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What Is the Link Between Vascular Dysregulation and Glaucoma?

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Abstract. The need of blood flow to different organs varies rapidly over time which is why there is sophisticated local regulation of blood flow. The term dysregulation simply means that blood flow is not properly adapted to this need. Dysregulative mechanisms can lead to an over- or underperfusion. A steady overperfusion may be less critical for long-term damage. A constant underperfusion, however, can lead to some tissue atrophy or in extreme situations to infarction. Unstable perfusion (underperfusion followed by reperfusion) leads to oxidative stress. There are a number of causes that lead to local or systemic vascular dysregulation. Systemic dysregulation can be primary or secondary of nature. A secondary dysregulation is due to other autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, systemic lupus erythematodes, multiple sclerosis, colitis ulcerosa, or Crohns disease. Patients with a secondary vascular dysregulation normally have a high level of circulating endothelin-1 (ET-1). This increased level of ET-1 leads to a reduction of blood flow both in the choroid and the optic nerve head but has little influence on autoregulation. In contrast, primary vascular dysregulation has little influence on baseline ocular blood flow but interferes with autoregulation. This, in turn, leads to unstable oxygen supply, which seems to be a relevant component in the pathogenesis of glaucomatous optic neuropathy. (**Surv Ophthalmol 52**:S144–S154, 2007. © 2007 Elsevier Inc. All rights reserved.)

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The main function of blood flow is to ensure adequate supply of oxygen and nutrients to the tissue in our body. The overall blood flow is equal to the cardiac output, and its distribution to different organs is regulated by the relative local resistance. The regulation of ocular blood flow (OBF) is complex.[30] It adapts to changing metabolic needs during changing visual function, compensates for varying perfusion pressure, and maintains the temperature at the back of the eye constant.[15] Many systems, such as endothelial cell layer, circulating hormones, and the autonomic nervous system are, among others, involved in this regulation. It is obvious that the more complex the regulative system (e.g., in the eye), the more susceptible it is for dysregulation and the more dramatic the potential for damage. Dysregulation of the resistance, in other words, of the blood vessels, denotes an inappropriate local regulation of arteries, veins, and capillaries.[31] As a consequence, local blood supply does not correspond to the local demand. This can imply over- or underperfusion and may result in a heterogeneous flow. Although it is currently less clear what degree of overperfusion is detrimental to the tissue,[80] underperfusion may be harmful and can lead in extreme situations even to infarctions. Thus, more attention is paid to underperfusion. Local reduction of blood flow is either due to an insufficient vasodilatation if needed or due to an inappropriate vasoconstriction (vasospasm). This condition is called *vascular dysregulation* and can occur globally, involving many different organs simultaneously or sequentially. Vascular dysregulation can be classified as primary vascular dysregula-

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tion (PVD) and secondary vascular dysregulation (SVD).[31] This review aims to summarize findings of vascular dysregulation relevant to eye diseases.

Ocular Blood Flow (OBF)

In the following sections we will discuss the regulation of blood flow, in particular, the autoregulation as it is relevant to the pathogenesis of glaucomatous optic neuropathy (GON). In terms of mechanisms, we particularly emphasize the role of the endothelium cell layer, as there are indications that the major cause of primary vascular dysregulation is a vascular endotheliopathy.[16,68,84,94]

REGULATION OF OCULAR BLOOD FLOW

The functions of the regulation of OBF are to adjust to changes in perfusion pressure (autoregulation), to keep the temperature of the back of the eye constant (thermoregulation), and to adapt to neural functions (neurovascular coupling).[50] Moreover, the circulation in the eye is regulated differently in different tissues. The retina is regulated mainly by the endothelial cells and by the neural and glial cells.[115] The choroid is regulated mainly by the autonomic nervous system and circulating hormones.[11,127] The blood flow in the optic nerve head (ONH) is regulated mainly by endothelial cells and circulating hormones.[125]

AUTOREGULATION

Autoregulation is defined as the component of regulation that compensates for variation in perfusion pressure. It functions sufficiently only within a certain range of perfusion pressure.[71,93,113,115,125] Several systems are involved in autoregulation, such as myogenic response, metabolic mechanisms, and endothelial cell function.[32,62,110]

