuals, people of type-A personality, and those with low body-mass index.

Both increased levels of ET-1[14,26] and matrix-metalloproteinases 9 (MMP-9)[29] are featured in subjects with vascular dysregulation,[26] most probably as a result of mild repeated ischemia-reperfusion injuries[47,54,83] somewhere in the body (e.g., of following silent myocardial ischemia).[85] We postulated that both ET-1 and MMP-9 are involved in the change of BBB function in and around the ONH.[32]

ET-1, a very potent vasoconstrictor, is physiologically produced mainly by endothelial cells and is secreted predominantly abluminally. One smaller part of ET-1 is secreted intraluminally leading to certain level of ET-1 in the circulating blood. In tissues with an intact BBB, circulating ET-1 only has access to the endothelial cell layer. The BBB is incomplete in the ONH or in pathological situations such a plaque of multiple sclerosis. We hypothesized that as a result of incomplete BBB, ET-1 may diffuse from the fenestrated capillaries of the choroid into the ONH but also into the adjacent retinal tissue reaching small muscle cells or pericytes[32] (Fig. 2). In pathologic condition, this may lead to vasoconstriction. But why do only some individuals with PVD have peripapillary vasoconstriction? The low prevalence of peripapillary vasoconstriction in patients with PVD might be explained by the following: plasma ET-1 levels must be high enough and must diffuse easily from the adjacent choroid into the retina. Thus, the case that both conditions are fulfilled might be rare.

In addition to the vasoconstrictive effect, ET-1 is an humoral factor, among others, modulating the BBB.[1,13,55,56] The modulation of the BBB (via ET-1) acts by local up-regulating prostaglandin-E2,[50,74] which reduces the function of the endothelial tight-junction complex.[10,17] Like ET-1, MMPs can also diffuse into adjacent retinal tissue (Fig. 2). MMPs are endopeptidases with the ability to degrade extracellular matrix. MMP-9, in particular, digests the basement membrane of the vascular wall,[60] and thereby opens the BBB.[67]

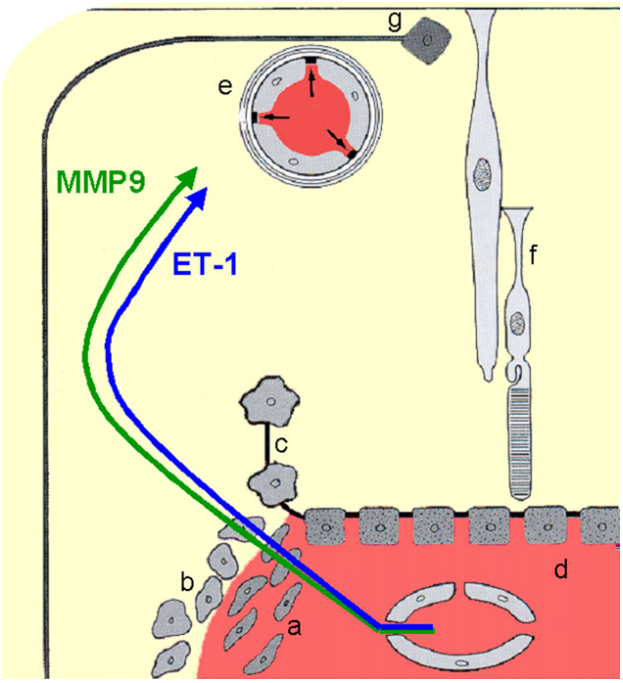


*Fig. 2.* Schematic illustration of the anatomy of the optic nerve head (ONH) and adjacent tissues. The outer blood–brain barrier (BBB) of the ONH is formed by the tissue of Elschnig and is incomplete allowing molecules, such as ET-1 and MMP-9, from the choroid to have direct access to the endothelial cells of the ONH and neighboring retina. (*a*) Tissue of Elschnig, (*b*) Glial tissue of Jacobi, (*c*) Tissue of Kuhnt, (*d*) choroid, (*e*) capillary of the prelaminar region of the ONH, (*f*) photoreceptors, (*g*) ganglion cell and nerve fiber layer.

