

Mechanisms Behind Disease: DME

Current knowledge of the pathophysiology and pathobiochemistry guides treatment

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Diabetic macular edema (DME) is one of the most debilitating complications of diabetes mellitus. New treatments, such as steroids and anti-vascular endothelial growth factor (VEGF) agents, are currently being studied for this potentially blinding disease. The pathogenesis, however, is still not completely understood. Inflammatory reactions and oxidative processes have gained increased attention as potential etiologic factors and have been studied by means of basic research and epidemiology.

A better understanding of the pathophysiology/pathobiochemistry of DME requires a detailed knowledge of the normal anatomy and physiology.

ANATOMY AND PHYSIOLOGY OF THE MACULA

The macular area is predisposed to the development of edema due to its unique anatomy. Within lies an extremely high concentration of cells with a high metabolic activity. The outer plexiform layer (Henle's fiber layer) courses laterally away from the central fovea. It is therefore a potential reservoir for the accumulation of extravascular fluid due to the thickness and laxity of this layer. The central avascular zone creates a watershed arrangement between the choroidal and retinal circulation, thus decreasing the resorption of extracellular fluid (Figure).

A number of different factors prevent the accumulation of extracellular intraretinal fluid by interacting with one another in order to maintain a balance. This means that the rate of capillary filtration is equal to the rate of fluid removal from the extracellular retinal tissue. Those forces are osmotic and hydrostatic, as well as the permeability of the capillaries and the tissue compliance. The precondition to maintain this physiological status is the existence

of tight junctions between endothelial cells (inner barrier) and between the apices of RPE-cells (outer barrier).

ANGIOTENSIN II

The pathobiochemistry is much more complicated, with inflammatory mediators from various origins being the primary cause of the barrier breakdown. The major players and possible therapeutic targets are angiotensin II, VEGF, and prostaglandins. Other molecules, however, as well as inflammatory cells with additional proinflammatory pathways are also of great importance.

There is clear evidence that angiotensin II is participating in the key events of inflammation in the vascular wall. It induces a breakdown of blood-retinal barrier through blood-pressure-dependent and blood-pressure-independent mechanisms and is therefore responsible for edema development. Angiotensin II thus plays a key role in the pathogenesis of vascular diseases.

The production of angiotensin II occurs via the renin-angiotensin system locally in the wall of the inflamed vessel. Angiotensin II has three major effects as a key mediator of inflammation:

(1) Angiotensin II leads to leukocyte infiltration—recruitment of leukocytes from the circulation to the perivascular space—by two methods: (a) upregulation of adhesion molecules (selectins, immunoglobulins, integrins) which leads to an adhesion of leukocytes to the target tissue; (b) upregulation of chemokines and cytokines such as monocyte chemoattractant protein-1 (MCP-1), interleukins-1, -6, -8 and -12 and TNF- α . All of these events then lead to a transmigration of leukocytes into the target tissue.

(2) Angiotensin II leads to an increase in vascular permeability by pressure-mediated

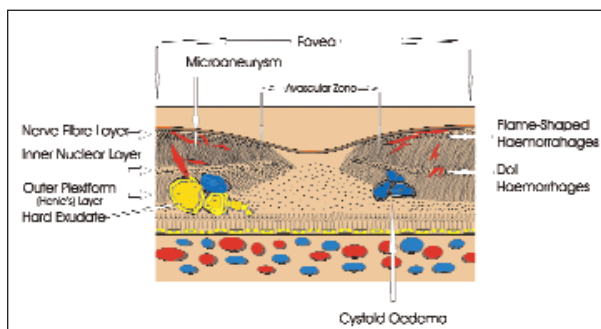


Figure. The macular space.

ated mechanical injury to the endothelium, by the release of eicosanoids, such as leukotrienes and prostaglandins, and VEGF upregulation.

(3) Angiotensin II is responsible for a remodeling process of the extracellular matrix, which prepares the way ("bed") for cell proliferation, hypertrophy, and fibrosis. This is supposed to be mediated by autocrine and paracrine growth-factors such as VEGF, PDGF, TGF- α , and bFGF.

