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EDITORS CHOICE

Kallikrein-kinin activation by altered vitreous pH: New perspectives for treatment and pathogenesis of diabetic macular edema?

Comment on: Gao BB et al. Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation. Nat Med. 2007 Feb;13(2):181-8.

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Abstract Recently, Gao et al. published an experimental study based on the pathophysiology of diabetic macular edema in Nature Medicine (Nat Med. 2007 Feb;13(2):181-8). They found an increased amount of carbonic anhydrase in the vitreous, which causes a pH shift. This activates the kallikrein–kinin system and leads to increased retinal vascular permeability. In this comment the clinical implications of this article are discussed.

Keywords Macular edema · diabetic retinopathy · carbonic anhydrase

Diabetic retinopathy is the most common reason for vision loss in industrialized societies, and diabetic maculopathy is one of the leading causes of acute vision loss [2]. To prevent blindness and reduce the economic burden, the pathogenesis of diabetic retinopathy is of special interest in current research [13]. Even though the understanding of the biological and molecular changes leading to breakdown of the retinal blood-barrier has been largely extended in recent years, the entire pathophysiology still remains the subject of ongoing research [12]. There are a variety of options in the treatment of macular edema, like systemic and topical steroids, non-steroidal anti-inflammatory agents, systemic and topical inhibitors of carbonic anhydrase and focal laser coagulation. All methods show different rates of success. Recently, vascular endothelial growth factor (VEGF) has been recognized as one of the factors increasing retinal vascular permeability in diabetic retinopathy. Therefore, anti-VEGF treatment has become an alternative tool in the treatment of diabetic macular edema [1, 11].

In February 2007, Gao et al. [8] published an experimental study suggesting that the vitreous plays a leading role in the development of diabetic vascular disease. From a proteomic analysis of non-diabetic and diabetic vitreous samples, they found significantly higher levels of carbonic anhydrase (CA) in the vitreous of patients with diabetic retinopathy than in non-diabetic controls. Furthermore, the concentration of CA was 8.3 times higher in the vitreous of patients with proliferative diabetic retinopathy than in the vitreous of patients with non-proliferative diabetic retinopathy. To elucidate the pathophysiological relevance of the result, the authors purified human CA and injected it intravitreally into rat eyes. Fluorescein angiography showed an early vascular leakage, which was not present in the sham-injected control group. If CA was co-injected with acetazolamide, a CA inhibitor, the vascular leakage was reduced. Fluorescein angiography results were confirmed by optical coherence tomography, which revealed retinal thickening in parallel to the grading of vascular leakage. However, where does the CA come from? As CA is a cytoplasmic protein commonly expressed in erythrocytes, Gao et al. suggested that the increased vitreous presence of CA in diabetic retinopathy was the result of intraocular (micro-)hemorrhage. They therefore lysed red blood cells and injected them intravitreally. This exerted the same effect on vascular leakage as the injection of purified human CA. To gain information on the biochemical

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mechanisms leading to vascular leakage, co-injections of CA with antagonists of the kallikrein-kinin system, a pathway known to lead to increased vascular permeability in diabetic retinopathy, were performed [9]. Depending on the antagonist, the CA-induced vascular leakage was reduced up to 81%. Since CA is a main regulator of extracellular pH, pH was investigated, which showed an alkalization of the vitreous by CA. Alkaline-adjusted balanced salt solution had the same effect on vascular leakage as injection of CA. To examine a general effect of CA on vasogenic edema, subdural CA infusions were additionally made in the rat model. These resulted in a cerebral vascular leakage similar to the increased retinal venous pressure detected after intravitreal injection.

In summary, the results of the study suggest that high levels of CA lead to an alkalization of the vitreous, which activates the kallikrein-kinin system. This results in increased retinal vascular permeability. Small hemorrhages may be the source of increased vitreal CA.

Inhibition of the CA has been known for many years to be an option for therapy for macular edema, and acetazolamide therapy has been used in treatment of macular edema in retinitis pigmentosa, after cataract surgery and in uveitis [3, 4, 17]. Although it is not the first-line therapy, there are reports on effectiveness of CA inhibition in diabetic macular edema [10]. It has been proposed that acetazolamide leads to an activation of retinal pigment epithelial transport and subsequent resorption of intraretinal fluid [18]. The results published by Gao et al. [8] show a novel direction to how inhibition of the CA may influence macular edema.

The classic treatment for diabetic retinopathy consists of laser therapy [5]. Macular edema can be treated with grid photocoagulation, which does not lead to resorption of fluid in each patient [7]. The mechanism behind grid laser therapy is thought to be a stimulation of retinal pigment epithelium. If vitreal pH and CA levels contribute substantially to the retinal leakage, this activation of the retinal pigment epithelium is, of course, not expected to be effective.

The data from Gao et al. [8] have also implications for vitrectomy in diabetic patients. Commonly, the release of traction and the removal of vitreous humor to reduce cytokines and angiogenic factors are thought to stand behind the success of vitrectomy in diabetic patients [14–16]. To achieve this, induction of a posterior vitreous detachment appears to be of particular importance [19]. The removal of CA and the normalization of pH might be a novel rationale for vitrectomy, but of course needs to be investigated in future studies. Furthermore, the results of Gao et al. would imply performing vitectomy in cases of vitreous hemorrhage at an earlier time point, since intravitreal hemolysis might promote vascular leakage.

In addition to diabetic retinopathy, it will be of interest and importance to investigate the role of CA in macular edema of other origin, like uveitic, or post-anterior segment surgery. These subtypes respond much better to acetazolamide or even to locally applied dorzolamide [6]. The work of Gao et al. [8] implies an involvement of CA in these disease entities.

In conclusion, the results from Gao et al. [8] give an interesting insight into the pathophysiological processes that may underlie increased vascular permeability in diabetes. The excellently designed experimental study raises new perspectives beyond anti-VEGF therapy of macular edema.

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