## Blood–brain Barrier and Glaucoma

The described anatomically incomplete BBB in the ONH is also clinically detectable. There is a minimal leakage of fluorescein from the microvessels of the ONH in the normal, non-glaucomatous eye (Fig. 3a).[6] This leakage was increased in glaucomatous eyes as determined by a semiquantitative digital image analysis of the leakage ratio (optic nerve head to retinal peripapillary fluorescence) in late-phase angiograms.[6] In addition to the intrapapillary leakage (Fig. 3b), slight late staining of the optic disk border[70,71,78,82] may reflect the impaired BBB in this region. In the presence of peripapillary retinal pigment epithelial atrophy, a well-known feature of glaucomatous optic neuropathy, such leakage may further be enhanced. It is unclear, however, whether there is a relationship between stage of glaucomatous damage and breakdown of the BBB. The tissue remodeling in glaucomatous optic neuropathy results in physical alterations influencing plastic and elastic properties of the connective tissue with an up-regulation of MMP.[2,88] It is part of our hypothesis that MMPs diffuse from the choroid to the ONH and modulate the BBB at the border of the ONH in glaucoma. In other words, the ONH may simply represent the tip of the iceberg of a disturbed BBB in that area.

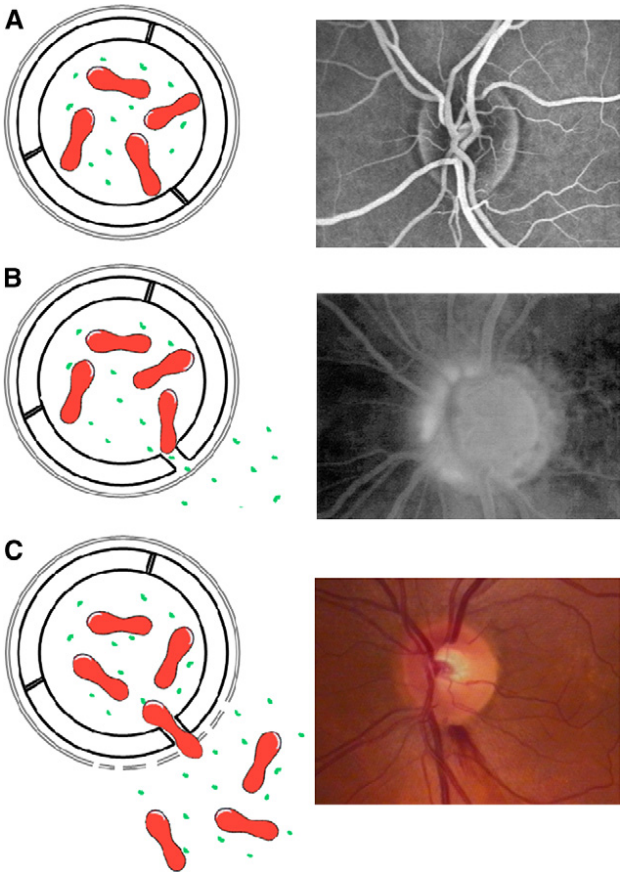


*Fig. 3.* Schematic representation of the blood–brain barrier (BBB); the microvessels (*left*) with the corresponding clinical pictures (*right*). (*A*) A physiological condition and minimal leakage of fluorescein. (*B*) A glaucomatous optic nerve head with a disturbed BBB, as a result of increase in ET-1 leading to dysfunction of tight junctions. Clinically, a marked increase in fluorescein leakage is detected. (*C*) If the basement membrane is simultaneously digested by MMP-9, erythrocytes may escape the vascular lumen leading to what is clinically observed as optic disk hemorrhages (ODH).