The overall effect of angiotensin II in vascular tissues is an endothelial malfunction and the release of eicosanoids such as leukotrienes and prostaglandins and VEGF upregulation.

VASCULAR ENDOTHELIAL GROWTH FACTOR

The second major player is VEGF. It is induced, upregulated and released by many mechanisms such as angiotensin II and retinal ischemia/hypoxia, as well as oxidative processes and inflammation. In patients with DME, VEGF levels are elevated and correlate with severity of the disease. We also know that VEGF contributes to the macular edema that accompanies retinal vein occlusion and uveitis.

VEGF has two major effects leading to macular edema:

(1) Inflammation: The inflammatory breakdown of the blood-retinal barrier occurs by the following mechanisms: VEGF receptors are present and active on all inflammatory cell subtypes, including platelets, and these cells also may produce and release VEGF. VEGF binds to leukocytes and leads to recruitment and an extensive leukostasis in the vascular tissue. This phenomenon is accompanied by an upregulation of ICAM-1.

(2) Direct influence on vascular permeability: The molecule VEGF directly induces an enhanced vascular permeability. This has been shown to occur via leukocyte-mediated endothelial injury and cell death. In addition, it induces conformational changes and a dissolution of tight junctions of endothelial cells by the phosphorylation of the tight junction protein occludin. It also activates protein kinase C.

PROSTAGLANDIN E1

Prostaglandin E1 leads to a breakdown of the blood-retinal barriers by opening the tight junctions. In the prostaglandin pathway, inflammation causes the enzyme phospholipase to release arachidonic acid from cell walls. Subsequently, cyclooxygenase-II converts the arachidonic acid to prostaglandins and many other proinflammatory and growth-promoting molecules.

OTHER FACTORS

In addition to the relevant pathobiochemical factors influencing vascular damage and development of DME that have been discussed already, we know that advanced glycation end products (AGEs) are believed to elevate the oxidative stress level. Moreover, inflammation is upregulated by

the hyperexpression of cytokines, lymphocyte adhesion-molecules (V-CAM1) and vasoactive mediators.

Hyperglycemia results in elevated levels of sorbitol through the polyol pathway. This leads to:

- (1) buildup of intracellular sorbitol and fructose,
- (2) disruption of osmotic balance in the cell,
- (3) loss of integrity of the blood-retinal barrier,
- (4) loss of pericytes due to their sensitivity to polyols, and
- (5) activation of protein kinase C.

Furthermore, hyperglycemia itself leads to an elevated oxidative stress level, which then again upregulates the inflammation in vascular tissues.

In diabetes mellitus, the pathobiochemical events that have been discussed in this article are accompanied by specific tissue alterations, which require detailed evaluation to create the best treatment strategy available. In diabetic patients the following phenomena are found:

- (1) loss of pericytes;
- (2) thickening of the basement membrane which finally results in an abnormal autoregulation;
- (3) leukocyte-mediated damage to endothelial cells by platelets binding to endothelial cells and inducing the expression of adhesion molecules;
- (4) VEGF-induced leukocyte-mediated endothelial injury; and
- (5) enhanced oxidative stress levels.

TARGETED APPROACH TO THERAPY FOR DME

Our major therapeutic targets to approach macular edema are prostaglandins, inflammatory mediators and cells, and VEGF. Our armamentarium today consists of non-steroidal antiinflammatory agents, steroids, and anti-VEGF agents. The products currently being evaluated in phase 3 trials suggest that a combination treatment is the most reasonable approach. The pathophysiology of DME with altered net driving forces of water makes laser treatment still an important treatment strategy, even in the era of intravitreal steroids and/or anti-VEGF drugs and/or a combination of different drugs. In addition, recent studies on the altered lipid pathway, nutrition, diet, and the application of statins show the importance of large trials investigating these factors in more detail. ■

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