ENDOTHELIUM-DERIVED VASOACTIVE FACTORS (EDVF)

The vascular endothelium is a confluent monolayer of flattened cells that lines the inner surface of the vasculature. The layer is not just a barrier but also an active regulator of vascular tone.[34] Endothelial cells function like a relay-station receiving physical information (e.g., sheer stress), chemical information (e.g., oxygen tension), and biological information (e.g., hormones). All of this information is integrated, giving rise to production and release of endothelial-derived vasoactive factors (EDVFs).[58] The EDVFs work in concert with other systems, such as the autonomic nervous system. The key EDVFs are nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin (PGI2).[49,57,59] There is a basal production of NO; a stimulation of endothelial cells (e.g., with acetylcholine) leads to an additional production of NO. NO diffuses into neighboring cells, including pericytes and smooth muscle cells. NO stimulates the guanylate cyclase, causing an increase in cyclic guanine monophosphate (cGMP) and thereby leading to relaxation of smooth muscle cells and pericytes, which, in turn, leads to vasodilation (Fig. 1).[60,136] The most important vasoconstrictive

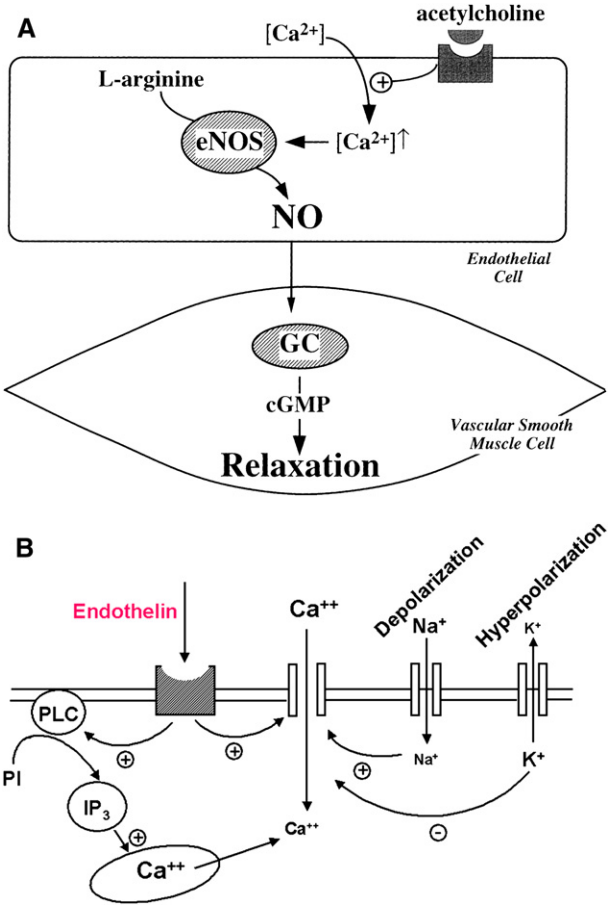

Fig. 1. A: Schematic representation of the nitric oxide synthase/guanylate cyclase pathway in a blood vessel wall. In endothelial cells nitric oxide (NO) is synthesized from L-arginine via the activation of a calcium (Ca^2+)-dependent nitric oxide synthase (NOS). NO production can be inhibited by false L-arginine analogs, such as L-N ^{G}-monomethyl arginine (L-NAME). In vascular smooth muscle cells, NO activates a soluble guanylate cyclase (sGC), which increases 3′5′-cyclic guanylate cyclase (cGMP) leading eventually to a relaxation. Receptor-operated agonists (R), such as acetylcholine (Ach) can stimulate the production of NO. (Reprinted from Haefliger et al[57] with permission of *Progress in Retinal and Eye Research.*) *B:* The calcium channels are regulated in part by both the potential of the cell membrane and the G-proteins. The G-proteins, in turn, are activated by various hormone receptors. (Reprinted with permission from Flammer J, Die Behandlung des Normaldruckglaukoms mit Kalziumantagonisten. Search on Glaucoma 5:3–7, 1997.)