## Blood–brain Barrier and Optic Disk Hemorrhages

The pathogenesis of optic disk hemorrhage (ODH) is not yet fully understood. Various hypotheses of underlying hemodynamic disturbances have been postulated. These include pulsatile pressure variations inside the rigid sclera, as well as turbulence due to abrupt pressure changes.[11] Further, presumed imbalance of IOP, venous pressure, flow velocity, and unstable closing pressure with a risk of collapse of the microvessels in the optic disk were also proposed as causative factors.[77] Recently, we have postulated that ODH is a manifestation of an extremely disturbed BBB of the ONH.[32] As mentioned previously, ET-1 weakens the endothelial tight-junctions allowing blood plasma to escape the vessel. However, the basement membrane inhibits the passage of red blood cells and therefore avoids ODH. If, at the same time, MMP-9 diffuses into the same area of the peripapillary retina acting at the microvessels of the ONH from the abluminal side, the basement membrane is weakened by enzymatic digestion to an extent that even red blood cells can escape, leading to what is clinically observed as ODH.[33]

MMP-9 in the circulating blood is increased if ischemia-reperfusion injury occurs somewhere in the body. The fact that both ET-1 and MMP-9 levels fluctuate and must be above a certain threshold at the same location simultaneously explains the relatively low prevalence of ODH. Typically, ODH is located at the border of the optic disk and are small in size (Fig. 3c). The location of ODH is related to the anatomical features of the ONH with lack of classical BBB characteristics and to the diffusion from the choroid, giving molecules direct access to endothelial cells in the ONH and the adjacent retina. The fact that ODH is consistently small in size may suggest that ODHs are not hemorrhages following rupture of the vessel's wall, but are rather due to transient increased vascular leakage.

Disturbed BBB of the ONH facilitates also the diffusion of other, potentially even noxious, molecules into the tissue. This might contribute to subsequent damage and may be the reason why recurrent ODHs are associated with glaucoma progression.[44] In the presence of chorioretinal atrophy, the diffusion is further facilitated and may explain the close relationship between peripapillary atrophy and ODH[3] and the recurrence of ODH in the same area of the optic disk.[8,18,45] The relationship between ODH and PVD may explain the high prevalence of ODH in early glaucoma,[5] in patients with normal-tension glaucoma,[36,45,76] as well as the relationship between ODH and progression of glaucoma,[4,20,43] as both ODH and PVD can be considered as risk factors for glaucoma damage.[25]

## Blood–ocular Barrier and Vein Occlusions

Retinal venous occlusions, both of central and branch retinal veins, are regarded as thrombotic processes in nature. However, the concept of a thrombotic process is challenged by the following observations: retinal vein occlusions occur even in patients with thrombocytopenia, in patients taking anticoagulation,[12,19] or in young non-arteriosclerotic patients.[49] In addition, residual blood flow, observed on fluorescein angiograms, indicates incomplete obstruction of the vessel's lumen.

Moreover, vasoconstriction has been described in the branch retinal[79] and central retinal veins.[86] Thus, we postulate that also a functional vasoconstriction also plays a role in retinal vein occlusions. A detailed description is, however, beyond the scope of this review.

In an eye with a disturbed BBB, an increase in the concentration of ET-1 around peri-papillary retinal vessels leads to some vasoconstriction, for example, in glaucoma,[52,53,64,65] as well as in other eye diseases where ET-1 is increased. This, in turn, may lead to increased venous pressure as has been measured in glaucoma and in extreme situations to venous occlusion.[52,53,64,65] Indeed, elevated levels of ET-1 have been described in patients with retinal vein occlusions by some, but not by all.[34,42,48]

## Conclusion

In conclusion, the ONH has distinctive features with regard to BBB already in normal anatomy. Moreover, this remaining barrier is disturbed in healthy subjects with PVD and in glaucoma patients. On average, subjects with PVD and patients with glaucoma have increased circulating ET-1 and MMP-9. The anatomical peculiarity of ONH enables a diffusion of these molecules, among others, into the peri-papillary tissue leading to vasoconstriction, and thereby also to an increased venous pressure, as well as to opening of the BBB, leading in extreme situations even to ODH.

## Method of Literature Search

A systematic search of the Medline database using the PubMed Web site, for the years 1966 through January 2007, was conducted using the following key words: *basement membrane, blood–brain barrier, Endothelin-1, glaucoma, glial cells, matrix metalloproteinase, optic nerve head, optic disk hemorrhage, tight-junction, vascular dysregulation, vasospasm.* All articles read were in English and German, and when articles in other languages were of relevance, their abstracts in English were read. The Old Medline was searched for articles published between 1953 and 1965 using the same key words.

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